Steroids from Carvone

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Contents

Wanneer jij je ogen opent
zullen wij, opnieuw, op weg gaan
tussen de uren en hun uitvindingen
en slenterend tussen de verschijningen
zullen wij de tijd en zijn vervoegingen bevestigen.
Wij zullen de deuren van de dag openen
en binnentreden in het onbekende.

Uit *De eerste januari* van Octavio Paz

Introduction

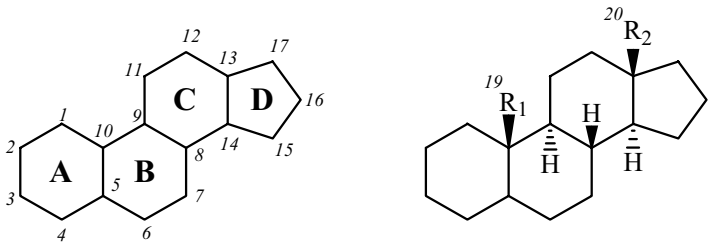
Chapter 1

1.1 Introduction

Steroids probably form one of the most investigated groups of natural products to this date. They are related to the group triterpenes, which, in turn, belongs to a larger class of compounds known as terpenes, or isoprenoids. Many of the smaller and more volatile terpenes have been used by mankind for at least two thousand years as flavours and fragrances, although at first as components of crude plant extracts. During the Middle Ages, for example, any herbalist had many recipes for the production of medicines and essences from herbs such as rosemary, thyme, tansy, etc., all rich in terpenes[1]. Today, terpenes are still widely used, with applications varying from their use in perfumes, cosmetics, soaps, detergents, toothpaste, confectionery, processed meats or tinned foods, to the use of turpentine in the paint industry. The use of steroidal hormones like adrenal hormones such as cortisone, sex hormones such as estradiol and testosterone, and vitamin D is widespread in the pharmaceutical and food (supplement) industries[1,2].

The group of steroids includes both synthetic and natural substances, of which the latter occur in a wide variety of marine and terrestrial organic organisms[3]. In essence, steroids all possess a similar structural feature, the tetracyclic perhydro-1,2-cyclopentenophenanthrene ring system (see figure 1), although the group actually also includes compounds with a somewhat modified structure. Deviations from the normal skeleton are indicated by prefixes. For example, compounds missing a ring junction, leading to an opened ring system, are generally referred to as 'seco' steroids (e.g. vitamin D and analogues). Another example comes from compounds with an extra C-atom, indicated with the term 'homo' preceded by the concerned ring or atom number and placed in front of the steroid name (e.g. D-homo steroids). When a carbon atom is missing the prefix used is 'nor', and the prefix 'cyclo' refers to an extra ring formed by bonding between two C-atoms of the steroid skeleton. The peculiar numbering system used (see figure 1) originates from the early erroneous structure assigned to cholesterol. When any of the carbon atoms is missing, the numbering of the others remains unchanged[4]. The definitive rules for steroid nomenclature were decided in 1971 by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry (IUB)[5].

Figure 1. Steroid numbering and general stereochemistry



The initially isolated solid crystalline secondary alcohols from non-saponifiable lipid extracts of plants and animals were called sterols (~ 'solid alcohol', in Greek), and their name later led to the terminology "steroid", which was introduced in 1936 for this whole class of compounds[4]. Early steroid research in the 19th century mainly involved isolation of the sterols, and bile acids, from natural sources. Cholesterol was one of the first sterols isolated, originally from human gallstones, but the compound was later found to be present in all animal tissues. The discovery of cholesterol is generally accredited to de Fourcroy in 1789[6]. However, its structural elucidation had to wait until the 20th century. In 1903 this elucidation was started and it was terminated only thirty years later, when X-ray crystallographic data became available. A first steroid total synthesis of equilenin was achieved also at that time, proving the tetracyclic structure of steroidal compounds[7-11]. In this same period, estrone, progesterone, estradiol and testosterone were isolated and their structures elucidated[10]. These different developments opened the road to further academic, and from then on, also industrial research on steroids, their (bio)synthesis and their biological activity, leading to an incredible amount of publications on this subject that continues to this date[1,2,4,11,12]. The pharmaceutical relevance of these compounds has proven to be exceptional and nowadays around 6% of the total drug marked is covered by steroid-based preparations[13].

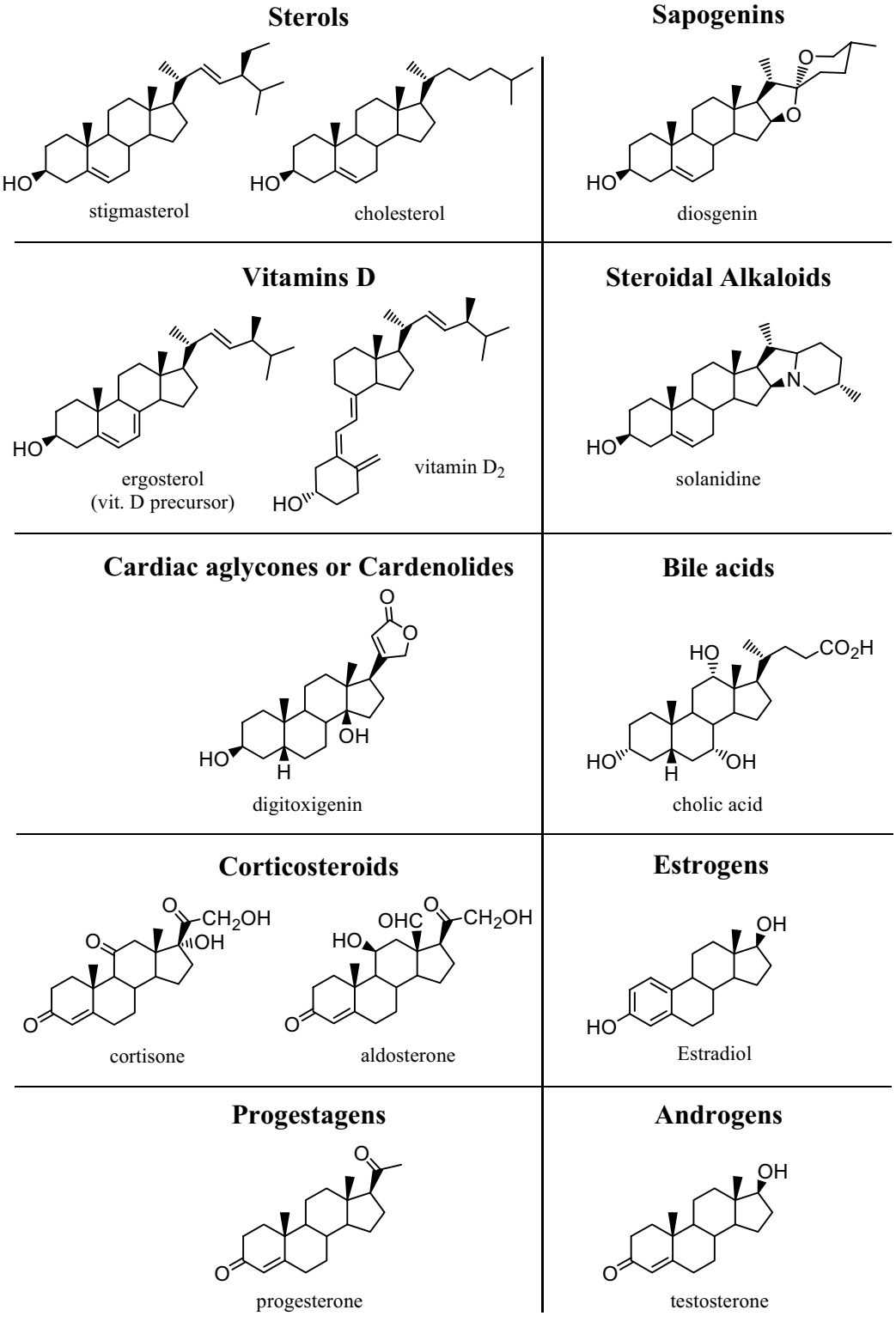
1.2 Biological relevance

The large group of steroids is subdivided into several subgroups, mainly according to the structure of the parent hydrocarbon from which they are derived. An important diversifying element in these parent hydrocarbons is the side chain attached to ring D[2,3]. The different subgroups that can be distinguished are sterols, sapogenins, cardiac aglycones and steroidal alkaloids, from plants, and sterols, bile acids, corticosteroids and the sex hormones estrogens, progestagens (both female) and androgens (male), from animals.

The corticoids and sex hormones are known to fulfil important hormonal functions in mammals and are therefore of most interest to the pharmaceutical industry. Besides that, the cardiac aglycones, such as digitoxigenin, are known to have powerful and specific actions on the heart muscle and are for this reason also valuable agents in the treatment of heart ailments. Diosgenin, isolated from Yams (*Dioscorea* sp.), has proven to be a very useful sapogenin, being a valuable starting material for several steroid hormone syntheses such as cortisone and synthetic male and female sex hormones[2].

The majority of the sterols appear to be very long-lived and thus not metabolised. Moreover, all eukaryotes synthesise sterols, or have an absolute requirement for them in their diet. They play a vital role in maintaining structural integrity of most membraneous structures in organisms. They

Figure 2. The different steroid groups and representative compounds

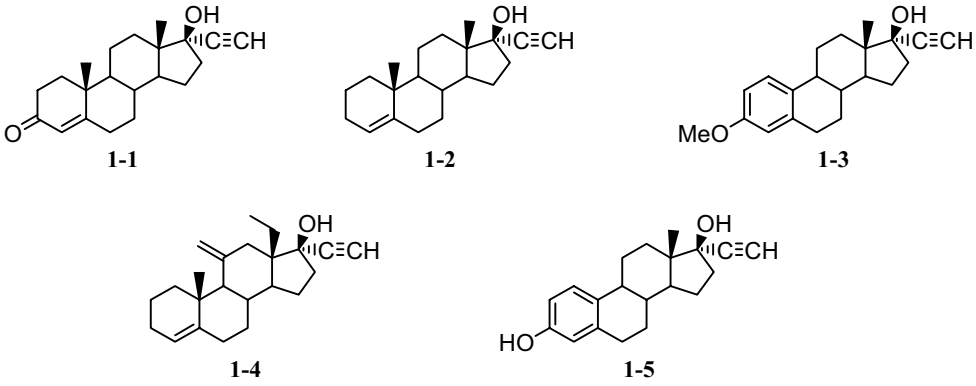


further appear to assist in the regulation of permeability of these membranes for various ions[1]. The vitamins D form a specific group of sterols having all the same seco-steroidal structure. They play an important role in the absorption and metabolism of calcium and phosphorus in animals but originate from steroidal precursors of plant origin, such as ergosterol[11]. The bile acids are known for their activity in the digestion processes. The active form of these compounds is actually the bile

salts. They emulsify fats present in partially digested foods to make them more accessible for enzymatic cleavage leading to lipid absorption in the gut[1,3,11].

In the family of the steroid hormones, corticosteroids, such as cortisone and aldosterone, have a broader spectrum of activity than the sex hormones. They help to control the metabolism of carbohydrates, proteins and fats, and play an important role in the regulation of the salt and water balances in our bodies[14]. The sex hormones, on the other hand, are responsible for fertility and the typical male and female characteristics, influencing the specific developments at puberty[15-18]. The progestagens are further responsible for the regulation of the menstrual cycle and the maintenance of pregnancy. Synthetic variants of these hormones, such as norethindrone **1-1**, lynestrenol **1-2** and mestranol **1-3** (see figure 3) are at the basis of the contraceptive pill and function by disrupting the natural balance of estrogens and progesterone in the ovaries[1,11,19]. A new generation of progestagens was introduced by desogestrel **1-4** in the early 1980s. The residual androgenic activity of these new compounds, common in synthetic progesterone analogues, was much reduced, lowering the negative side effects, such as an increased risk of thrombosis. Desogestrel, together with ethinylestradiol **1-5**, is widely used in oral contraceptives on the market today[19-24].

Figure 3



Androgens are known to the wider public for their anabolic function inducing growth of muscle mass due to the increase in muscle protein. This originates in their function as sex hormone, causing the increase in height and weight in boys during puberty[16,18,25].

1.3 Biosynthesis

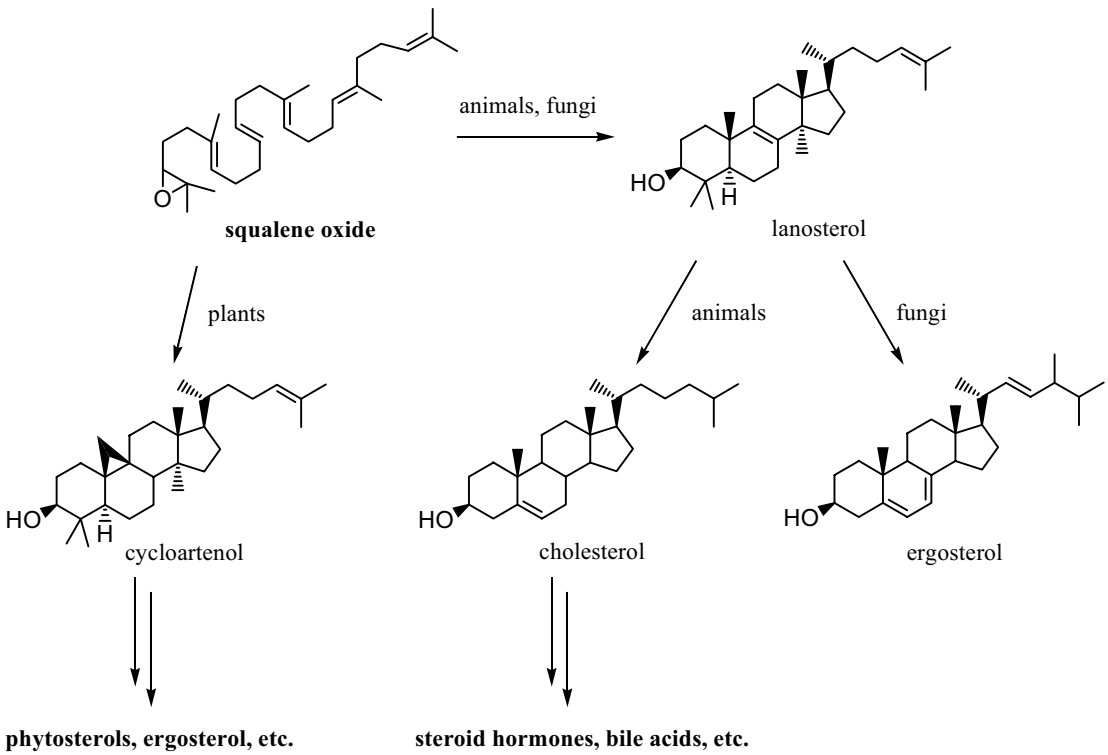
Triterpenoid skeletons have been found in ancient sediments, fossils and spores, and these compounds usually possess the same stereochemistry as their modern counterparts[26-29]. The three-dimensional structure of triterpenes has an obvious role in information translation, as an extensive variety of different shaped terpenoid molecules is in theory accessible from a same

precursor. It is therefore not surprising that these compounds play important roles in a large amount of biological processes and that such processes including triterpenoids have existed for almost as long as life on this planet.

Steroids are not true triterpenes in that they usually possess C_{19}-C_{29} skeletons, rather than a C_{30} skeleton, but they all derive from the same C_{30} precursor, squalene[1,11]. The squalene molecule consists of two all-*trans* farnesyl units joined together in the unusual 'head-to-head' fashion[30]. It was first isolated from shark liver oil in the 1920s (*Squalus* spp.), but was soon found to be widely distributed over living organisms[2,11]. Actually, only insects are known to be unable to manufacture their own steroids *de novo* and rely on dietary sources of cholesterol or phytosterols. They are then capable of processing these compounds into suitable materials for, for example, hormonal functions[31,32].

The squalene to steroid pathway has mainly been delineated by subsequent works of Bolch, Lynen, Cornforth and Popjak (see scheme 1)[11,33]. Cyclisation is usually initiated by acid catalysed ring opening of a monoepoxide derivative of squalene, and proceeds *via* a series of carbocationic intermediates[34]. The steric structures of the steroidal products can usually be rationalised from the possible foldings (pseudo chair or boat) of the polyprenyl chain on the enzyme surface[1,2]. In animals, squalene is first converted into lanosterol, which is then further transformed in cholesterol. From cholesterol, the hormonal steroids are then obtained through various pathways. In plants, on

Scheme 1



the other hand, squalene is converted into cycloartenol from which the different phytosterols and other plant steroids are synthesised. In fungi and other lower organisms, squalene appears also to be converted into lanosterol, but is then further converted into ergosterol, also found in plants[34] (for a more detailed discussion on the possible pathways involved in the different conversions see references[3,11,34,35]).

1.4 Synthesis of steroids

As described above, steroids have important and many different biological functions in living organisms. Since this discovery, it has been of interest to synthesise natural steroids of low availability and to prepare novel steroidal compounds in order to find new potent biological activities. To achieve these goals, several approaches are available to the synthetic organic chemist, such as partial synthesis, modification of readily available steroidal compounds or total synthesis. The latter is often the most versatile and therefore the most applied method. This is why steroid total synthesis has been widely studied during most of the 20th century, the first total synthesis of a steroid being reported in 1939 by Bachmann, Cole and Wilds[36]. It remains to this day a topic of interest for synthetic organic chemists and the pharmaceutical industry, even though many elegant syntheses have been developed. However, the efficiency of the routes towards adequately functionalised steroid skeletons, which, in the ideal case, should also be chiral, short and versatile, can be improved, which explains why research in this area is still ongoing.

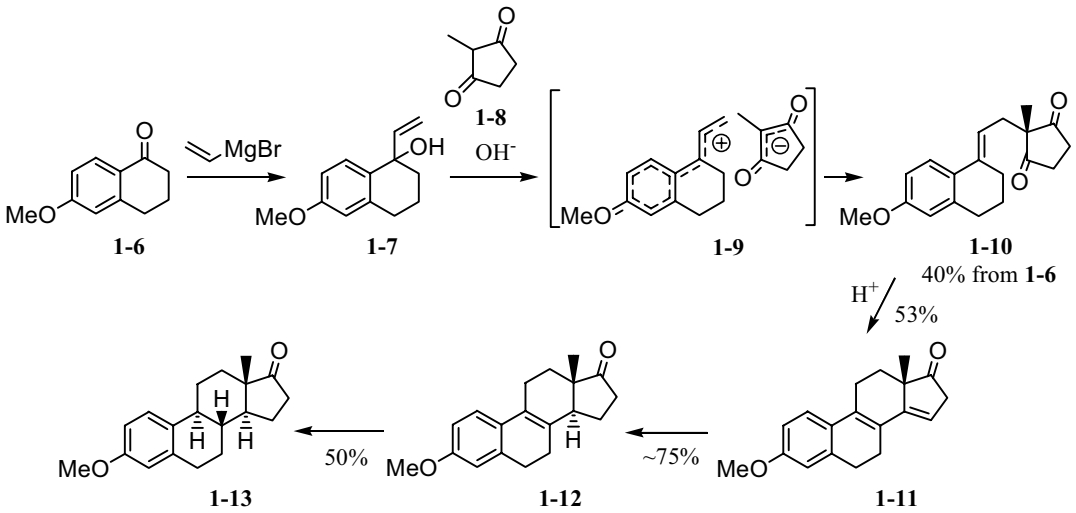
When reviewing steroid total syntheses, it is possible to organise the material according to different criteria, for example according to the type of steroid obtained, the chemistry used in the key reaction step or the sequence of ring closure. Since an enormous amount of synthetic research has been devoted to steroid synthesis, we have focussed the discussion on approaches in which the formation of ring C is the final or crucial step. This was decided because in our own work on steroid total synthesis the closure of ring C is also the key transformation. Several publications have appeared over the years giving a good overview of the complete field of steroid total synthesis[37-40].

1.5 Ring C closure as key step

In the group of total syntheses where ring C closure can be pin pointed as the key step towards the steroidal structure, most of the approaches can again be subdivided into different groups in several ways: for example, according to the last formed bond (9-11, 11-12 or 12-13) or according to the method used for ring construction. We have chosen here to follow more or less the latter subdivision, giving a clearer view on the different types of chemistry used in steroid total synthesis.

The publication by Torgov and co-workers on their method for steroid total synthesis has marked an important development in the early days in this field. In this method ring C is closed by means of an acid catalysed cyclisation reaction of a ketone with a double bond (scheme 2)[41-46]. The method has proven to be highly versatile and, as a consequence, has been extensively used and modified since its introduction, leading to estrone and its derivatives, homo steroids, hetero steroids, ring A non-aromatic steroids (see also scheme 4) and also non-steroidal ring structures[47-61]. The method involves the condensation of a reactive alcohol **1-7**, with its hydroxyl group located at an allylic as well as benzylic position, with a 1,3-cyclodione, mostly 2-methylcyclohexane-1,3-dione or 2-methylcyclopentane-1,3-dione **1-8**. Subsequent cyclisation of the obtained intermediate **1-10**, leads directly to steroid skeleton **1-11**, which can then be modified further.

Scheme 2



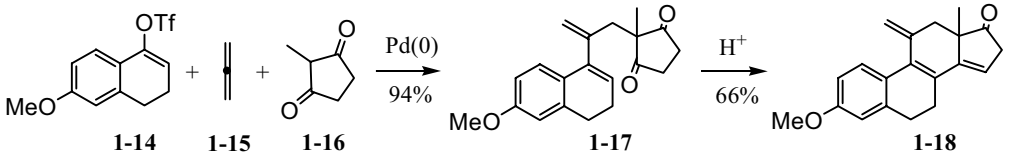
Although at first the condensation step was believed to be base-catalysed, Kuo, Taub and Wendler proposed for this step an acid-base reaction mechanism proceeding through an ion-pair intermediate (**1-9**)[62]. Simultaneously they reported that the condensation and cyclisation steps could be performed in a one-pot reaction sequence, yielding 60% of the tetracyclic steroid skeleton[51].

The standard Torgov reaction leads to racemic mixtures of the steroid skeletons. Several routes using this chemistry and leading to enantiomerically pure compounds have however been published over the years. These routes use either chemical[47,54] or enzymatic[50,52,53] resolution, a chiral ring D precursor[57] or a chiral catalyst[58]. For a more extended discussion on these routes, see chapter 5 (paragraph 1).

Gore and co-workers published in 1991 a method using carbopalladation of allenic compounds to obtain ring A-aromatic steroids. Using this method they could synthesise steroid skeletons in two steps, with interesting overall yields (40%-70%), starting from ζ-tetralones and cyclopentanediones

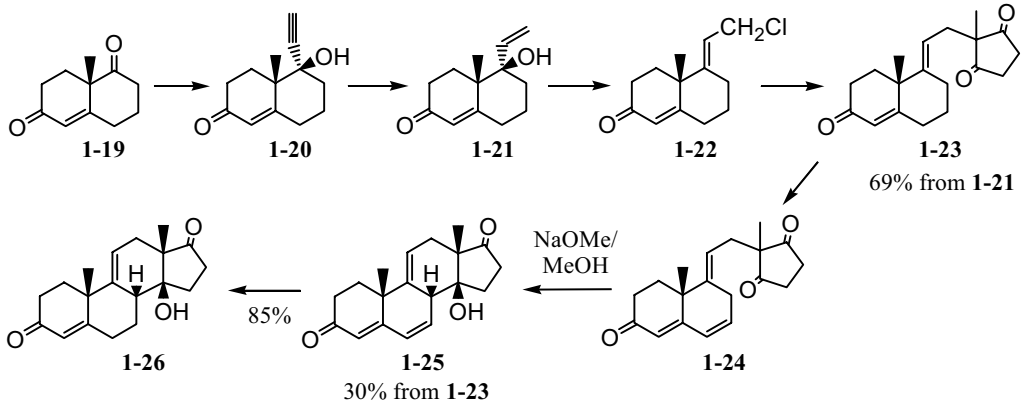
(scheme 3)[63,64]. The intermediates obtained after the first step resemble intermediates from the Torgov route. Some of these intermediates were already known[56] and cyclisation was performed accordingly. Unfortunately this method is limited to ring A-aromatic steroids and, as for the Torgov synthesis, does not proceed with any stereoselectivity, yielding only dienic compounds with the double bonds situated at C-8/C-9 and C-14/C-15.

Scheme 3



A comparable approach using a Torgov-like addition step but with an extended aldol condensation as final cyclisation step was used by the groups of Wiechert[65] and Daniewski[66]. This method gave access to non-aromatic ring A steroids bearing a C-19 methyl group (scheme 4). As compound **1-19** was a racemate, this synthesis led again to a racemic steroidal product. Similar routes were published by Yates and co-workers in 1985, giving access to racemic steroids having a non-aromatic bridged A ring[67], Taguchi in 1991, yielding two diastereomers of a C10-trifluoromethyl substituted steroid [68], and Zard in 1993, leading to 19-nor-steroids as single diastereomers in good yields[49].

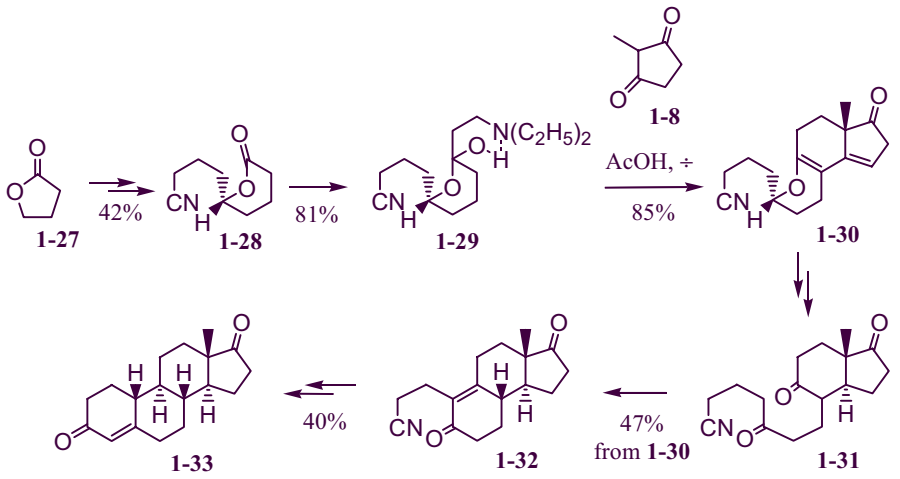
Scheme 4



A second group of steroid syntheses relies on Michael-type additions and often also includes an addition with 2-methyl-1,3-cyclopentadione. One of the first was developed by Saucy and co-workers and has been referred to as the Hoffmann-LaRoche synthesis (scheme 5)[69-76]. It was used to produce various steroid hormones using the condensation of a Mannich base with 2-methyl-1,3-cyclopentanedione. The route could even be applied to synthesise optically pure steroids when an

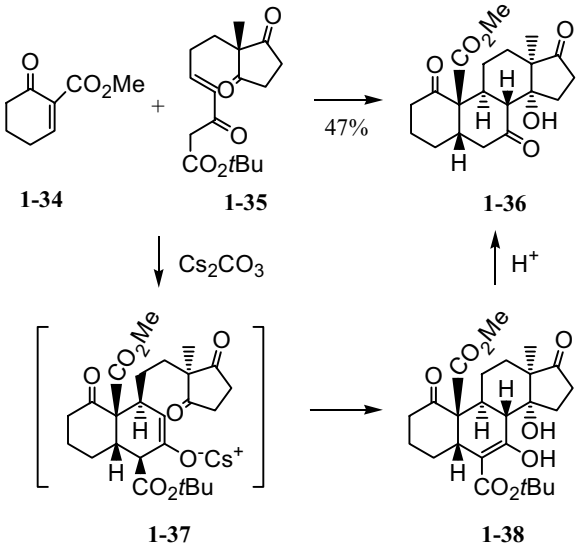
optically active variant of the Mannich base, **1-29**, was used leading to intermediate **1-30**, which was then further converted to steroid **1-33**. The enantiomerically pure Mannich base **1-29** was obtained *via* resolution of its oxalic acid salt derivative. The condensation reaction and cyclisation of ring C take place consecutively in the same reaction vessel and occur with high asymmetric induction, giving a diene with the natural configuration around C-13 as the major product.

Scheme 5



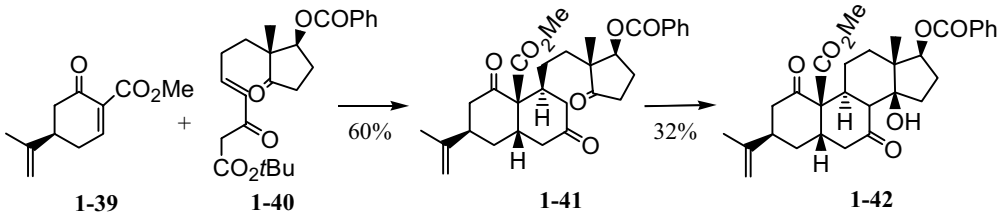
Deslongchamps developed a one-step stereo controlled method using an anionic cycloaddition catalysed by cesium carbonate as polycyclisation reaction and yielding 13,14-cis ζ-steroids (scheme 6)[77,78]. Addition of the Nazarov type reagent **1-35** to 2-carbomethoxy-2-cyclohexenone **1-34**, intermediately followed by trapping of enolate **1-37** *in situ*, yielded a tetracyclic steroid skeleton. After selective decarboxylation, 13ζ-methyl,14ζ-hydroxy steroid **1-36** was obtained.

Scheme 6



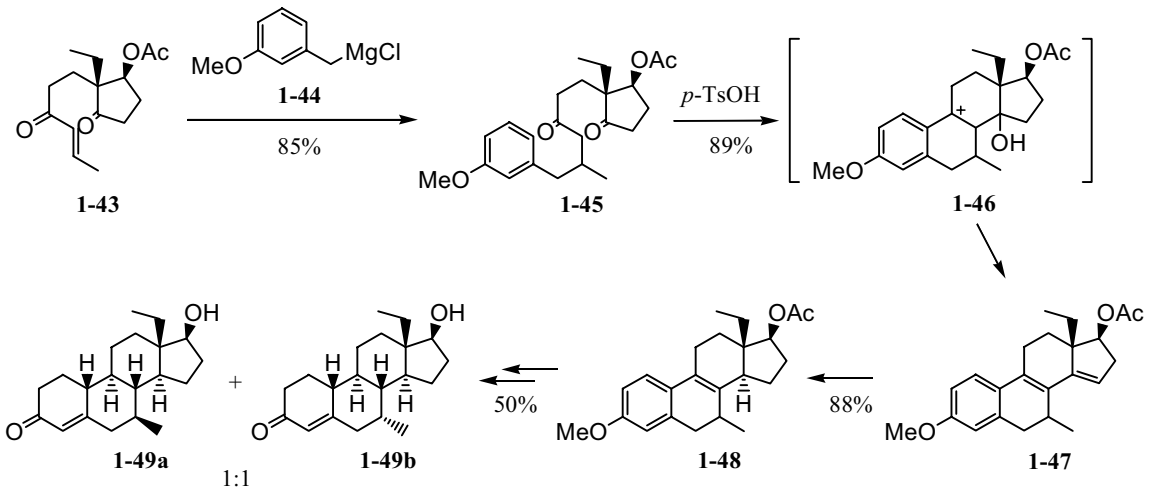
Later syntheses, developed to obtain stereoselectively the more desired η-configuration on C-13 and C-14 did not yield directly a steroid skeleton in a one-step procedure, but led to intermediates like **1-41**. Intermediate **1-41** was then cyclised using aldol condensation producing steroid **1-42** as the sole product, although in a low yield which couldn't be improved[79-81].

Scheme 7



A method where ring C and ring B are closed simultaneously was reported by the groups of Kurosawa and Zhou[82,83]. This method was actually a modification of a route reported first by Smith in 1963[84,85], and later also used and adapted by several other groups[86-97]. These routes relied on the formation of an 2-methoxyphenylethyl substituted indanone ring system, yielding rings A, C and D, followed by an acid catalysed closure of ring B. Kurosawa and Zhou however, cyclised both rings B and C in one step. The reaction probably goes *via* an acid-catalysed aldol reaction closing ring C, immediately followed by a Friedel-Crafts type reaction, followed by dehydration, closing ring B. This leads to intermediate **1-46** and dehydration then gives steroidal diene **1-47**. Zhou synthesised 7η,18- and 7ζ,18-dimethyl-19-nor-testosterone (respectively **1-49a** and **1-49b**) in 6 steps from intermediate **1-43** (scheme 8). This compound was obtained in 25% overall yield from acrolein in a sequence of steps involving the conversion of acrolein into a ν-keto-sulfoxide, which was then coupled to 2-ethyl-1,3-cyclopentadione. A consecutive microbial asymmetric reduction and further conversion then led to compound **1-43**[82].

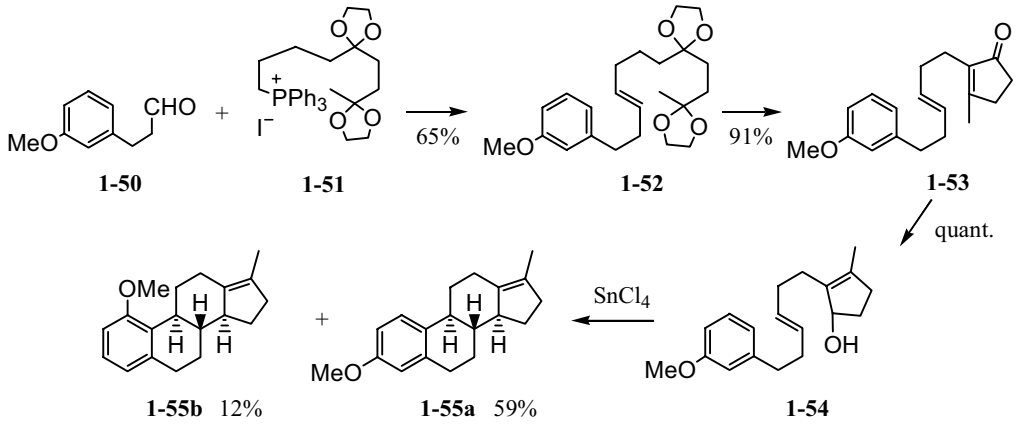
Scheme 8



Bartlett and Johnson also developed a synthesis where rings B and C were closed simultaneously, but using a polyene cyclisation reaction (scheme 9)[98]. In contrast with the Smith cyclisations, ortho cyclisation can also take place, which leads to products like **1-55b**, and can lower the yield considerably. The method consists of a Wittig-Schlosser condensation of an aldehyde with a phosphonium iodide, which proceeded with greater than 98% trans-stereoselectivity. This leads, after hydrolysis of the diketal, aldol cyclisation, dehydration and reduction, in a few steps to steroid precursor **1-54**. Cyclisation was catalysed by stannic chloride and gave compound **1-55a** in 59% yield. Further conversion lead to estrone in 22% overall yield from **1-53**.

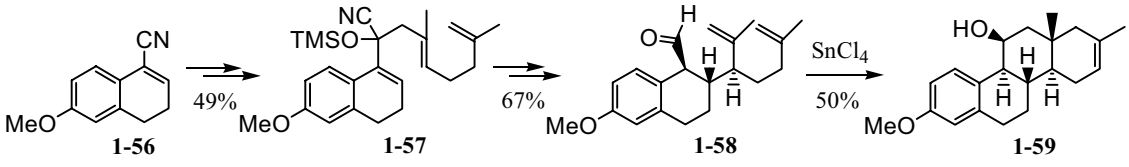
This method has also been applied by Groen and Zeelen[39,99,100] and by the group of Speckamp[101] for the synthesis of steroids and steroid-like compounds. Johnson also used similar chemistry in the development of his bio mimetic pathway, which will not be discussed here[102,103].

Scheme 9



Also using a polyene cyclisation, Ziegler and Wang reported the C/D-cyclisation of the oxo-diene **1-58**, which leads to D-homo steroid **1-59** (scheme 10)[104,105]. Aryl triene **1-57** was prepared in 49% yield from nitrile **1-56**[106,107], and converted into the oxo-diene through a (trimethylsilyl)cyanohydrin Cope rearrangement, wherein the stereochemistry at C-8 and C-9 is controlled. Acid catalysed cyclisation then leads to the D-homo steroid skeleton. Using a slightly modified approach, a compound with a five-membered D ring could also be obtained by the same group[105]. Ziegler also investigated a similar route involving a Cope-Claisen rearrangement, but this method showed low

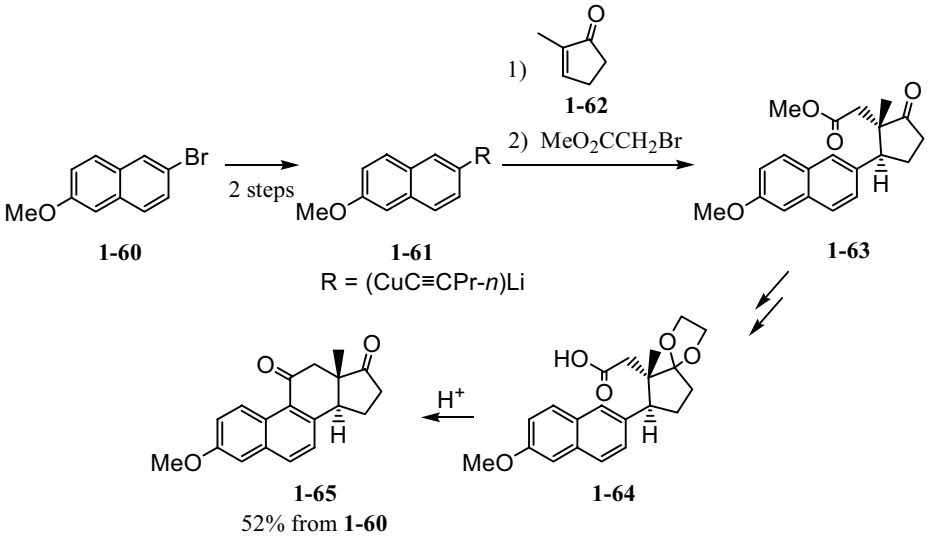
Scheme 10



stereoselectivity (see chapter 3, scheme 3)[108].

Posner developed a short and stereoselective synthesis using Friedel-Crafts chemistry where C-ring formation is the key step (scheme 11)[109,110]. Using this method 11-oxoequilenin methyl ether **1-65** was synthesised in only six steps from readily available 6-methoxy-2-bromonaphthalene **1-60** (52% yield). Later Posner's group also devised a one-pot sequence following tandem Michael-Michael additions and using an intramolecular Wittig reaction for ring C closure (see chapter 3, scheme 2)[111]. This method was used for the synthesis of 9,11-dehydroestrone methyl ether, unfortunately in only 8% yield. The Wittig reaction was also used by Groen and co-workers for the closure of ring C in a route further resembling chemistry used by the group of Mikami (see below and chapter 3, schemes 5 and 6)[112-114].

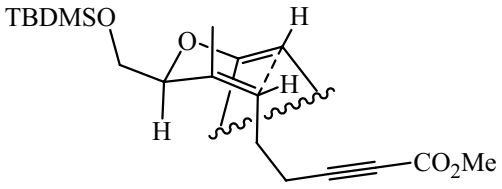
Scheme 11



Research on tandem reaction sequences has been growing more and more popular as an efficient strategy for the stereocontrolled synthesis of more complex molecules. In 1990, Mikami and co-workers published a tandem Claisen-ene approach to the synthesis of (+)-9(11)-dehydroestrone methyl ether **1-75**, where ring D and part of ring C were formed through this chemistry in a one-pot procedure (scheme 12)[113,114].

Particularly noteworthy is the stereoselectivity of this reaction. The Claisen rearrangement proceeds through a chair like transition state yielding only the S-configuration on C-14 and a high 8,14-syn selectivity. The transition state of the second step (ene-cyclisation) has an endo-bicyclic form, with the A,B-ring system in favourable pseudo equatorial position, which leads to the 13,14-trans configuration found in the final product (both transition states respectively I and II in figure 5).

Figure 5



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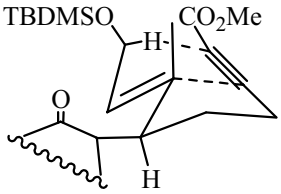
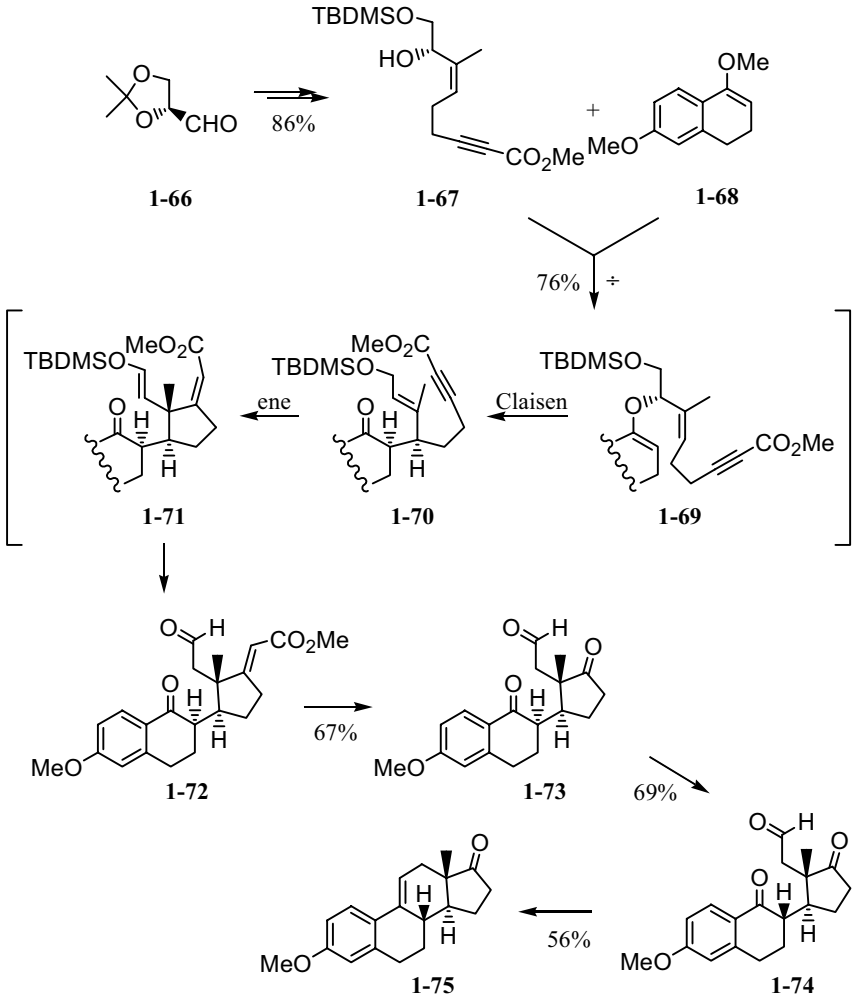


II

The final ring C-closure was performed using a modified McMurry coupling reaction, described before by Ziegler (see chapter 3)[108]. In that case however, the final McMurry coupling had given a lower yield (37%). A problem that was also confronted by Posner in his stereospecific synthesis of the same compound based upon an asymmetric Michael addition to an unsaturated sulfoxide (see chapter 3, scheme 4)[115].

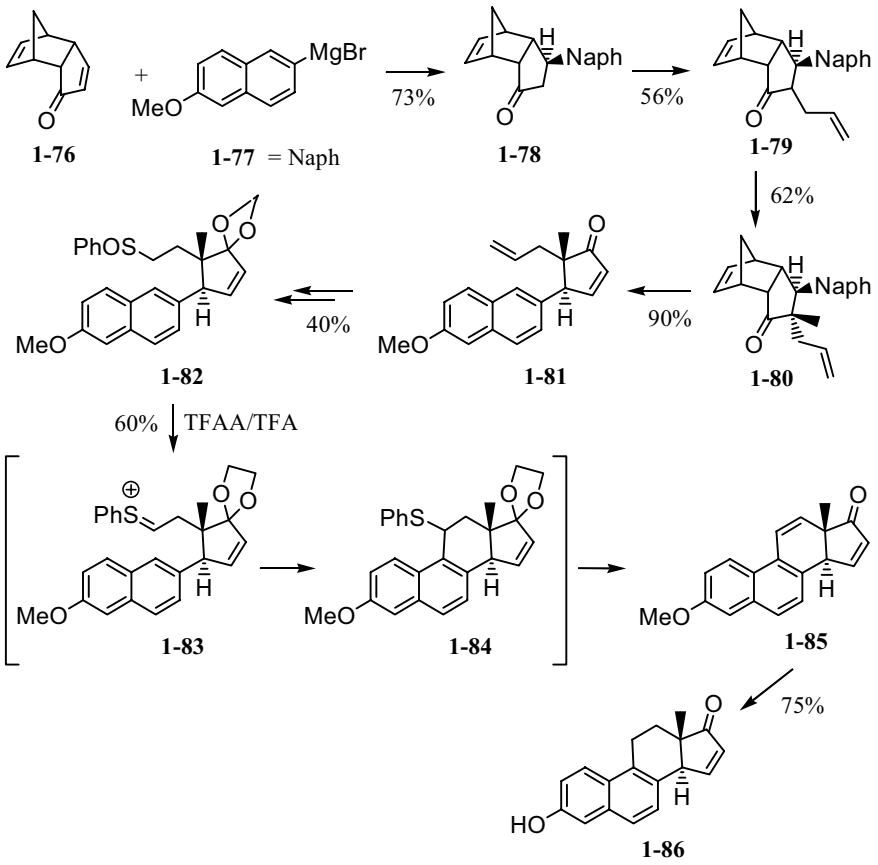
Scheme 12



As mentioned previously, a synthesis similar to the Mikami method was performed by Groen[112]. Remarkably the ene reaction did in this case not show any stereoselectivity, yielding the two isomers on C-13 in an almost 1:1 mixture. The troublesome McMurry coupling reaction used for ring C-closure was here replaced by an intramolecular Wittig reaction, which, unfortunately, did not give better results, having modest yields and producing the wrong stereoisomer at C-8 (see chapter 3, scheme 6).

A method was developed by Takano and co-workers where they used stereoselective introduction of nucleophiles at the η4carbon of tricyclic dienone **1-76**, which they had designed for the enantiocontrolled synthesis of natural compounds. They applied this method to the synthesis of (+)-equilenin (scheme 13)[116]. Compound **1-76** had been previously synthesised by the same group in an efficient conversion from dicyclopentadiene, using kinetic resolution by lipase in the key stage[117]. Closure of ring C was performed via acid-catalysed cyclisation of sulfone **1-82**. Racemic **1-81** has also been used for the synthesis of racemic equilenin in earlier work by Horeau and co-workers[118].

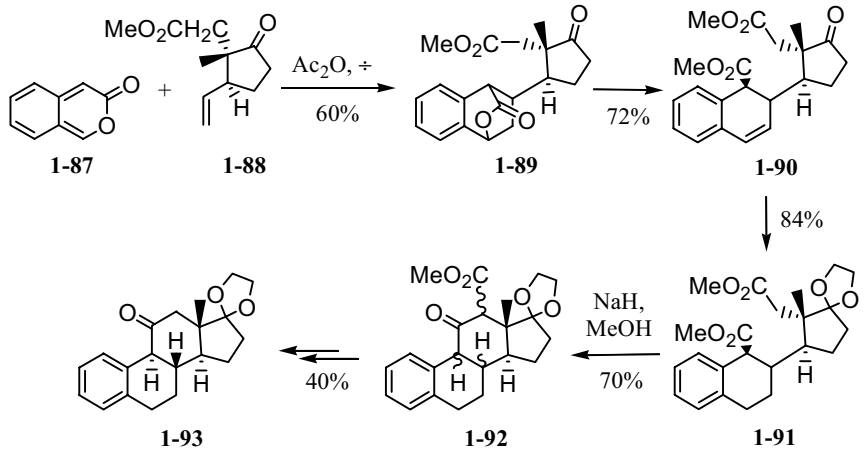
Scheme 13



Bleasdale and Jones used an intermolecular Diels-Alder reaction followed by a Dieckmann cyclisation to synthesise estra-1,3,5(10)-triene-11,17-dione 17-ethylene ketal **1-93** (scheme 14)[119,120]. The Diels-Alder reaction between 2-benzopyran-3-one **1-87** and the readily available

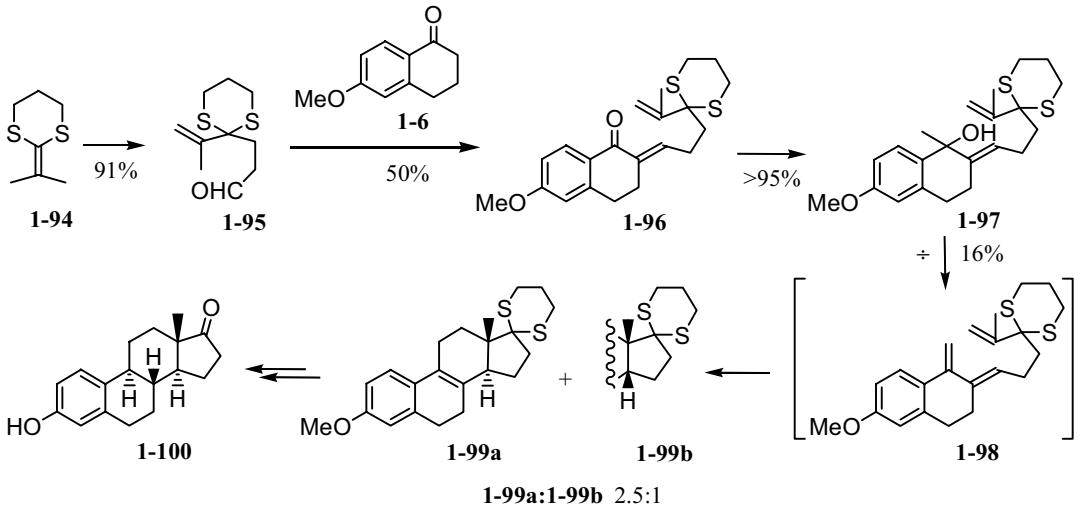
Oppolzer olefin **1-88** appeared to be highly regioselective and gave the right regioisomer for steroid synthesis in 60% yield. When the methoxy-pyrone homologue of **1-87** was used as starting material, the reactions gave similar results and methoxy analogue of **1-93** was obtained.

Scheme 14



Jung and Halweg published a method using an intramolecular Diels-Alder reaction for ring closure to synthesise estrone **1-100** (scheme 15)[121]. Unfortunately, the olefination from **1-96** to **1-98** proved extremely difficult. According to them, the presence of the 6-methoxy group in the tetralone ring decreased considerably the ketone reactivity, rendering the molecule inert to normally successful methods such as (silyl-)Wittig reaction or Tebbe reagent. Finally they resorted to thermal dehydration of tertiary carbinol **1-97**, giving a yield of 16% of cyclised compound **1-99**.

Scheme 15



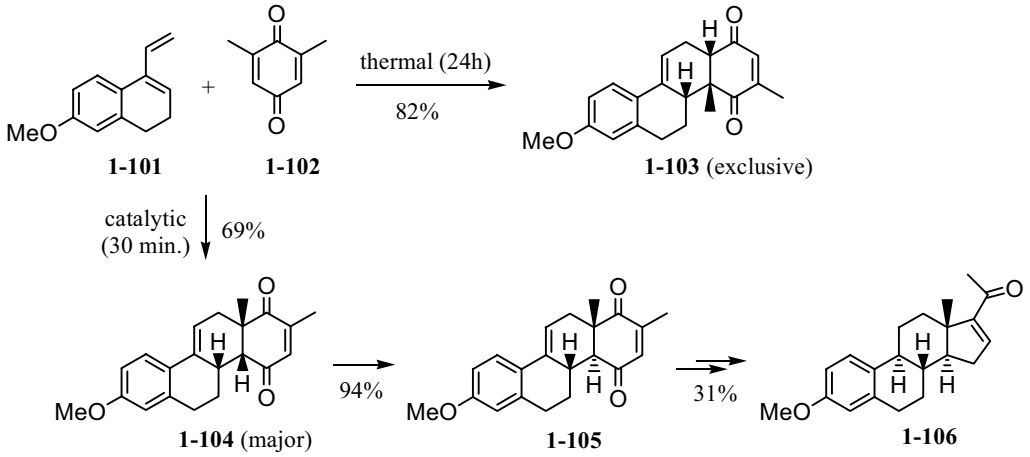
Intermolecular Diels-Alder reaction in steroid synthesis were investigated as early as 1939 but very quickly turned down because of failure[122-124]. Indeed, it appeared that the products did not only have

the unwanted configuration but had mostly also the wrong constitution, the reaction being entirely unselective[125,126].

However, when several groups tried the use of Lewis acids to catalyse the Diels-Alder reactions, those showed not only to influence the reaction rate positively but also the stereoselectivity of the addition was greatly improved. Catalysed intermolecular Diels-Alder reactions were used by Valenta and co-workers to obtain D-homo steroid skeletons (scheme 16), which, after further conversion and ring contraction, gave a precursor of estrone **1-106** in 13 steps (starting from **1-101** and **1-102**) with an overall yield of 22%[125]. This intermediate was converted to estrone in 31% yield according to a method described previously[127-129]. Similar work was done by Quinkert and co-workers, also leading to estrone[126,130].

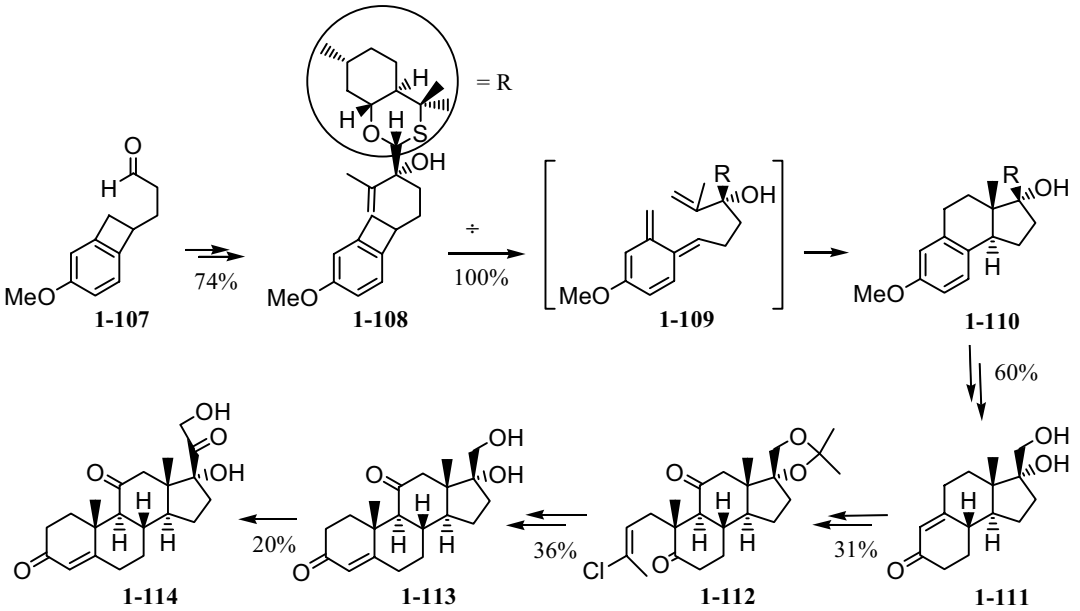
A variation on these syntheses came from Narasimhan and Bapat, who used a silyl ether substituent with intermolecular Diels-Alder chemistry to achieve regioselectivity in their synthesis of equilenin[131]. A chiral variation on this chemistry has been published by the group of Takano[132] and the regioselectivity of the reaction was investigated by Taticchi and co-workers[133].

Scheme 16



Other methods, using also Diels-Alder chemistry but intramolecular this time, were for example developed by Kametani, Nemoto and co-workers. This group used the thermolytic chemistry of benzocyclobutenes, giving orthoquinodimethanes, such as **1-109**, as intermediates[134], to synthesise estrone and estradiol[135], ring-D aromatic steroids[136,137], pregnanes[138], (+)-chenodesoxycholic acid[139], C-17 spiro steroids[140], (+)-11-deoxy-19-norcorticosterone[141,142], des-A steroids[143,144], (+)-cortisone[145]. In their synthesis of this last compound, using a chirally directing substituent, easily and in high yield available from (+)-pulegon[146], they were able to produce enantiopure steroids (scheme 17).

Scheme 17

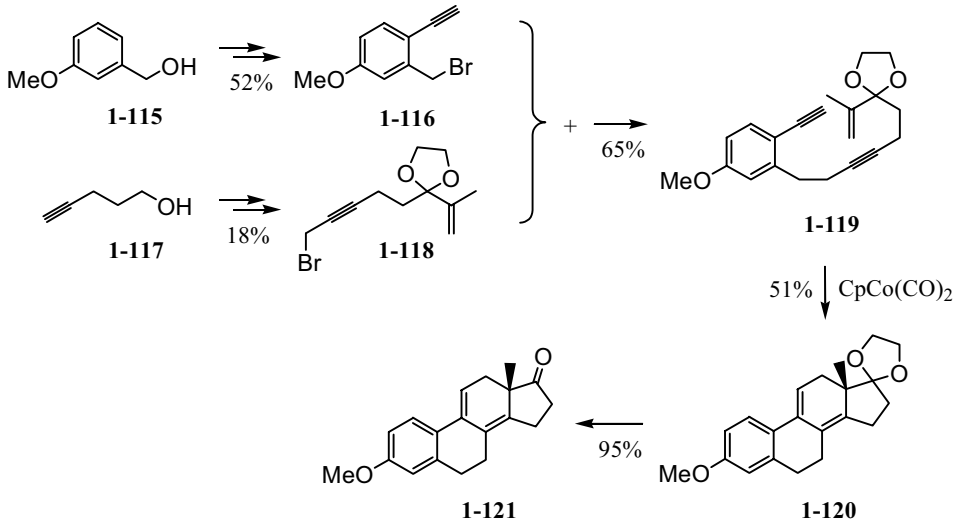


At approximately the same time as Kametani and Nemoto, Oppolzer's group developed a synthesis route using similar chemistry, again orthoquinodimethane intermediates were used but they were produced via an alternate approach[147,148]: thermal elimination of sulfurdioxide from sulfones yielded the dimethanes, after which further conversion to steroids could take place.

Over the years, a few other groups have published similar methods involving orthoquinodimethane intermediates for the synthesis of steroids [149-152].

The main drawback of the orthoquinodimethane chemistry was the fact that the stereochemical course of these reactions was highly dependent of the substituents used[153-156]. To circumvent this problem Vollhardt and co-workers explored a new route using a cobalt-catalysed cyclisation of an enediyne (scheme 18)[157-160]. The enediyne steroid precursor was prepared by coupling compounds

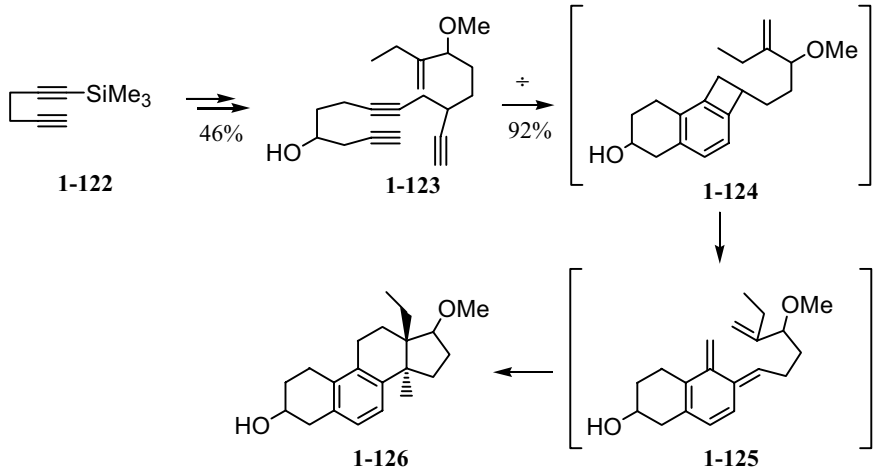
Scheme 18



1-116 and **1-118** (which were respectively prepared from **1-115** and **1-117**). Compound **1-121** is an intermediate in the Torgov synthesis of estrone and can be converted to this compound in only 2 more steps[44].

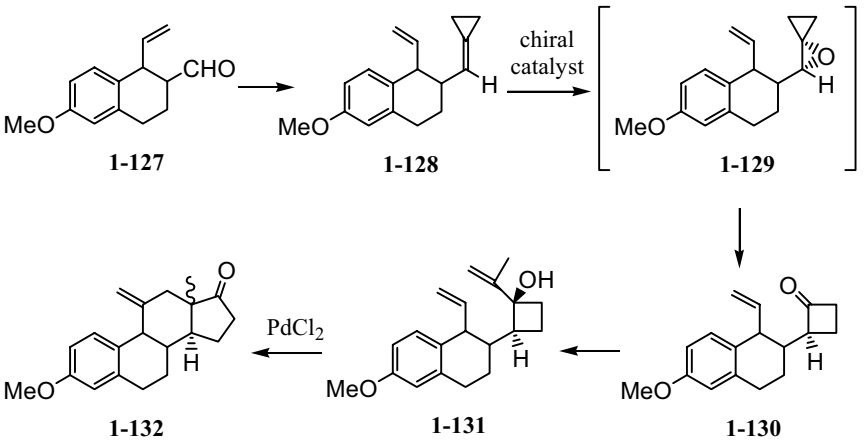
Developing this method further, they used co-oligomerisation of three acetylenic units in the presence of a cobalt carbonyl catalyst leading to B-ring aromatic steroids, again via an orthoquinodimethane intermediate (**1-124**) (scheme 19)[161]. In this reaction sequence, the four rings of the steroid skeleton were assembled in only one step with good yields and with complete control of the *trans*-stereochemistry around the C,D-ring junction.

Scheme 19



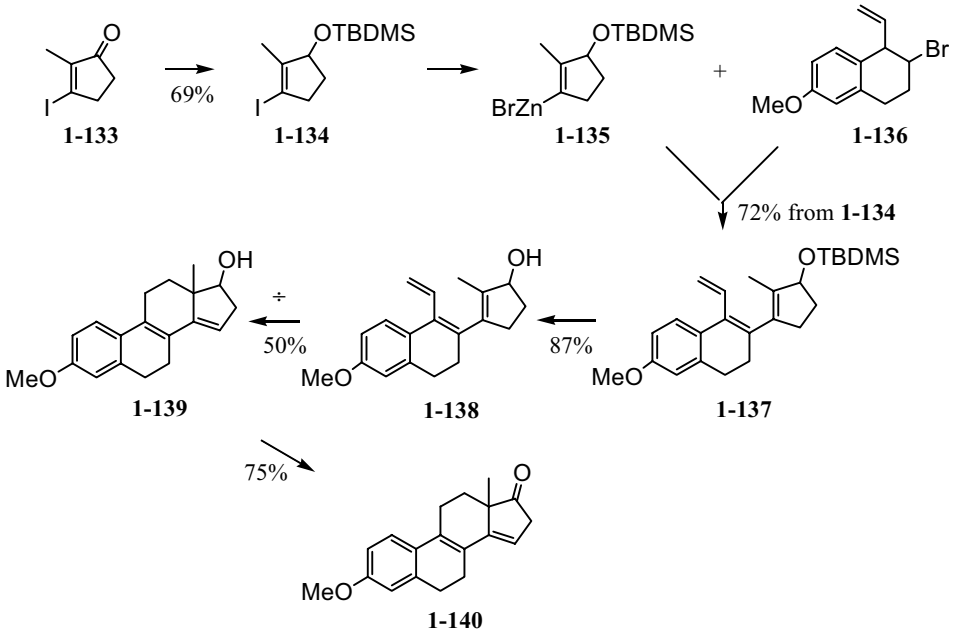
Another method published by the group of Nemoto, and also having a cyclobutane intermediate, relies on a palladium catalysed rearrangement leading to formation of rings C and D (scheme 20)[162,163]. Through separation of the obtained diastereomers and further conversion, they were able to synthesise enantiomerically pure (+)-equilenin using this method.

Scheme 20



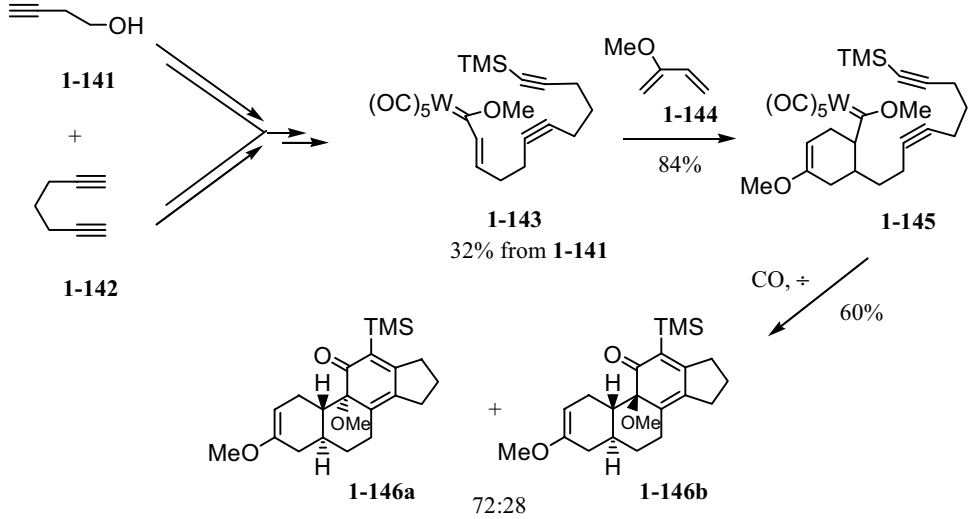
Gilchrist and co-workers described an approach making use of an electrocyclic ring-closure of trienic systems to close ring C (scheme 21)[164]. The trienes were prepared using a palladium(0) catalysed cross coupling reaction of vinyl and aryl halides. This group prepared several known steroidal compounds of the estrone family, such as compound **1-140**, using this chemistry[164-167].

Scheme 21



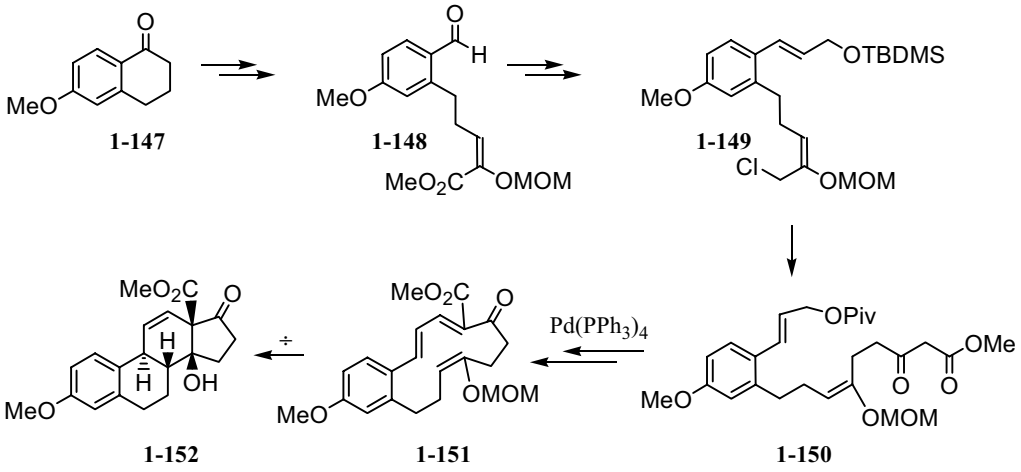
Wulff and co-workers used a tandem coupling of a Diels-Alder reaction of Fischer carbene complexes with a double intramolecular two-alkyne annelation to synthesise steroidal ring systems in which rings A and C are aromatic. From compound **1-145**, this method accessed a tetracyclic ring system in a one-pot tandem reaction sequence, but the product bears no methyl on C13 (scheme 22)[168].

Scheme 22



The group of Deslongchamps recently published a transannular Diels-Alder strategy (scheme 23)[169,170]. The sequence started from 6-methoxytetralone and led in twelve steps to macrocyclic precursor **1-150**. A palladium catalysed cyclisation then led to macrocycle **1-151** and consecutive dehydrogenation gave the macrocyclic triene. This compound was then cyclised to steroid skeleton **1-152**.

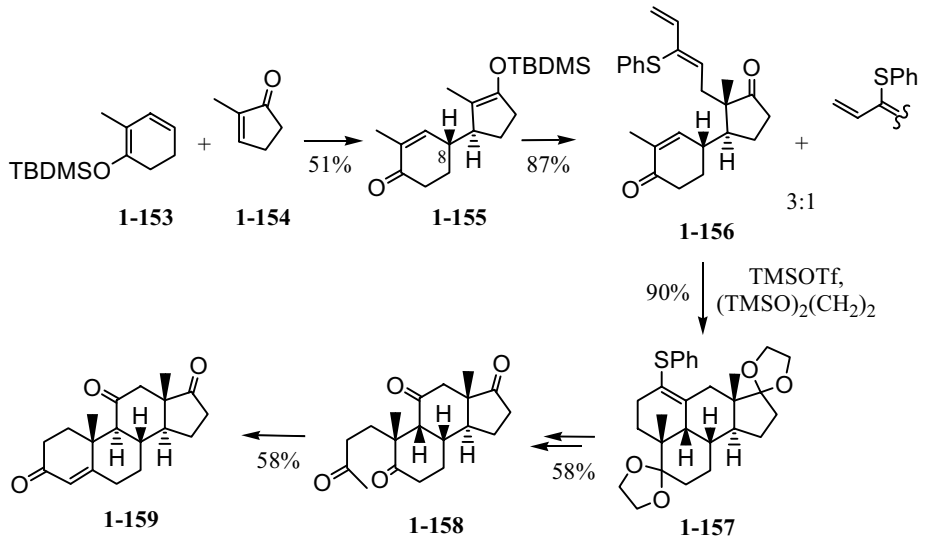
Scheme 23



An original method for steroid synthesis was published in 1998 by Grieco and coworkers[171]. This method involved a 1,4-Michael addition followed by subsequent alkylation, yielding compound **1-153** with the correct *trans* stereochemistry at C13 and C14. A tandem intramolecular Diels-Alder cycloaddition/olefin isomerisation leads to tetracyclic compound **1-157** (scheme 24). This intermediate could then be converted into adrenosterone **1-159** via replacement of the thiophenyl group by a methyl, followed by ozonolysis and ring closure under basic conditions.

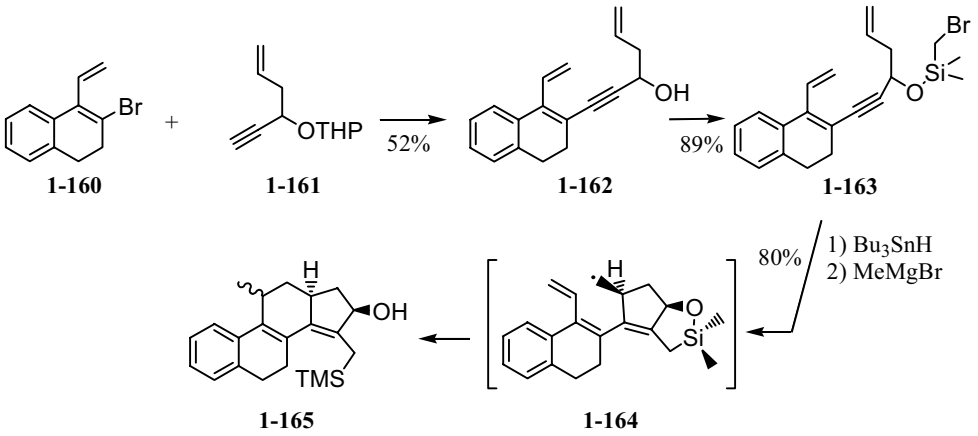
Finally, radical cyclisation was used by Malacria to synthesise a steroid skeleton in a one-pot

Scheme 24



procedure giving only two diastereomers **1-165** in 3:10 ratio, unfortunately both with the less desirable 13ζ-configuration and missing the usual methyl substituent on this position[172]. The key step of this reaction sequence consists of a tandem radical cyclisation of compound **1-167** (scheme 25), which was obtained using a palladium-catalysed coupling reaction between an alkyne and the corresponding aryl bromide.

Scheme 25



1.6 Aim of the project

The development of new, highly selective methods for the synthesis of relevant organic compounds, such as natural products and their analogues, pharmaceuticals or agrochemicals, is one of the main research areas of academic and industrial chemistry. In recent years, the importance of efficiency in the used syntheses has become ever more apparent. The relationship between structural complexity and the number of steps used to attain the desired compound is of significance, not only for economical reasons but also out of ecological considerations.

Although research on steroid total synthesis has already led, over the past century, to a vast amount of publications, the development of short, efficient and stereoselective routes to these compounds is still ongoing. Especially the development of short, versatile reaction sequences leading to polyfunctionalised steroid skeletons enabling the selective attachment of a wide variety of groups would be interesting. This could lead to the ability of making steroid compounds on custom demand.

Domino reactions are particularly suited for the development of short syntheses of complex molecules. The discovery that such a domino reaction sequence could give a rapid access to tricyclic systems in a one pot reaction, led to the initiative to investigate the usefulness of this approach for the synthesis of tetracyclic steroid skeletons as well (chapters 2 and 3).

The results obtained from this research led to the conclusion that maybe even better results could be obtained with a modified two- or three-step procedure in which the addition of an easily generated carbocation to a silyl enol ether is applied as the key reaction. We saw possibilities for the development of both and intramolecular and an intermolecular variation of this approach, leading respectively to CD-*cis* and CD-*trans* fused (D-homo) steroids (chapter 4 and 5). In addition, we saw potential for the use of the reaction of carbocations with silyl enol ethers in the development of new bisannelation procedures, which was also investigated (chapter7).

Moreover, carvone is a well known chiral starting material in enantioselective natural product synthesis and a long dating experience with the use of this compound has been established in the research group involved. Therefore the use of this compound has been incorporated in all aspects of this project, including the novel synthesis of a chiral ring D precursor starting from carvone (chapter 6). Finally, the use of cyanocarvone in steroid total synthesis has also been investigated (chapter 8).

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Domino Mukaiyama reactions to polycyclic systems

Chapter 2

2.1 Introduction

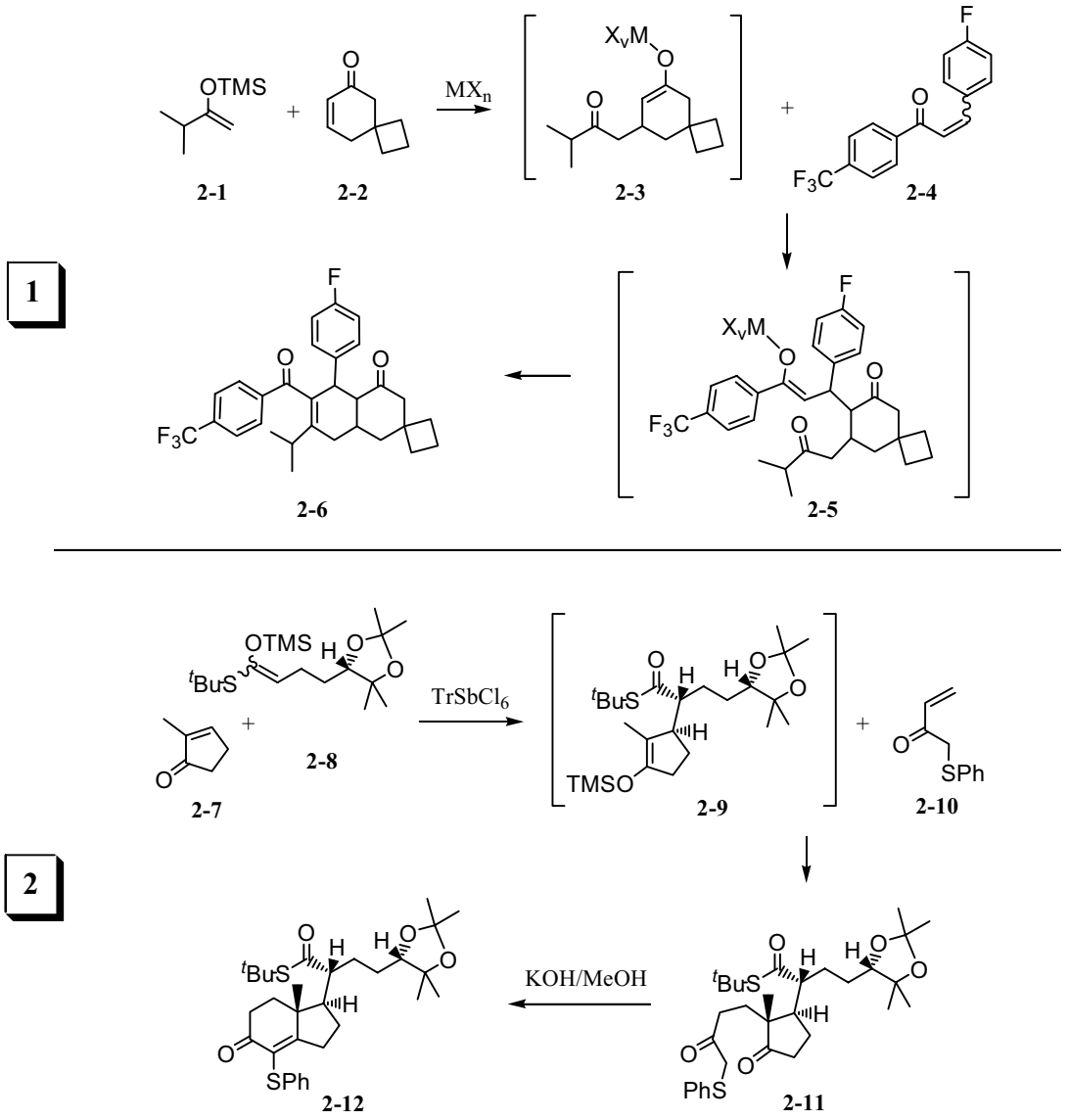
One-pot multi-component domino reactions provide a short and efficient way for the construction of highly functionalised compounds starting from structurally simple molecules. This explains the wide interest this chemistry has received over the pas few decades, as shown by the numerous reviews on the subject that have appeared since the early nineties, clearly stressing the importance of this approach[1-18]. Several reaction types using different intermediates have been applied in domino reactions and to get an overview of the chemistry a few excellent reviews can be consulted[1,11,14,15,18]. The usefulness of sequential Michael additions in domino reactions has been demonstrated for several sequences[19-33], including a double Michael addition followed by an intramolecular 1,6-aldol condensation, leading to highly substituted cyclohexanes[19,30-33].

The Lewis acid promoted Michael addition of silyl enol ethers to ζ-enones, originally devised by Mukaiyama and co-workers, is a variation on the traditional Michael addition which makes selective 1,4-addition possible under mild conditions and without side reactions such as the 1,2-addition[34,35]. The Mukaiyama-Michael addition lends itself particularly well for domino reaction sequences. Using this methodology, a highly substituted cyclohexane compound has been obtained in a domino reaction sequence using a double Mukaiyama-Michael addition, followed by an intramolecular 1,6-aldol condensation (see scheme 1, entry 1)[19]. Furthermore, making use of a chiral precursor, an enantiomerically pure *trans*-hindrane derivative was synthesised (see scheme 1, entry 2, and also chapter 6, scheme 9)[22,24].

Clearly, it is crucial for the application of this chemistry in a sequence of consecutive steps to retain the intermediate enol product so that the second Michael addition can be performed. The transfer of the silyl group from the starting silyl enol ether to the receiving enone, as is the case in entry 2 in scheme 1, is therefore a very convenient side reaction that has been noticed early on to occur in some of the Mukaiyama additions[36]. This newly formed silyl enol ether can undergo a second Mukaiyama addition, potentially with a different enone, or with other reagents like carbonyl groups, acetals, ortho esters or unsaturated (thio)esters[19-29]. Many different Lewis acids have been used as catalysts in Mukaiyama reactions (for a selection see references[35,37-49]), but relatively few have been reported to give this silyl group transfer[49-57]. Usually these are salts of highly coordinated metal ions with a large delocalised anion like Cu, Zn, Sn, Sb, Sm, Sc etc.

The exact mechanisms for the Mukaiyama reaction and the silyl group transfer are still debated. Most mechanistic investigations on Mukaiyama chemistry focus on the aldol reaction[58-67] but several have dealt with the Michael addition[68-72], and in both cases similar conclusions were drawn as to the general reaction mechanisms. The main view at present is that usually catalysis either takes place *via* coordination of the transition metal of the Lewis acid with the oxygens of the enol ether

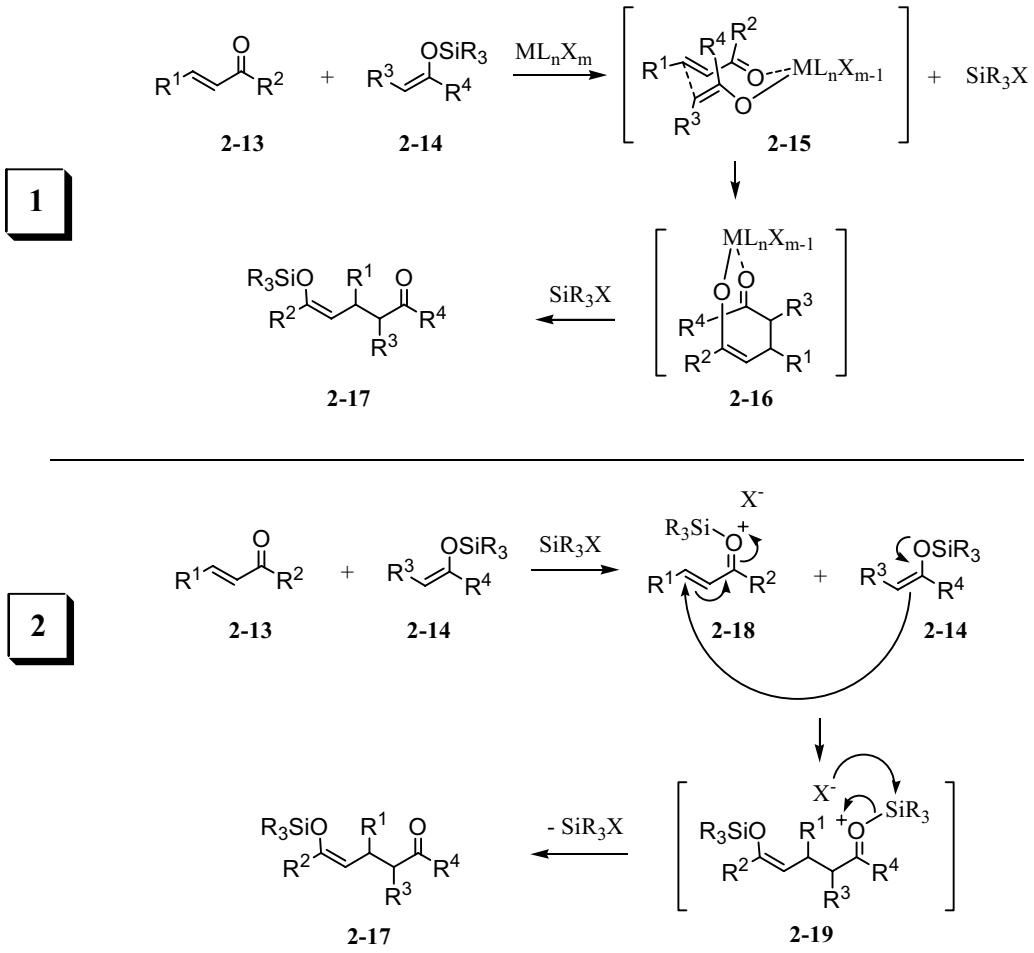
Scheme 1



and the accepting enone, also referred to as chelation, or the reaction is Si-catalysed (scheme 2, respectively entries 1 and 2). The SiR_3^+ catalyst originates from the reaction medium, either liberated from reacted material in which silyl transfer to the carbonyl oxygen atom has not taken place or through protolysis of a part of the starting silyl enol ether. Results have been published in favour of both mechanisms and they probably often occur beside one another. Which one is predominant is presumably dependent on the catalyst, solvent and reagents used, as all these determine the electronic and steric environment of the reaction[58-63,68-70,73]. When the Lewis acid is not capable of chelation because it does not possess a transition metal atom, the catalyst will only coordinate with the carbonyl of the receiving molecule (see scheme 3)[64,74]. Otera and co-workers mentioned a radical mechanism initiated by an electron transfer from the silyl enol ether to the Lewis acid as an alternative possibility[75]. However, this was restricted to ketene silyl acetals, and

specifically the less bulky ones, as already the more sterically hindered ketenes seemed to switch to a more nucleophilic mechanism as described in scheme 2.

Scheme 2

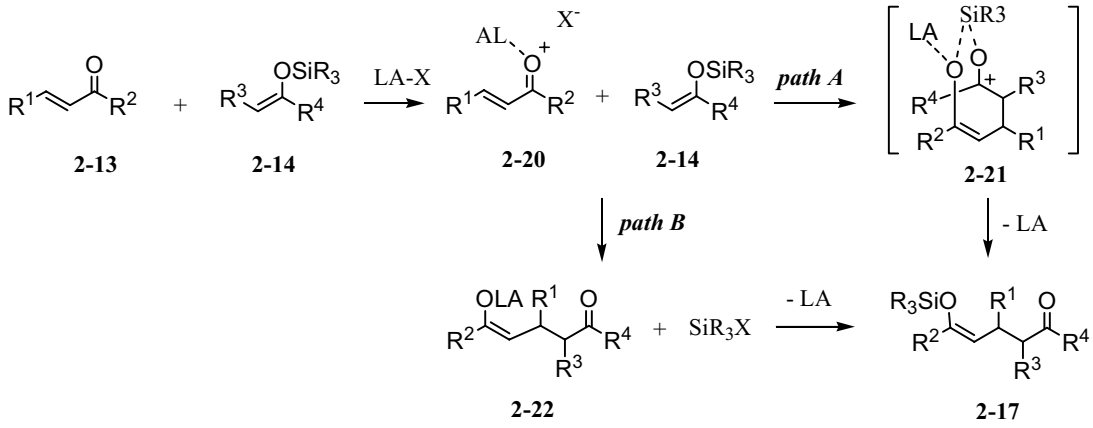


In accordance with the discussed mechanisms for the Mukaiyama addition, the silyl group transfer most often takes place *via* an intermolecular process. Indeed, in the mechanism depending on chelation of the transition metal with both starting compounds, the silyl group is simply released in the solvent and, if occurring, silyl group transfer then takes place intermolecularly by uptake of a new silyl group from the solvent[65,72]. When Si-catalysis takes place, a free SiR_3^+ species coordinates with the receiving carbonyl group and, remains in the molecule after the addition, while a new SiR_3^+ is released from the original silyl enol ether moiety (scheme 2, entry 2)[59,64,74,76].

On the other hand, when the Lewis acid coordinates only with the receiving carbonyl to activate it for addition, the silyl group transfer can take place either *via* an intramolecular[70,76] or an intermolecular[64,74] process (scheme 3, respectively paths A and B). Which of these two paths is actually followed is still unclear and contradictive results have been published[26,59,74]. Whatever the exact mechanism might be, the outcome of the reaction is the same: a selective Michael addition

with transfer of the silyl group creating a new silyl enol ether.

Scheme 3



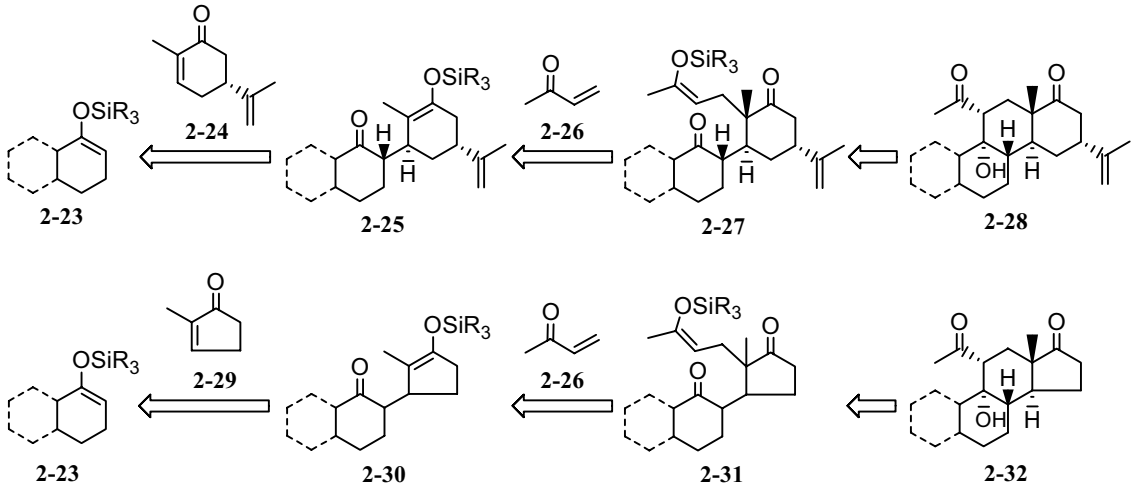
The stereoselectivity of the reaction is also dependent on the Lewis acid used. With Lewis acids capable of chelation the stereoselectivity of the reaction is controlled by its cyclic transition state[60,62-65]. This can even lead to high enantioselectivity when a chiral catalyst is used[58,62,66,67]. Without the use of a chelating catalyst, enantioselectivity in the reaction could, for example, be introduced through the use of a chiral reagens[22].

Considering everything mentioned, the enantioselective construction of highly substituted polycyclic compounds should in principle be possible using a Mukaiyama-domino reaction of three different components, which take part in two consecutive Michael additions, followed by a 1,6-aldol cyclisation. The catalyst used should be chiral, and capable of chelation, or at least one of the starting compounds used should be optically active. The best catalysts for the Mukaiyama-Michael addition of simple carbonyl derived silyl enol ethers with simple enones, giving the highest yields together with silyl group transfer and the broadest substrate tolerance, belong to the group of trityl salts. These catalysts are not composed of transition metals and a chiral starting material is therefore needed to achieve enantioselectivity in the addition reactions.

A reaction sequence starting from a cyclohexanone derived silyl enol ether in an addition with carvone as the chiral receiving enone, followed by an addition with a second enone, such as methyl vinyl ketone (MVK), was considered to be a potential successful option (see scheme 4). This should lead to an adduct that could undergo an intramolecular 1,6-aldol condensation with the carbonyl group that originates from the first silyl enol ether, and in this way result in a tricyclic compound with potential as intermediate in the synthesis of polycyclic natural products. Variations in the starting silyl enol ether would open possibilities for modification or further transformation of the tricyclic system and the exact configuration around the ringfusion points would depend on the isomer of carvone used as the starting material. Replacing carvone by a five-membered ring like 2-

methyl-2-cyclopentenone should lead to tricyclic compounds with potential as intermediates for polyfunctionalised steroid type skeletons, though the products would be racemic.

Scheme 4

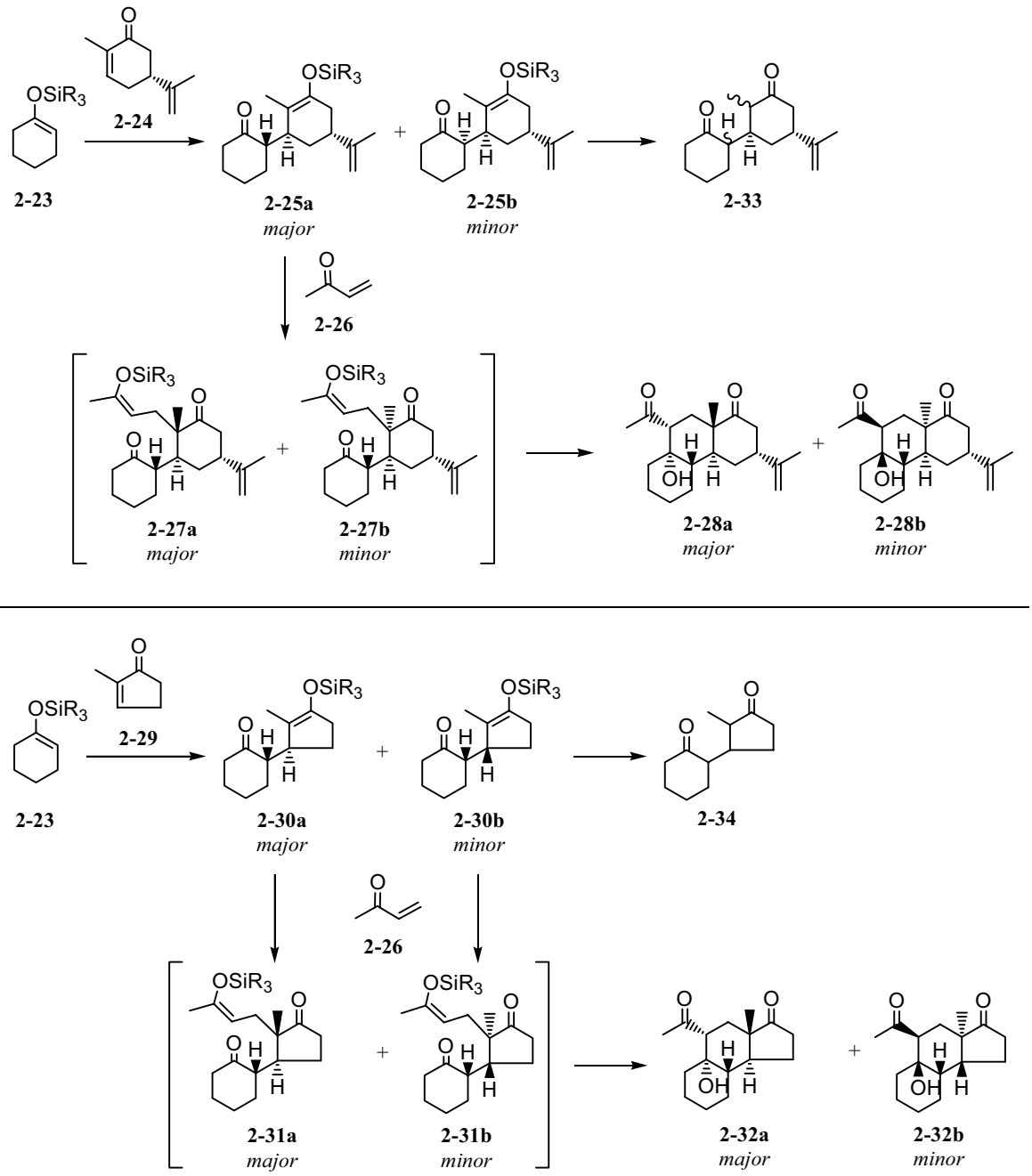


2.2 Synthesis of the tricyclic systems

The reaction sequences were first carried out with cyclohexanone as the starting silyl enol ether. 2-Methyl-2-cyclopentenone and the (*R*)-(-)-isomer of carvone were used as enones. The latter was expected to give a configuration around the ring system corresponding to the all-*trans* fusion typical for natural steroid skeletons. With the aim of finding the optimal conditions and stoichiometry of the reaction sequence, several catalysts, different addition orders, reaction temperatures and reagent ratios were tried, and three silyl enol ethers with different bulk effects (TMS, TBDMS and TES) were tested. Moreover, to get an impression on the stereoselectivity of the separate steps of the domino reaction, the reactions were initially quenched after the first Michael addition, and then reacted further. The intermediates originating from the second Michael addition (with MVK) were never isolated, nor even detected on TLC, because they apparently reacted immediately further to the cyclised products *via* the 1,6 aldol cyclisation. From both reaction sequences two isomers of the final tricyclic products were isolated, but no other isomers have been detected (see scheme 5).

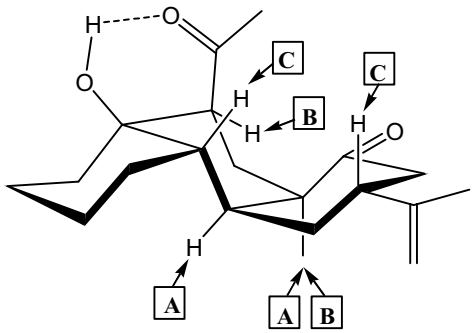
The major isomer in both reaction sequences had the all-*trans* configuration around the ring system but, while in the sequence with 2-methyl-2-cyclopentenone both intermediates **2-30a** and **2-30b** reacted further with MVK in a *trans* fashion to give respectively the final tricyclic products **2-32a** and **2-32b**, this was not the case in the sequence with carvone. Indeed, here only the major isomer of intermediate **2-25** reacted further, and this time in both a *trans* and a *cis* fashion, giving products with either *cis* or *trans* fusion (respectively **2-28b** and **2-28a**) between rings C and D in the final tricyclic products (steroid nomenclature, see chapter 1). Apparently, in intermediate **2-25a**, the steric hindrance coming from the isopropenyl tail and the cyclohexanone substituent in the carvone

Scheme 5



ring counteract each other, reducing the stereoselectivity of the addition reaction with MVK. The configurations of compounds **2-28a, 2-32a** and **2-32b** were determined by X-ray crystallography (see appendix for crystalstructures) and for compound **2-28b** this was done using COSY and NOESY experiments (for most important NOE interactions see figure 1), as this compound could not be obtained in a crystalline form. The position of the hydroxygroup was determined using IR-concentration experiments, showing an intramolecular H-bridge, between the hydroxy- and the acetylgroup. Next to the tricyclic end-products, some desilylated material (**2-33** and **2-34**) originating from the intermediate compounds was isolated in both reaction sequences.

Figure 1. NOE interaction in compound 2-28b



From literature a selection of catalysts was made to be tried in our Mukaiyama addition reaction (SmI_2, $TMSN(Tf)_2$, $BuSn(OTf)_2$, $TrClO_4$ and $TrSbCl_6$). Of these, the trityl salts gave the best results, as was already expected from literature results (see introduction). As $TrSbCl_6$ is commercially available and can be stored at +4 ^oC for a longer period of time without decomposition or loss of activity, this catalyst was chosen as the best option for our reactions. While the addition order of reagents and catalyst did not influence in any way the reaction yield or product ratios, the reaction temperature had to be kept low (-78 ^oC) to avoid desilylation of the starting silyl enol ether. Already when the temperature was increased to –60 ^oC an increase in desilylated starting material could clearly be detected on TLC. Therefore, the reaction mixtures were always carefully kept at temperatures never rising above –70 ^oC. The used ratios of starting compounds had also an important influence on the reaction yields: an excess of silyl enol ether compared to receiving enone is needed to reach high yields (see table 1). This was tested on the addition using the TMS-enol ether of cyclohexanone, and an excess of 1.5 equivalents or higher was applied in all reactions performed thereafter.

Table 1

Equivalents of TMS-enol ether used	1	1.25	1.5
Yield	50-72%	82%	89%

Different silyl enol ethers have been tested under the abovementioned conditions (1.5 eq. silyl enol ether, $TrSbCl_6$ as catalyst, at –78 ^oC) and the TBDMS-enol ether proved to give the best result in reactions with carvone as the accepting enone (see table 2). The consecutive reaction with MVK gave a slightly higher yield with the TMS-enol ether. The investigation of the TES-enol ether was quickly stopped as the yield for the first addition step with carvone was already halved, compared to the other silyl groups, and also the domino reaction sequence (see table 2 and further below) gave an extremely low yield.

Upon use of 2-methyl-2-cyclopentenone as the receiving enone, no difference in yields between the TMS and TBDMS groups was found in the first step, but for the second Michael addition best results were again obtained with the TMS-enol ether. Apparently steric hindrance from the bulky TBDMS group has a greater influence in the second addition step, even drastically lowering the yield in the case of the five-membered ring.

Table 2

Enone	Silyl group	Yield first addition	Isomeric ratio (a:b)	Y. second addition	Isomeric ratio (a:b)	Y. domino reaction
Carvone	TMS	89%	2:1	49%	5:1	45%
Carvone	TBDMS	94%	2:1	45%	1 (**2-28a**)	38%
Carvone	TES	46%	3:2	-	-	5%
Pentenone	TMS	85%	6:5		4:1	61%
Pentenone	TBDMS	83%	4:1	-	2:1	32%

When closer attention was paid to the stereoselectivity in the different steps, the enol ethers in the addition with carvone gave similar ratios of isomers but in the consecutive MVK addition step, the TBDMS-enol ether led to a much higher stereoselectivity than the TMS-enol ether. Heathcock and co-workers, who investigated stereoselectivity within Mukaiyama reactions, found that TMS compounds showed a lower stereoselectivity than their TBDMS congeners, which was attributed to the increased bulkyness of the latter[77,78]. In our case, the absence of steric hindrance in the starting enol ether gives the bulky TBDMS group the possibility to steer out of range, in this way not interfering with the approach to the enone for addition. But as soon as more substituents are present in the neighbourhood of the enol ether moiety, the TBDMS-group can not freely rotate and consequently its bulkyness interferes with the approach to the enone and influences the stereoselectivity of the reaction, corroborating the findings of Heathcock *et al*. Moreover, from the intermediate product of the first Michael addition the *anti* isomer[79] appears to react more easily than the *syn* isomer, both in the case of the TMS and the TBDMS enol ethers, as no final product having *syn* fusion around the first formed C-C bond has been isolated.

In the Mukaiyama addition with 2-methyl-2-cyclopentenone, the TBDMS-group already influences the stereoselectivity of the first Mukaiyama reaction, improving the isomeric ratio from approximately 1:1 to 4:1. However, in the second Michael addition with MVK, the increased stereoselectivity of the first TBDMS addition was annulled. In fact, the isomeric ratio is even deteriorated. A conceivable explanation could be that the *syn* isomer reacts more easily and, consequently, faster with MVK than the *anti* isomer, possibly due to the much higher steric strain in

the system, in combination with an easy desilylating side-reaction in the *anti* isomer. These factors could also explain the much lower yield of the domino reaction (see below), due to a low yielding second addition step. Interestingly, MVK addition in the cyclopentene TMS enol ether resembles the one in the carvone route, having a strong preference for the *anti* isomer of the intermediate.

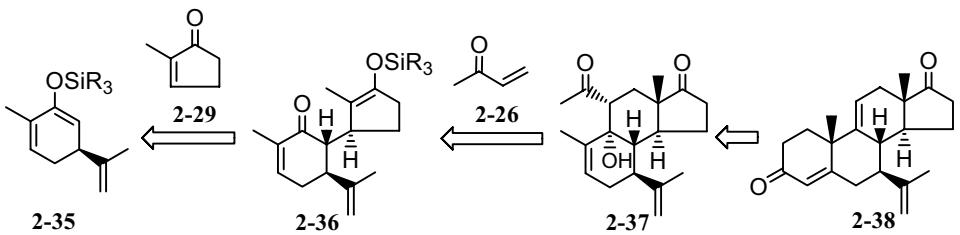
For all cases discussed above, the reaction sequences were also performed as one-pot procedures, in which the second enone (MVK) was added at low temperature to the reaction mixture after completion of the first Mukaiyama-Michael addition. Although this domino reaction procedure[80] did not usually increase the overall yield dramatically, giving typically 40-50% of the tricyclic products, it did simplify the total reaction process, taking out one isolation and purification step. As silyl enol ethers are generally labile compounds, this purification is usually fastidious and cautious work. Moreover, the overall yields coincided rather truthfully with the total yields of the separate steps. Therefore the domino reaction sequence was further on always used to perform the second addition step and usually only small amounts of the intermediate products from the first Mukaiyama addition were isolated for analytical purposes.

2.3 Investigations of steric and electronic effects on the domino reaction

As mentioned in the introduction, variation in the starting silyl enol ether would open more synthetic possibilities, for example, for the enantioselective synthesis of steroids and D-homo steroids. (D-homo) steroid skeletons should become accessible by replacement of cyclohexanone by compounds with suitable functionalities, enabling ring A attachment in a later stage (steroid nomenclature), or by a compound possessing the complete AB-ring system.

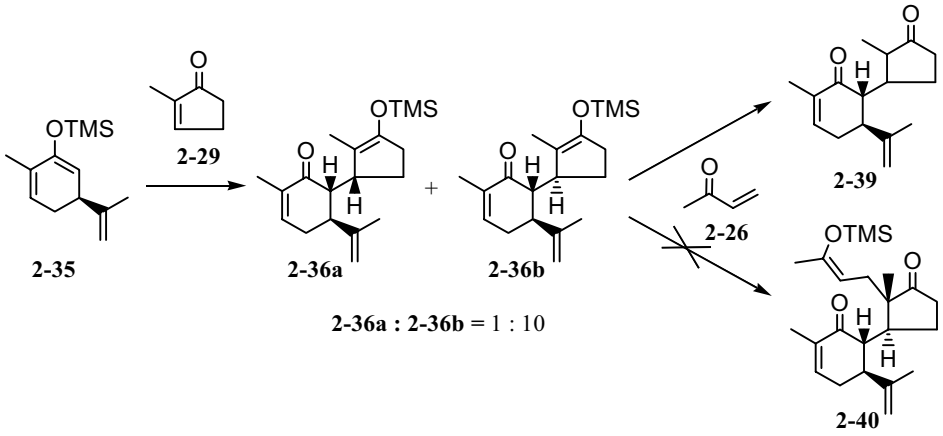
To reach this goal, we saw a possibility, eventually leading to steroid skeletons with a natural ABCD-ring system with all-*trans* fusion, in the use of (*S*)-(+)-carvone as starting silyl enol ether in an addition with 2-methyl-2-cyclopentenone as the receiving enone (see scheme 6). In this way, enantioselective synthesis of a tricyclic system with a five-membered ring in the D-position (steroid nomenclature) and possessing functionality in ring B, enabling relatively easy ring A attachment, should become accessible.

Scheme 6



When the reaction sequence was attempted using the TMS-enol ether, the first Mukaiyama addition went relatively well, giving 68% of the desired product **2-36**, as a mixture of 2 isomers in a 10:1 ratio (see scheme 7). Unfortunately, when the consecutive addition of MVK was attempted, no reaction occurred and only desilylation of **2-36** could be detected.

Scheme 7

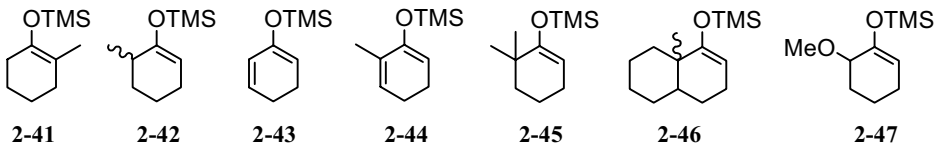


The absence of MVK addition could, in our opinion, either be caused by the increase in steric hindrance in the starting enol ether or by electronic effects due to the delocalisation of the electrons over the conjugated system present in the carvone moiety of the intermediate **2-36**. The steric hindrance could either block the MVK addition or the 1,6-aldol cyclisation. The electronic effects would probably mostly interfere with this second step. To obtain a clearer view on these effects, several different starting silyl enol ethers were investigated.

Although in the previous results, with the cyclohexanone derived silyl enol ethers, the TBDMS enol ether gave the best and most selective domino-Mukaiyama addition, this silyl group was not used here. The use of the TBDMS group was attempted but either the starting materials appeared troublesome to obtain or the first addition reaction with carvone gave limited to no results and better yields were obtained with TMS-enol ethers. Therefore, to keep the conditions used in the Mukaiyama sequences with the different starting materials as similar as possible, it was decided to use the TMS-enol ethers in all studied reactions. A selection was made of the starting materials to be used in which either a double bond conjugated with the carbonyl of the starting silyl enol ether precursor (compounds **2-43** and **2-44**) was present, or more steric hindrance, as compared to cyclohexanone, was introduced (compounds **2-41**, **2-42**, **2-44**, **2-45** and **2-46**) (figure 2). A reaction sequence with compound **2-44** would only be attempted if a reasonable result was obtained with compound **2-43** first. Compound **2-47** was selected to introduce a functionality enabling further conversion to a (D-homo) steroid skeleton *via* ring A attachment, if the Mukaiyama reaction sequence would give a positive result.

In table 3, the yields and isomeric ratios of the Mukaiyama addition between (*R*)-(-)-carvone and the different starting silyl enol ethers and, if this first reaction worked, the results of the domino reaction are rendered.

Figure 2



2-41 **2-42** **2-43** **2-44** **2-45** **2-46** **2-47**

Table 3

Starting material	Yield first addition	Isomeric ratio	Yield domino reaction	Isomeric ratio
2-41	30%	3:1	14%	One isomer
2-42	52%	8:7:1:1	24%	6:1
2-43	44%	2:1	No addition	-
2-45	~ (very slow)	-	-	-
2-46	53%	4:1	No addition	-
2-47	No addition	-	-	-

Both silyl enol ethers **2-41** and **2-42** gave tricyclic products in the domino reaction sequence, although in lower yields than in the reaction with the TMS-enol ether of cyclohexanone. For compound **2-41** two isomers were obtained in the intermediate product of which probably only one reacted further to give the final tricyclic product, in a similar fashion to compound **2-25**. With compound **2-42** four different isomers of the intermediate product were obtained after the addition with carvone, this amount was reduced to only two in the final product, with a strong preference for one of these two isomers. Although the exact configuration of the final products could not be elucidated, it can be assumed upon the results obtained in the reactions described above (paragraph 2.2) that the products with the all-*trans* fusion around the ring system predominate.

With compounds **2-45** and **2-46** no tricyclic product was detected. The first Mukaiyama-Michael addition with compound **2-45** proceeded extremely slowly and, although some product formation could be detected on GC after one day, no product was recovered upon purification of the reaction mixture. The domino reaction sequence was also attempted but, as mentioned above, did not yield any tricyclic product. Compound **2-46** gave a reasonable yield in the first addition step when the reaction temperature was increased to –40 ^{o}C, but again no tricyclic product could be detected upon

consecutive MVK addition. These results show an important influence of steric hindrance on the reaction yields.

On the other hand, the double bond present in compound **2-43** also seems to block the MVK addition. Indeed, once more, the addition with carvone did take place in a reasonable yield, but again the consecutive Mukaiyama addition to the tricyclic system was frustrated and desilylation of the intermediate was the only reaction. Although the intermediate product from the first Mukaiyama-Michael addition could be isolated, it was too unstable for good purification and no satisfying data analysis, other than GC-MS and rough ^{1}H NMR analysis, could be performed on this compound.

Finally, when reaction was attempted with compound **2-47**, already the first Michael addition gave a negative result. The methoxygroup was not expected to generate any problem in the Mukaiyama additions but apparently does interfere with the reaction. Steric hindrance in this compound is not increased as compared to compound **2-42** as the methyl ether can steer away from the reaction centre. A possible explanation could be that the catalyst complexates with the ether oxygen(s) in the silyl compound instead of the carbonyl group in carvone; in this way not being free to catalyse the addition reaction.

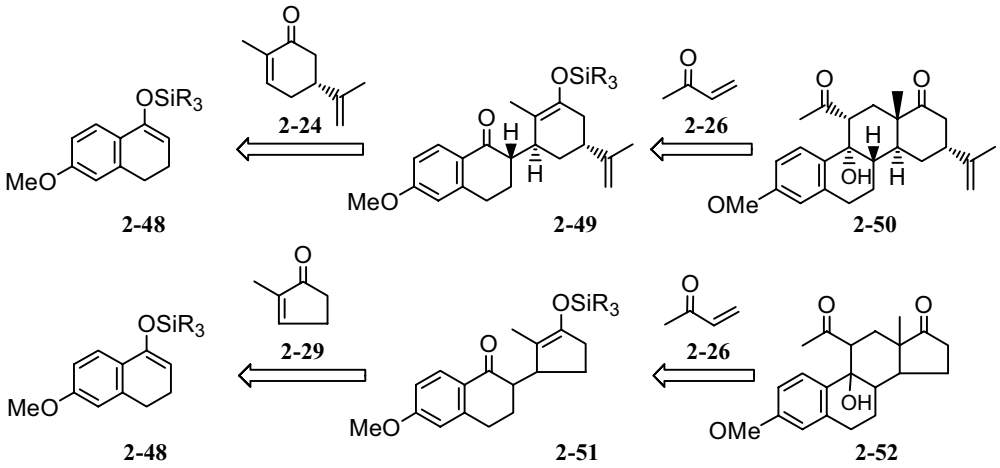
From the results above cannot clearly be concluded if the absence of MVK addition in intermediates **2-36** is due to electronic factors alone or if steric hindrance is also interfering with the addition reaction. It is very well possible that the lack of reactivity is caused by a combination of these factors. We decided however to attempt one more approach to steroid total synthesis using the Mukaiyama chemistry. 6-Methoxy-1-tetralone is a starting material belonging to the class of compounds already possessing the complete AB-ring system and, owing to its flat three dimensional structure, the aromatic ring should not cause to much steric hindrance. Using the silyl enol ether derived from this compound, a D-homo steroid skeleton should be accessible in only three steps (see scheme 8). Similarly, a racemic product with a five-membered D-ring should be accessible if 2-methyl-2-cyclopentenone is used.

2.4 Approach to steroid skeletons

6-Methoxy-1-tetralone has been extensively used in steroid total synthesis, its advantage evidently being that this compound already possesses the complete AB-ring system[81-87]. The silyl enol ether of 6-methoxy-1-tetralone has been used before to generate the corresponding enolate for a Michael reaction with cyclopentenone[82]. The resulting enolate has been reacted further with suitable electrophilic reagents, with the ultimate purpose of constructing steroid skeletons. To the best of our knowledge no Mukaiyama-Michael reaction of the silyl enol ether of methoxytetralone with methyl

cyclopentenone, accompanied by transfer of the silyl group to the carbonyl group of methyl cyclopentenone, has been reported.

Scheme 8



Preliminary results showed that such a reaction can proceed in high yield, leading to inseparable mixtures of diastereomers of the new silyl enol ether. To minimize these complications in product separation and identification, our efforts were concentrated first on carvone as acceptor in the Mukaiyama-Michael reaction. According to our results in the additions with the cyclohexanone derived silyl enol ethers, it was expected that the asymmetric centre in carvone would direct the addition to the enone from the least hindered side, opposite to the isopropenyl group and, in this way, only diastereomeric mixtures of adducts would be formed differing in configuration at C8[88]. Again, the stereoselectivity proved to be dependent on the nature of the starting silyl enol ether. When the TMS enol ether was used, a 3:2 ratio of diastereomers **2-49a** and **2-49b** was obtained in 56% yield. With the TBDMS ether, the ratio of **2-49a:2-49b** could be improved to 4:1 and the yield was quantitative. A good yield could this time also be obtained using the TES enol ether. A 7:1 ratio of diastereomers was obtained in 88% yield, and the main isomer could even be obtained pure through recrystallisation (scheme 9).

Scheme 9

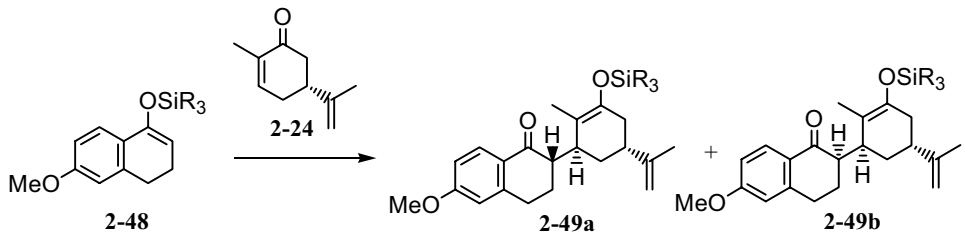
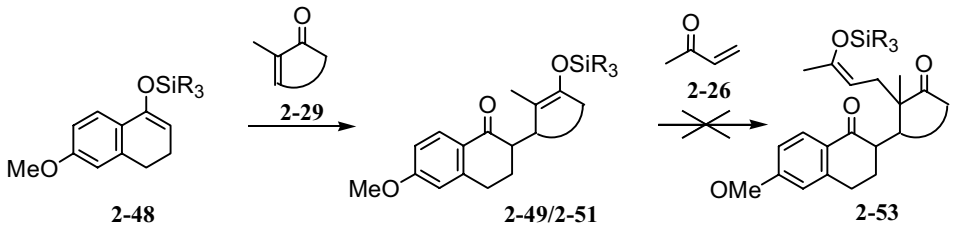


Table 3

Silyl group	Yield	Isomeric ratio 2-49a:2-49b
TMS	56%	3:2
TBDMS	Quant.	4:1
TES	88%	7:1

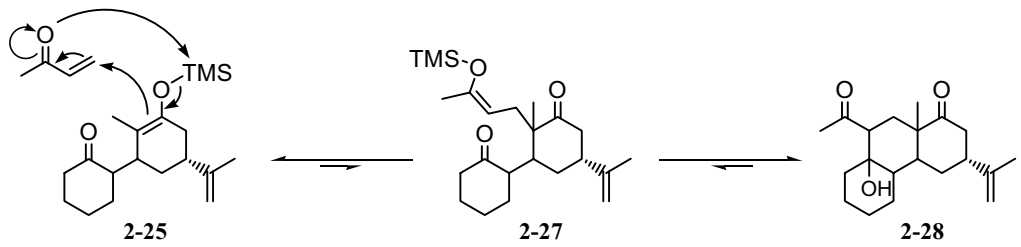
Unfortunately, when the consecutive addition of MVK was attempted, again no reaction occurred and only desilylation of **2-49** could be detected. Also when the same reaction sequence was tried with 2-methyl-2-cyclopentenone, using TMS or TBDMS enol ethers, excellent yields of the first Mukaiyama reaction were obtained (respectively 90% and quantitative) but no addition of MVK could be detected.

Scheme 10



Taking into account the results described in chapter 3, we now believe that electronic effects, and not as much steric hindrance, are causing this unreactivity towards the addition with MVK. Indeed, it appeared possible to react intermediates **2-49** and **2-51** with more reactive carbocation precursors. Therefore we believe that, when the ketone in ring B (steroid nomenclature) is conjugated with a double bond or aromatic system, the positive polarisation of the C-atom of the carbonyl group is less pronounced and hence this group is less reactive to aldol cyclisation. However, also uncyclised products like compound **2-27** were never isolated. This can be explained by the equilibrium of the MVK addition lying on the side of the intermediate originating from the first Mukaiyama addition (like **2-25**) (scheme 11).

Scheme 11



Only if ring closure takes place, the equilibrium is shifted to the MVK-added product. When ring closure does not take place, MVK will leave the molecule again after addition, explaining why almost no uncyclised product, even desilylated, could ever be isolated.

From the above, it is clear that further development of the Mukaiyama addition sequence for the synthesis of more complex polycyclic systems such as steroid skeletons is problematic. The results discussed in chapter 3 did however open new possibilities for the application of the Mukaiyama intermediates **2-49** and **2-51** in steroid total synthesis.

Experimental

General procedure. All reagents used were purchased from Aldrich or Acros, except for carvone, which was donated by Quest, and used without further purification unless otherwise stated. Carvone, however, was distilled prior to its use in the different reactions. The used solvents were freshly distilled, except for benzene, which was stored over mol sieves (4Å); dichloromethane was distilled over calcium hydride and tetrahydrofuran (THF) over sodium benzophenone ketyl. The glass equipment used was dried overnight in an oven at 150 ºC and cooled down to room temperature under nitrogen. Reactions under dry conditions were performed under a steady flow of dry nitrogen or argon.

Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ plastic sheet plates and compounds were visualized by permanganate or by molybdate solution and subsequent heating. Product solutions were dried over Na_2SO_4 or $MgSO_4$ before evaporation under reduced pressure using a rotary evaporator. Column chromatography was performed with Fluka silica gel mean pore size 60 (SiO_2, 230 – 400 mesh) with mixtures of distilled petroleum ether, boiling range 40-60 ºC (PE) and distilled ethyl acetate (EtOAc) as eluents, unless reported otherwise. ^{1}H-NMR and ^{13}C- NMR experiments were, unless otherwise stated, conducted on a Bruker AC-E 200, at 200 MHz and 50 MHz respectively, using $CDCl_3$ or C_6D_6 as solvents. Chemical shifts are reported in ppm (parts per million) (ŭ), referenced to residual $CHCl_3$ or C_6H_6 as internal standard, and coupling constants (*J*) are expressed in Hz. ^{1}H-NMR multiplicities are mentioned as singlet (s), doublet (d), triplet (t), quadruplet (q), broad singlet (bs), multiplet (m), double doublet (dd), etc. Multiplicities of the ^{13}C-NMR signals were determined using the DEPT technique and are mentioned as q (CH_3), t (CH_2), d (CH) or s (C). When two isomers were detected and specific peaks could be assigned in the spectra, the data referred to the major isomer are marked as (*M*) and those of the minor isomer as (*m*). When the isomers are equally present, both signals are mentioned together but not specified (e.g. 1.00 & 1.05 (s, 3H)). Melting points are uncorrected and determined on a C. Reichert, Vienna, hot stage apparatus, and are uncorrected. Infrared spectra

were recorded on a FT-IR Biorad FTS-7 spectrometer using tetrachloride (CCl_4) or chloroform ($CHCl_3$) as solvents when a solution was used. Usually, only the characteristic absorptions are reported. The isomeric ratio of the rough products was determined using GC-MS detection at 70 eV on a Hewlett Packard 5890B series Mass Selective Detector, coupled with a Hewlett Packard 5973 GC provided with a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 σm with helium as the carrier gas, programmed from 100-250 ^oC at a rate of 10 ^oC/min, followed by an isothermic period at 250 ^oC. Isomeric ratios of unseparable mixtures were determined using NMR when mentioned. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. The ratios *m/e* and relative intensities (%) are indicated for significant peaks. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 20 ^oC in chloroform solutions, unless mentioned otherwise, and concentrations are specified in units of g/100 ml.

General method for thermodynamic silylation

(1-cyclohexen-1-yloxy)(trimethyl)silane (2-23[TMS])[89]

To a stirred solution of cyclohexanone (2.45 gram, 25 mmol) in CH_3CN (100 ml) under nitrogen were added Et_3N (5.56 ml, 40 mmol), TMSCl (4.32 gram, 40 mmol) and NaI (6,00 gram, 40 mmol), in this order. After overnight stirring at room temperature, the reaction mixture was diluted with PE (100 ml), the layers separated and the water layer was extracted with PE (2 x 100 ml). The combined organic layers were washed with a saturated $NaHCO_3$ solution (100 ml) and brine (100 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to give **2-23[TMS]** as a colourless liquid (3.32 gram, 78%). IR (CCl_4 sol.) cm^{-1} 2933, 1668, 1549, 1252; ^1H NMR ($CDCl_3$): –0.12 (s, 9H), 1.30-1.38 (m, 2H), 1.38-1.53 (m, 2H), 1.77-1.92 (m, 4H), 4.66-4.71 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.3 (3q), 22.3 (t), 23.2 (t), 23.8 (t), 29.9 (t), 104.3 (d), 150.3 (s). HRMS: M^+, found 170.1123. $C_9H_{18}OSi$ requires 170.1127. MS *m/e* (%) 170 (M^+, 100), 169 (41), 155 (64), 142 (23), 127 (49), 75 (86), 73 (55). Data were in accordance with literature values.

***tert*-butyl(1-cyclohexen-1-yloxy)dimethylsilane (2-23[TBDMS])**[90]

Yield: 83%, as a clear oil. IR (CCl_4 sol) cm^{-1}: 2931, 2859, 1668, 1549, 1254; ^1H NMR ($CDCl_3$): 0.01 (s, 9H), 0.12 (s, 6H), 1.45-1.59 (m, 2H), 1.59-1.72 (m, 2H), 1.94-2.08 (m, 4H), 4.85-4.90 (m, 1H); ^{13}C NMR ($CDCl_3$): -4.4 (q), -2.9 (q), 18.0 (s), 22.4 (t), 23.2 (t), 23.8 (t), 25.7 (3q), 29.9 (t), 104.3 (d), 150.5 (s). HRMS: M^+, found 212.1598. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%): 212 (M^+, 22), 75 (80), 73 (19). Data were in accordance with literature values.

(1-cyclohexen-1-yloxy)(triethyl)silane (2-23[TES])[91]

Yield: quantitative, as a colourless oil. IR (CCl_4 sol) cm^{-1}: 2956, 2877, 1667, 1550; ^1H NMR ($CDCl_3$): 0.60 (s, 9H), 0.60-0.88 (m, 6H), 1.50-1.58 (m, 2H), 1.58-1.71 (m, 2H), 1.96-2.00 (m, 4H), 4.84-4.87 (m, 1H); ^{13}C NMR ($CDCl_3$): 5.0 (q), 5.8 (t), 6.4 (t), 6.5 (q), 6.8 (q), 23.8 (t), 23.9 (t), 29.8 (t), 41.5 (t), 41.9 (t), 103.9 (d), 150.4 (s). HRMS: M^+, found 212.1598. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%): 212 (M^+, 23), 169 (18), 156 (12), 155 (17), 103 (47), 75 (43). Data were in accordance with literature values.

[(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](trimethyl)silane (2-48[TMS])[92]

Yield: 92%. IR (CCl_4 sol.) $cm^{-}1$: 2958, 2835, 1683, 1639, 1607, 1252; ^1H NMR ι: 0.31 (s, 9H), 2.24-2.35 (m, 2H), 2.79 (t, *J* = 7.8, 2H), 3.83 (s, 3H), 5.12 (t, *J* = 4.6, 1H), 6.74 (s, 1H), 6.76 (d, *J* = 8.6, 1H), 7.41 (d, *J* = 8.2, 1H); ^{13}C NMR ι: 0.2 (3q), 22.2 (t), 28.7 (t), 55.1 (q), 102.9 (d), 110.7 (d), 113.2 (d), 123.1 (d), 126.6 (s), 138.9 (s), 147.9 (s), 158.9 (s). HRMS: M^+, found 248.1229. $C_{14}H_{20}O_2Si$ requires 248.1233. MS *m/e* (%) 248 (M^+, 100), 247 (64), 233 (30), 217 (13), 73 (21). Data were in accordance with literature values.

[(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](dimethyl-*tert*-butyl)silane (2-48[TBDMS])

Yield: quantitative.^1H NMR ι:0.21 (s, 6H), 1.02 (s, 9H), 2.30 (m, 2H), 2.74 (t, *J* = 7.8, 2H), 3.80 (s, 3H), 5.06 (t, *J* = 4.6, 1H), 6.72 (m, 2H), 7.40 (d, *J* = 8.2, 1H). ^{13}C NMR ι: - 4.4 (2q), 18.4 (s), 22.3 (t), 25.9 (3q), 28.7 (t), 55.2 (q), 102.6 (d), 110.7 (d), 113.2 (d), 123.2 (d), 126.8 (s), 139.0 (s), 148.2 (s), 158.9 (s). HRMS: M^+, found 290.1704. $C_{17}H_{26}O_2Si$ requires 290.1702. MS *m/e* (%) 290 (M^+, 54), 275 (5), 234 (28), 233 (100), 203 (38), 73 (8).

[(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](triethyl)silane (2-48[TES])

Yield: 83%. IR (CCl_4) cm^{-1}: 2956, 2877, 1682, 1600, 1271; ^1H NMR ι: 0.78 (q, *J* = 7.6, 6H), 1.06 (t, *J* = 7.6, 9H), 2.30-2.38 (m, 2H), 2.73-2.81 (t, *J* = 7.8, 2H), 3.81 (s, 3H), 5.11 (t, *J* = 4.2, 1H), 6.72-6.77 (m, 2H), 7.45 (d, *J* = 8.2, 1H). ^{13}C NMR ι: 5.1 (3t), 6.8 (3q), 22.3 (t), 28.7 (t), 55.1 (q), 102.2 (d), 110.7 (d), 113.2 (d), 123.1 (d), 126.8 (s), 138.9 (s), 148.2 (s), 158.9 (s). HRMS: M^+, found 290.1707. $C_{17}H_{26}O_2Si$ requires 290.1702. MS *m/e* (%) 290 (M^+, 100), 261 (81), 233 (9), 232 (9), 231 (38), 159 (8).

[(2-methyl-cyclohex-1-enyl)oxy](trimethyl)silane (2-41)[93]

Yield: 90%. ^1H NMR ($CDCl_3$) 0.15 (s, 9H), 1.50 (s, 3H), 1.43-1.72 (m, 4H), 1.85-2.09 (m, 4H). Data are in accordance with literature values.

[(6,6-dimethyl-1-cyclohexen-1-yl)oxy](trimethyl)silane (2-45)[94]

Yield: 64%. IR(CCl_4 sol) cm^{-1}: 2931, 1655, 1252; ^1H NMR ($CDCl_3$) 0.17 (s, 9H), 1.00 (s, 6H), 1.44-1.68 (m, 4H), 1.94-2.02 (m, 2H), 4.66 (t, J = 3.92, 1H); ^{13}C NMR ($CDCl_3$) 0.4 (3q), 19.6 (t), 24.8 (t), 27.1 (2q), 34.9 (s), 39.0 (t), 101.5 (d), 156.9 (s). HRMS: M^+, found 198.1437. $C_{11}H_{22}OSi$ requires 198.1440. MS *m/e* (%): 198 (M^+, 48), 183 (100), 142 (52), 82 (19), 75 (61), 73 (75). Data were in accordance with literature values.

[(8a-methyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl)oxy](trimethyl)silane (2-46)

Yield: 90% (2 isomers 3:1). ^1H NMR ($CDCl_3$) 0.17 (s, 9H), 0.96 (*m*) & 1.00 (*M*) (s, 3H), 1.05-2.20 (m, 13H), 4.66 (m, 1H).

General method used for kinetic silylation

{[(3*S*)-3-Isopropenyl-6-methyl-cyclohexa-1,5-dienyl]oxy}(trimethyl)silane (2-35[TMS])[95]

A solution of diisopropylamine (2.25 ml, 16 mmol) in THF (20 ml) was cooled to –10 ^oC, and butyllithium (1.45 M in THF, 10 ml) was added in one portion. The solution was allowed to warm to 0 ^oC and stirred for 30 min, after which the solution was cooled to –78 ^oC and a solution of (*S*)-(+)-carvone (2.0 g, 13.2 mmol) in THF (20ml) was added dropwise. The solution was kept at –78 ^oC and stirred for 20 min, followed by dropwise addition of TMSCl (2.0 ml, 16 mmol). The solution was allowed to warm to room temperature over a period of 1 hr and poured in a cold solution of brine and $NaHCO_3$ (10%). The water-layer was extracted with PE, and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by bulb-to-bulb distillation yielding 2.76 g of **2-35** (94%). IR (CCl_4 sol) cm^{-1} 2963, 1660, 1605, 1550, 1451, 1375, 1253, 1214. ^1H NMR ($CDCl_3$) 0.18 (s, 9H), 1.67 (s, 3H), 1.71 (s, 3H), 2.11 (m, 2H), 2.99 (m, 1H), 4.69 (m, 1H), 4.76 (m, 2H), 5.54 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.1 (3q), 17.3 (q), 20.5 (q), 28.6 (t), 41.8 (d), 105.7 (d), 109.9 (t), 123.0 (d), 131.8 (s), 148.4 (s), 149.8 (s). HRMS: M^+, found 222.1439. $C_{13}H_{22}OSi$ requires 222.1440. MS *m/e* (%) 222 (100, M^+), 207 (83), 181 (65), 165(62), 91 (24), 82 (17), 75 (21), 73 (79), 45 (16). Data were in accordance with literature values.

[(6-methyl-cyclohex-1-enyl)oxy](trimethyl)silane (2-42)[89]

Yield: 96%. IR (CCl_4 sol) cm^{-1}: 2933, 1715, 1660, 1252; ^1H NMR ($CDCl_3$) 0.17 (s, 9H), 1.00 (d, J = 6.82, 3H), 1.21-1.88 (m, 4H), 1.93-2.21 (m, 3H), 4.79 (t, J = 3.90, 1H); ^{13}C NMR ($CDCl_3$) –0.5 (q), 0.4 (q), 0.7 (q), 0.9 (q), 20.3 (t), 24.4 (t), 31.6 (t), 33.6 (d), 103.5 (d), 154.2 (s). HRMS: M^+, found 184.1286. $C_{10}H_{20}OSi$ requires 184.1283. MS *m/e* (%): 184 (M^+, 100), 169 (87), 142 (42), 112 (33), 75 (75), 73 (82), 68 (52). Data were in accordance with literature values.

(1,5-cyclohexadien-1-yloxy)(trimethyl)silane (2-43)[96]

At room temperature, TMSTf (5.96 ml, 33 mmol) was added to a stirred solution of 2-cyclohexenone (2.88 gram, 30 mmol) and Et_3N (6.26 ml, 45 mmol) in dichloromethane (20 ml) under nitrogen. After 15 min the reaction mixture was diluted with ether and the organic layer was washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to give **2-43** as a colourless oil (4.36 gram, 87%). IR (CCl_4 sol) cm^{-1}: 2961, 1649, 1251; ^1H NMR ($CDCl_3$) 0.22(s, 9H), 2.06-2.21 (m, 4H), 4.87 (d, J = 2.51, 1H), 5.63-5.70 (m, 1H), 5.83-5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) 0.0 (3q), 21.6 (t), 22.4 (t), 102.2 (d), 126.2 (d), 128.7 (d), 147.9 (s). HRMS: M^+, found 168.0972. $C_9H_{16}OSi$ requires 168.0970. MS *m/e* (%): 168 (M^+, 100), 167 (20), 153 (24), 151 (37), 75 (42), 73 (92), 45 (10). Data were in accordance with literature values.

[(6-methoxy-1-cyclohexen-1-yl)oxy](trimethyl)silane (2-47)[97,98]

At room temperature, a small crystal of iodide was added to stirred suspension of magnesium (0.66 gram, 27.5 mmol) in THF (10 ml) under nitrogen. 2-Chloro-2-methylpropane (4.4 ml, 41 mmol) in THF (10 ml) was added dropwise over a period of 15 min. When the reaction mixture started to boil, the flask was cooled on ice and addition was slowly continued. After stirring at room temperature for 1 hr, the reaction mixture was cooled to 0 ºC and diisopropylamine (4.21 ml, 30 mmol) in THF (10 ml) was added dropwise over a period of 30 min. After stirring for another 30 min, 2-methoxycyclohexanone (2.51 ml, 20 mmol) in THF (10 ml) was added dropwise within 10 min. The mixture was stirred for 45 min at 0 ºC. Then, TMSCl (5.05 ml, 40 mmol) in THF (10 ml) was added over a period of 15 min. After 30 min of stirring, the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 36 hrs at room temperature and then carefully diluted with a saturated NH_4Cl solution (50 ml). Ether (50 ml) was added and the layers were separated. The water layer was extracted with ether (2 x 50 ml). The combined organic layers were washed with brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to give **2-47** as a colourless oil (2.28 gram, 57%). IR (CCl_4 sol) cm^{-1}: 2942, 1664, 1549, 1201; ^1H NMR ($CDCl_3$) 0.16 (s, 9H), 1.44-1.63 (m, 3H), 1.83-2.03 (m, 3H), 3.37 (s, 3H), 3.48 (t, J = 2.73, 1H), 4.94 (t, J = 3.57, 1H); ^{13}C NMR ($CDCl_3$) 0.4 (3q), 17.8 (t), 23.9 (t), 28.1 (t), 57.5 (q), 76.5 (d), 107.7 (d), 149.8 (s). HRMS: M^+, found 200.1232. $C_{10}H_{20}O_2Si$ requires 200.1233. MS *m/e* (%): 200 (M^+, 34), 185 (32), 142 (12), 89 (68), 73 (100). Data were in accordance with literature values.

General method for Mukaiyama-Michael addition with (*R*)-(-)carvone

2-{(5*R*)-5-isopropenyl-2-methyl-3[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}cyclohexanone (2-25[TMS])

(*R*)-(-)-carvone (150 mg, 1 mmol) and **2-23[TMS]** (255 mg, 1,50 mmol) were dissolved in dichloromethane (6 ml) and stirred under nitrogen. The reaction mixture was cooled to –78 ºC. Trityl hexachloroantimonate ($TrSbCl_6$) (29 mg, 0.05 mmol) was added and the reaction was followed by TLC. When all the carvone had reacted (1 hr), the catalyst was quenched by adding a few drops of pyridine, until the yellow colour disappeared. The reaction mixture was allowed to warm to room temperature and diluted with dichloromethane. The mixture was washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a short SiO_2 column (PE:EtOAc:pyridine 98:1:1) to give **2-25[TMS]** (286 mg, 89%) as a colourless oil, composed of two isomers which could not be separated, in a ratio of 2:1 (GC). IR (film) cm^{-1}: 2936, 1709, 1644, 1251; ^1H NMR ($CDCl_3$): 0.15 (s, 9H), 1.53 (s, 3H), 1.52-1.69 (m, 5H), 1.69 (s, 3H), 1.91-2.07 (m, 4H), 2.20-2.40 (m, 4H), 2.91 (m, 1H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$): 0.8 (3q), 17.5 (q), 20.5 (q), 25.4 (*M*) & 27.1 (*m*) (t), 27.9 (*M*) & 28.6 (*m*) (t), 29.2 (*m*) & 32.6 (*M*) (t), 33.7 (t), 35.1 (t), 35.7 (d), 37.8 (*M*) & 39.2 (*m*) (d), 42.4 (t), 52.9 (*m*) & 56.3 (*M*) (d), 109.0 (t), 112.9 (s), 144.9 (s), 148.7 (*m*) & 148.9 (*M*) (s), 212.4 (s). HRMS: M^+, found 320.2173. $C_{19}H_{32}O_2Si$ requires 320.2172. MS *m/e* (%): 320 (M^+, 100), 181 (12), 75 (5), 73 (33).

2-{(5*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-5-isopropenyl-2-methyl-2-cyclohexen-1-yl}cyclohexanone (2-25[TBDMS])

Yield: 94%, as a colourless oil (2 isomers, 2:1). IR (film) cm^{-1}: 2932, 1710, 1678, 1449, 1254; ^1H NMR ($CDCl_3$): 0.11 (s, 6H), 0.88 (*m*) & 0.94 (*M*) (s, 9H), 1.52-1.72 (m, 5H), 1.51 (*m*) & 1.54 (*M*) (s, 3H), 1.69 (*M*) & 1.70 (*m*) (s, 3H), 1.85-2.11 (m, 5H), 2.12-2.50 (m, 4H), 2.86 (m, 1H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$): –3.7 (2q), 14.4 (*m*) & 17.9 (*M*) (q), 18.2 (s), 20.5 (*M*) & 20.7 (*m*) (q), 25.4 (t), 25.9 (3q), 27.2 (*m*) & 28.0 (*M*) (t), 28.7 (*M*) & 29.3 (*m*) (t), 32.7 (*m*) & 33.6 (*M*) (t), 35.1 (*m*) & 35.3 (*M*) (t), 35.8 (*m*) & 36.1 (*M*) (d), 37.8 (*M*) & 39.3 (*m*) (d), 42.2 (*m*) & 42.4 (*M*) (t), 52.9 (*m*) & 56.4 (*M*) (d), 109.0 (t), 111.4 (*m*) & 112.6 (*M*) (s), 145.0 (s), 148.7 (*m*) & 148.9 (*M*) (s), 212.6 (*M*) & 212.8 (*m*) (s). HRMS: M^+, found 362.2652. $C_{22}H_{38}O_2Si$ requires 362.2641. MS *m/e* (%): 362 (M^+, 9), 305 (2), 155 (10), 75 (12), 73 (31).

2-{(5*R*)-5-isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}cyclohexanone (2-25[TES])

Yield: 46%, as a colourless oil (2 isomers, 3:2). IR (film) cm^{-1}: 2936, 1710, 1449, 1238; ^1H NMR (C_6D_6): 0.64 (q, *J* = 7.9, 6H), 0.97 (t, *J* = 7.9, 9H), 1.53 (*m*) & 1.56 (*M*) (s, 3H), 1.70 (s, 3H), 1.45-1.71 (m, 5H), 1.88-2.12 (m, 4H), 2.26-2.45 (m, 4H), 2.89 (m, 1H), 4.70 (s, 2H); ^{13}C NMR (C_6D_6) 5.9 (3t), 6.9 (3q), 14.9 (*m*) & 17.6 (*M*) (q), 20.4 (*M*) & 20.7 (*m*) (q), 25.2 (t), 26.9 (*m*) & 27.6 (*M*) (t), 28.6 (*m*) & 32.4 (*M*) (t), 29.2 (*m*) & 33.7 (*M*) (t), 35.2 (*m*) & 35.5 (*M*) (t), 35.6 (*m*) & 36.1 (*M*) (d), 38.1 (*M*) & 39.5 (*m*) (d), 41.9 (t), 53.5 (*m*) & 56.1 (*M*) (d), 109.2 (t), 113.1 (s), 145.9 (s), 149.2 (*m*) & 149.6 (*M*) (s), 210.6 (*M*), 210.7 (*m*) (s). HRMS: M^+, found 362.2648. $C_{22}H_{38}O_2Si$ requires 362.2641. MS *m/e* (%): 362 (M^+, 26), 333 (9), 239 (12), 115 (13), 87 (24), 59 (11).

Desilylated intermediate 2-25: (5*R*)-5'-Isopropenyl-2'-methyl-bicyclohexyl-2,3'-dione (2-33)

Major isomer. ^1H NMR ι: 0.75-0.90 (m, 1H), 1.02 (d, *J* = 7.2, 3H), 1.10-2.15 (m, 9H), 1.77 (s, 3H), 2.15-2.72 (m, 6H), 4.69 (s, 1H), 4.85 (s, 1H); ^{13}C NMR ι: 13.2 (q), 21.6 (q), 25.3 (t), 27.4 (t), 27.6 (t), 28.1 (t), 37.3 (d), 40.9 (d), 42.5 (t), 44.2 (t), 47.2 (d), 51.1 (d), 111.7 (t), 146.9 (s), 211.5 (s), 213.5 (s).

Minor isomer. ^1H NMR ι: 0.97 (d, *J* = 6.8, 3H), 1.63 (s, 3H), 1.00-2.82 (m, 16H), 4.62 (s, 1H), 4.75 (s, 1H); ^{13}C NMR ι: 13.9 (q), 21.6 (q), 25.0 (t), 27.7 (t), 28.1 (t), 31.7 (t), 40.3 (d), 40.5 (d), 42.7 (t), 43.7 (t), 46.6 (d), 51.1 (d), 111.7 (t), 146.7 (s), 212.2 (s), 213.5 (s).

2-{(1*S*,5*R*)-5-isopropenyl-2-methyl-3-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (2-49[TMS])

Yield: 56%, as a mixture of 2 isomers (3:2), white crystals (mp 55-56^{0}C from pentane). IR (CCl_4) cm^{-1}: 2939, 1680, 1602, 1252; ^1H NMR ι: 0.15 & 0.19 (s, 9H), 1.39 & 1.58 (s, 3H), 1.68 & 1.73 (s, 3H), 1.45-2.65 (m, 6H), 2.75 (dt, J_1 = 13.0 & J_2 = 3.7, 1H), 2.92 (m, 2H), 3.23 & 3.35 (br s, 1H), 3.83 (s, 3H), 4.73 (m, 2H), 6.67 (br s, 1H), 6.80 (dd, J_1 = 8.7 & J_2 = 2.5, 1H), 8.02 (d, *J* = 8.7, 1H); ^{13}C NMR (*isomer 1*) ι: 1.3 (3q), 11.9 (q), 21.4 (q), 25.5 (t), 27.2 (t), 28.1 (t), 34.4 (d), 40.6 (d), 42.2 (t), 46.6 (d), 55.4 (q), 77.0 (s), 111.7 (t), 112.3 (d), 113.4 (d), 125.9 (s), 129.9 (d), 145.6 (s), 146.7 (s), 163.5 (s), 198.9 (s), 213.8 (s); (*isomer 2*) 1.9 (3q), 12.2 (q), 21.1 (q), 26.8 (t), 29.1 (t), 29.5 (t), 36.5 (d), 42.4 (d), 44.1 (t), 47.9 (d), 55.4 (q), 77.7 (s), 111.0 (t), 112.3 (d), 113.2 (d), 125.2 (s), 130.0 (d), 145.8 (s), 147.0 (s), 163.5 (s), 198.8 (s), 213.8 (s). HRMS: M^+, found 398.2275. $C_{24}H_{34}O_3Si$ requires 398.2277. MS *m/e* (%) 398 (M^+, 12), 329 (3), 248 (31), 223 (100), 222 (49), 176 (21), 73 (33).

2-{(1*S*,5*R*)-5-isopropenyl-2-methyl-3-[(dimethyl-*tert*-butylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (2-49[TBDMS])

Yield: quantitative, as a mixture of 2 isomers (4:1, NMR determination), white crystals (mp 72-73°C from pentane). IR (CCl_4 sol.) cm^{-1}: 2931, 1678, 1602, 1253; ^1H NMR ι: 0.11 (*m*) & 0.14 (*M*) (s, 6H), 0.92 (*m*) & 0.94 (*M*) (s, 9H), 1.42 (*m*) & 1.60 (*M*) (s, 3H), 1.68 (*M*) & 1.72 (*m*) (s, 3H), 1.50 – 2.40 (m, 7 H), 2.74 (dt, J_1= 13.0 & J_2= 3.8, 1 H), 2.90 (m, 2 H), 3.22 (*M*) & 3.32 (*m*) (br s, 1 H), 3.82 (s, 3 H), 4.70 (m, 2 H), 6.66 (d, *J*= 2.2, 1 H), 6.77 (dd, J_1= 8.7 & J_2= 2.2, 1 H), 7.99 (*m*) & 8.00 (*M*) (d, *J*= 8.8, 1 H). ^{13}C NMR ι: *Main isomer*: -3.661 (2q), 14.254 (q), 18.247 (s), 20.797 (q), 25.438 (t), 25.932 (3q), 29.334 (t), 30.509 (t), 35.221 (t), 36.560 (d), 39.404 (d), 50.555 (d), 55.371 (q), 109. 154 (t), 111.204 (s), 112.446 (d), 112.989 (d), 126.970 (s), 129.845 (d), 145.283 (s), 146.557 (s), 148.502 (s), 163.333 (s), 198.514 (s). *Minor isomer*: -3.736 (2q), 16.535 (q), 20.983 (q), 22.642 (s), 25.781 (3q), 27.288 (t), 28.828 (t), 29.987 (t), 34.857 (t), 36.340 (d), 38.567 (d), 53.603 (d), 55.237 (q), 109.998 (t), 110.634 (s), 112.276 (d), 113.086 (d), 126.408 (s), 130.130 (d), 144.852 (s), 146.113 (s), 148.684 (s), 158.559 (s), 198.030 (s). HRMS: M^+, found 440.2746. $C_{27}H_{40}O_3Si$ requires 440.2747. MS *m/e* (%) 440 (M^+, 8), 383 (2), 266 (22), 265 (100), 264 (31), 233 (6), 176 (7), 73 (28).

2-{(1*S*,5*R*)-5-isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (2-49[TES])

Yield: 88%, as a colourless oil (2 isomers, 7:1). ^1H NMR ι: 0.69 (q, *J* = 7.9, 6H), 1.00 (t, *J* = 7.9, 9H), 1.61 (s, 3H), 1.67 (s, 3H), 1.50-2.40 (m, 7H); 2.76 (dt, *J* = 13.0, 3.7, 1H), 2.92 (m, 2H), 3.22 (br s, 1H), 3.83 (s, 3H), 4.66 (d, *J* = 5.6, 2H), 6.66 (d, *J* = 2.4, 1H), 6.82 (dd, J_1 = 8.6 & J_2 = 2.4, 1H), 8.02 (d, *J* = 8.6, 1H). ^{13}C NMR (*main isomer*) ι: 5.7 (3t), 6.8 (3q), 13.9 (q), 20.8 (q), 25.4 (t), 29.4 (t), 30.5 (t), 35.1 (t), 36.5 (d), 39.5 (d), 50.6 (d), 55.4 (q), 109.1 (t), 111.1 (s), 112.5 (d), 112.9 (d), 126.9 (s), 129.9 (d), 145.3 (s), 146.6 (s), 148.6 (s), 163.3 (s), 198.6 (s); (*minor isomer*) 5.8 (3t), 6.6 (3q), 16.2 (q), 20.4 (q), 27.1 (t), 29.9 (t), 30.5 (t), 35.0 (t), 36.1 (d), 38.5 (d), 53.6 (d), 55.3 (q), 108.9 (t), 110.5 (s), 112.1 (d), 112.9 (d), 126.3 (s), 130.0 (d), 144.7 (s), 144.9 (s), 146.1 (s), 163.2 (s), 198.1 (s). HRMS: M^+, found 440.2749. $C_{27}H_{40}O_3Si$ requires 440.2747. MS *m/e* (%) 440 (M^+, 10), 290 (8), 265 (100), 223 (5), 176 (7), 115 (8), 87 (21).

General method for Mukaiyama-Michael addition with 2-methyl-2-cyclopentenone

2-{2-methyl-3-[(trimethylsilyl)oxy]-2-cyclopenten-1-yl}cyclohexanone (2-30[TMS])

2-Methyl-2-cyclopentenone (384 mg, 4 mmol) and **2-23[TMS]** (1.36 g, 8 mmol) were dissolved in dichloromethane (25 ml) and stirred under nitrogen. The reaction mixture was cooled to –78 ºC. $TrSbCl_6$ (58 mg, 0.05 mmol) was added and the reaction was followed by TLC. When all the 2-methyl-2-cyclopentenone had reacted (1 hr), the catalyst was quenched by adding a few drops of pyridine, until the yellow colour disappeared. The reaction mixture was allowed to warm to room temperature and diluted with dichloromethane. The mixture was washed with a saturated $NaHCO_3$ solution (25 ml) and brine (25 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a short column (PE:EtOAc:pyridine 98:1:1) to give **2-30[TMS]** (906 mg, 85%) as a colourless oil composed of two isomers which could not be separated, in a ratio of 6:5 (GC). IR (film) cm^{-1}: 2937, 2860, 1709, 1691, 1330, 1252, 1211; ^1H NMR ($CDCl_3$): 0.01 (s, 9H), 1.24 (s, 3H), 1.11-2.38 (m, 13H), 2.86-3.09 (m, 1H)s; ^{13}C NMR ($CDCl_3$): 0.6 (3q), 10.1 (*M*) & 12.1 (*m*) (q), 22.9 (t), 24.9 (*M*) & 25.4 (*m*) (t), 26.5 (*M*) & 27.0 (*m*) (t), 27.2 (*M*) & 28.5 (*m*) (t), 32.6 (*m*) & 33.2 (*M*) (t), 42.0 (*m*) & 42.2 (*M*) (t), 42.7 (*m*) & 43.2 (*M*) (d), 52.3 (*M*) & 54.8 (*m*) (d), 113.1 (*M*) & 114.4 (*m*) (s), 147.7 (*M*) & 148.3 (*m*) (s), 211.9 (*m*) & 212.8 (*M*) (s). MS *m/e* (%): 266 (M^+, 2), 169 (100), 155 (3), 75 (11), 73 (66).

2-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methyl-2-cyclopenten-1-yl)cyclohexanone (2-30[TBDMS])

Yield: 83%, as a colourless oil (2 isomers, 4:1). IR (CCl_4 sol) cm^{-1}: 2923, 2858, 1711, 1549, 1253; ^1H NMR ($CDCl_3$) 0.10 (s, 6H), 0.93 (s, 9H), 1.31-1.52 (m, 5H), 1.54-1.70 (m, 2H), 1.79-2.53 (m, 9H), 3.09 (s, 1H); ^{13}H NMR ($CDCl_3$) –4.0 (2q), 10.1 (q), 18.1 (s), 22.9 (t), 25.1 (t), 25.7 (3q), 26.5 (t), 27.2 (t), 33.2 (t), 42.4 (t), 43.1 (d), 52.4 (d), 112.7 (s), 147.9 (s), 213.1 (s). HRMS: M^+, found 308.2178. $C_{18}H_{32}O_2Si$ requires 308.2172. MS *m/e* (%): 308 (M^+, 14), 75 (25), 73 (33).

Desilylated intermediate 2-30: 2-(2-Methyl-3-oxo-cyclopentyl)-cyclohexanone (2-34)

^1H NMR ι: 1.02 (*M*) & 1.07 (*m*) (d, *J* = 6.9, 3H), 1.28-2.75 (m, 15H).

6-Methoxy-2-(2-methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-3,4-dihydro-2H-naphthalen-1-one (2-51[TMS])

Yield: 90%, as a colourless oil (2 isomers, 2:1). IR (CCl_4 sol.) cm^{-1}: 2941, 2851, 1673, 1600, 1333, 1252; ^1H NMR ($CDCl_3$) ι: 0.14 (*M*) & 0.18 (*m*) (s, 9H), 1.27 (*M*) & 1.50 (*m*) (s, 3H), 1.41-2.73 (m, 7H), 2.86-3.00 (dd, J_1 = 3.7 & J_2 = 8.3, 2H), 3.40-3.55 (*m*) & 3.55-3.65 (*M*) (m, 1H), 3.83 (s, 3H), 6.66 (d, *J* = 2.5, 1H), 6.81 (dd, J_1 = 2.5 & J_2 = 8.7, 1H), 8.00 (*m*) & 8.01 (*M*) (d, *J* = 8.7, 1H); ^{13}C

NMR ($CDCl_3$) ι: 0.6 (3q), 10.3 (*m*) & 11.9 (*M*) (q), 22.4 (*m*) & 23.6 (*M*) (t), 22.9 (*m*) & 25.0 (*M*) (t), 29.8 (*M*) & 29.9 (*m*) (t), 32.9 (*M*) & 33.1 (*m*) (t), 43.3 (*M*) & 43.9 (*m*) (d), 49.7 (*m*) & 52.2 (*M*) (d), 55.4 (q), 112.4 (d), 113.0 (d), 114.4 (s), 126.5(*M*) & 127.1 (*m*) (s), 129.7 (*m*) & 123.0 (*M*) (d), 146.5 (*M*) & 146.8 (*m*) (s), 147.9 (*m*) & 148.1 (*M*) (s), 163.3 (s), 197.8 (*M*) & 199.0 (*m*) (s). HRMS: M^+, found 344.1807. $C_{20}H_{28}O_3Si$ requires 344.1808. MS *m/e* (%) 344 (M^+, 9), 249 (8), 248 (34), 138 (8), 176 (36), 170 (15), 169 (100).

2-[3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-cyclopent-2-enyl]-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (2-51[TBDMS])

Yield: quantitative, as a colourless oil (2 isomers, 5:1). IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2857, 1677, 1601, 1334, 1251, 1224; ^1H NMR (C_6D_6) ι: 0.13 (s, 6H), 0.94 (*m*) & 1.04 (*M*) (s, 9H), 1.20-1.50 (m, 1H), 1.55 (*M*) & 1.59 (*m*) (s, 3H), 1.60-1.85 (m, 2H), 2.05-2.32 (m, 3H), 2.38-2.63 (m, 3H), 3.33 (*m*) 3.34 (*M*) (s, 3H), 3.75-3.85 (*M*) & 3.85-3.98 (*m*) (m, 1H), 6.53 (d, J = 2.6, 1H), 6.67 (dd, J_1 = 2.6 & J_2 = 8.7, 1H), 8.32 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: -4.1 (2q), 10.1 (*M*) & 12.0 (*m*) (q), 18.0 (s), 22.6 (*M*) & 23.9 (*m*) (t), 22.8 (*M*) & 25.0 (*m*) (t), 25.6 (3q), 29.7 (t), 33.3 (t), 43.4 (*m*) & 43.9 (*M*) (d), 49.6 (*M*) & 52.0 (*m*) (d), 54.5 (t), 112.7 (2d), 113.9 (s), 129.6 (*M*) & 129.8 (*m*) (d), 146.1 (*m*) & 146.4 (*M*) (s), 148.0 (s), 163.2 (s), 196.2 (*m*) & 197.2 (*M*) (s). HRMS: M^+, found 386.2274. $C_{23}H_{34}O_3Si$ requires 386.2277. MS *m/e* (%) 386 (M^+, 4), 233 (3), 211 (100), 176 (14), 97 (3), 75 (7), 73 (33).

(5*S*,6*R*)-5-Isopropenyl-2-methyl-6-(2-methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-cyclohex-2-enone (2-36)

Yield: 68% (2 isomers, 10:1). IR (CCl_4) cm^{-1}: 2960, 2957, 2945, 1741, 1671; ^1H NMR ($CDCl_3$): -0.01 (s, 9H), 1.28 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 1.15-2.68 (m, 9H), 4.59 (s, 2H), 6.38-6.44 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.6 (3q), 10.7 (q), 15.6 (q), 18.8 (q), 22.9 (t), 30.3 (t), 32.6 (t), 45.1 (d), 46.2 (d), 50.0 (d), 113.0 (t), 114.8 (s), 136.1 (s), 142.0 (d), 146.1 (s), 146.5 (s), 200.3 (s). HRMS: M^+, found 318.2017. $C_{19}H_{30}O_2Si$ requires 318.2015. MS *m/e* (%): 318 (M^+, 9), 222 (15), 182 (6), 169 (100), 150 (5), 73 (34).

Desilylated intermadiate 2-36: (5*S*)-5-Isopropenyl-2-methyl-6-(2-methyl-3-oxo-cyclopentyl)-cyclohex-2-enone (2-39)

^1H NMR ($CDCl_3$): 0.97 (d, J = 6.9, 3H), 1.63 (s, 3H), 1.67 (s, 3H), 1.63-3.01 (m, 10H), 4.77 (s, 1H), 4.80 (s, 1H), 6.62-6.67 (m, 1H); ^{13}C NMR ($CDCl_3$): 12.8 (q), 15.8 (q), 17.8 (q), 21.0 (t), 30.9 (t), 37.1 (t), 44.1 (d), 47.1 (d), 47.2 (d), 47.5 (d), 114.0 (t), 135.9 (s), 143.3 (d), 145.0 (s), 200.8 (s), 220.6 (s).

(3*R*)-9-acetyl-8a-hydroxy-3-isopropenyl-10a-methyldodecahydro-1(2*H*)-phenanthrenone (2-28)

Mukaiyama-Michael addition of intermediate **2-25** with MVK

A stirred solution of $TrSbCl_6$ (29 mg, 0,05 mmol) in dichloromethane (10 ml) under nitrogen was cooled to –78 ºC. A solution of **2-25** (1 mmol) and methyl vinyl ketone (MVK, 0,1663 ml, 2 mmol) in dichloromethane (5 ml) was added dropwise over a period of 2.5 hrs. The reaction mixture was stirred at –78 ºC for another 2 hrs and was then allowed to warm to room temperature. Water (10 ml) was added and, after stirring for a further 1 hr, the reaction mixture was diluted with dichloromethane (20 ml) and washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc 9:1) to give two isomers **2-28a** (cryst.) and **2-28b** (oil). **2-28a** was recrystallised in pentane to give white crystals (needles).

From **2-25[TMS]**: 49%, ratio **2-28a:2-28b** 5:1.

From **2-25[TBDMS]**: 45%, as single isomer **2-28a**.

Domino Mukaiyama reaction

At room temperature, (*R*)-(-)-carvone (450 mg, 3 mmol) was added to a stirred solution of **2-23** (4.5 mmol) in dichloromethane (20 ml) under nitrogen. The solution was cooled to –78 ºC and $TrSbCl_6$ was added (87 mg, 0.15 mmol). After 2.5 hrs of stirring at –78 ºC, MVK (0.5 ml, 6 mmol) was added dropwise over a period of 3.5 hrs. The reaction mixture was stirred for another 2 hrs at –78 ºC, before slow warming to room temperature overnight. No TLC control was done during the reaction due to the sensitivity of the compounds towards desilylation. Water (10 ml) was added and after further stirring for 1 hr the reaction mixture was diluted with dichloromethane (20 ml). The organic layer was washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE:EA 20:1, with 1% pyridine) to give **2-28a** and **2-28b**, as above.

From **2-23[TMS]**: 45%, ratio **2-28a:2-28b** 5:1.

From **2-23[TBDMS]**: 38%, as single isomer **2-28a**.

2-28a. mp 68-72 °C (from pentane); IR (CCl_4 sol) cm^{-1}: 3488, 2937, 1707, 1252; ^1H NMR ($CDCl_3$) 1.01-1.22 (2H, m), 1.18 (3H, s), 1.22-1.48 (4H, m), 1.55-1.84 (9H, m), 1.88-2.13 (2H, m), 2.19 (3H, s), 2.35-2.55 (2H, m), 2.64 (d, J = 6.7, 1H), 3.02 (dd, J_1 = 3.3 & J_2 = 9.9, 1H), 3.99 (OH), 4.65 (1H, s), 4.81 (1H, s); ^{13}C NMR ($CDCl_3$) 19.9 (q), 22.3 (q), 23.8 (t), 25.7 (t), 26.4 (t), 26.9 (t), 31.6 (q), 31.9 (t), 33.6 (d), 38.8 (t), 40.5 (d), 41.1 (t), 45.6 (d), 47.4 (s), 48.2 (d), 72.1 (s), 112.5 (t), 146.6 (t), 214.6 (s), 215.4 (s). HRMS: M^+, found 318.2203. $C_{20}H_{30}O_3$ requires 318.2195. MS *m/e* (%): 318 (M^+, 42), 248 (86), 221 (63), 204 (96), 179 (77), 161 (84), 151 (98), 98 (67).

2-28b. IR (CCl_4 sol) cm^{-1}: 3488, 2937, 1707, 1252; ^1H NMR ($CDCl_3$) 1.14 (3H, s), 1.04-1.28 (2H, m), 1.32-1.85 (9H, m), 1.93-2.12 (2H, m), 2.17 (3H, s), 2.50-2.62 (2H, m), 2.62-2.74 (1H, m), 3.67 (OH), 4.69 (1H, s), 4.80 (1H, s); ^{13}C NMR ($CDCl_3$) 16.9 (q), 20.7 (t), 21.5 (q), 23.7 (t), 25.3 (t), 26.1 (t), 31.4 (q), 32.1 (t), 36.3 (d), 37.5 (t), 39.4 (d), 40.7 (t), 42.8 (d), 47.2 (s), 53.3 (d), 70.8 (s), 112.0 (t), 146.8 (s), 215.7 (s), 215.9 (s). HRMS: M^+, found 318.2203. $C_{20}H_{30}O_3$ requires 318.2195. MS *m/e* (%): 318 (M^+, 42), 248 (86), 221 (63), 204 (96), 179 (77), 161 (84), 151 (98), 98 (67).

5-acetyl-5a-hydroxy-3a-methyldodecahydro-3*H*-cyclopenta[a]naphtalen-3-one (2-32)

For general procedures see syntheses of **2-28**.

From **2-30[TMS]**: 61%, ratio **2-32a**:**2-32b** 4:1

From **2-30[TBDMS]**: 32%, ratio **2-32a**:**2-32b** 2:1.

2-32a. mp 86-90 °C (from pentane); IR (CCl_4 sol) cm^{-1}: 3469, 2933, 2860, 1739, 1692, 1398, 1359, 1190; ^1H NMR ($CDCl_3$) 0.92 (s, 3H), 1.08-2.18 (m, 15H), 2.18 (s, 3H), 2.41 (dd, J_1 = 8.0 & J_2 = 16.4, 1H), 2.61 (dd, J_1 = 5.1 & J_2 = 11.5, 1H), 3.81 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.4 (q), 21.1 (2t), 23.4 (t), 25.7 (t), 31.3 (q), 31.8 (t), 35.7 (t), 37.0 (t), 42.8 (d), 42.9 (d), 47.2 (s), 53.7 (d), 72.0 (s), 215.9 (s), 219.5 (s). MS *m/e* (%): 264 (M^+, 2), 246 (5), 203 (16), 194 (43), 105 (15), 98 (81), 97 (100), 43 (58).

2-32b. mp 79-82 °C (from pentane); ^1H NMR ($CDCl_3$) 1.05 (s, 3H), 1.05-1.55 (m, 5H), 1.64-1.93 (m, 9H), 2.12 (dd, J_1 = 8.5 & J_2 = 19.1, 1H), 2.24 (s, 3H), 2.32-2.57 (m, 2H), 3.10 (dd, J_1 = 5.1 & J_2 = 11.1, 1H), 4.19 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.9 (q), 20.8 (t), 24.0 (t), 25.7 (t), 26.1 (t), 31.5 (q), 31.7 (t), 35.7 (t), 38.8 (t), 41.6 (d), 46.3 (2d), 46.6 (s), 73.1 (s), 215.4 (s), 219.0 (s).

Addition sequence with 2-41

For general procedures see syntheses of **2-25** and **2-28**.

Product First Mukaiyama-Michael reaction: (5'*S*)-5'-Isopropenyl-1,2'-dimethyl-3'-trimethylsilanyloxy-bicyclohexyl-2'-en-2-one

Yield: 30%, as a colourless oil (2 isomers, 3:1, GC detection).

Main isomer ^1H NMR ($CDCl_3$) 0.14 (s, 9H), 1.04 (s, 3H), 1.49 (s, 3H), 1.66 (s, 3H), 1.23-2.79 (m, 13H), 2.95-3.07 (m, 1H), 4.65 (s, 1H), 4.68 (s, 1H).

Product Domino Mukaiyama reactions: (3*S*)-9-Acetyl-8a-hydroxy-3-isopropenyl-4b,10a-dimethyl-dodecahydro-phenanthren-1-one

Yield: 14%. *Main isomer*. ^1H NMR ($CDCl_3$) 0.99 (s, 3H), 1.6 (s, 3H), 1.20-1.69 (m, 5H), 1.70 (s, 3H), 1.72-2.11 (m, 5H), 2.22 (s, 3H), 2.42-2.80 (m, 3H), 3.25 (dd, J_1 = 3.0 & J_2 = 13.4, 1H), 3.86 (s, 1H), 4.69 (s, 1H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$) 20.1 (q), 20.8 (q), 21.3 (t), 21.8 (q), 22.7 (t), 23.6

(t), 31.4 (q), 31.5 (2t), 33.9 (t), 39.9 (d), 40.7 (t), 41.0 (d), 41.7 (s), 46.2 (d), 47.9 (s), 73.5 (s), 112.6 (t), 146.3 (s), 214.6 (s), 215.8 (s).

Addition sequence with 2-42

For general procedures see syntheses of **2-25** and **2-28**.

Product First Mukaiyama-Michael reaction: 2-{(5*R*)-5-isopropenyl-2-methyl-3-[(trimethyl-silyl)oxy]-2-cyclohexen-1-yl}-6-methylcyclohexanone

Yield: 52%, as a colourless oil (4 isomers, 8:7:1:1, GC detection).

Two main isomers: IR (CCl_4 sol) cm^{-1} 2933, 1707, 1252; ^1H NMR ($CDCl_3$) 0.17 (9H, s), 1.04 (*M*) & 1.08 (*m*) (d, *J* = 7.1, 3H), 1.28-2.79 (m, 22H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$) 0.6 (3q), 15.3 (q), 15.7 (q), 18.1 (*m*) & 20.8 (*M*) (q), 20.32 (*M*) & 20.47 (*m*) (t), 28.5 (*M*) & 30.7 (*m*) (t), 29.3 (*M*) & 32.5 (*m*) (t), 34.4 (*M*) & 35.1 (*m*) (t), 35.3 (t), 37.8 (*m*) & 37.9 (*M*) (d), 37.9 (d), 42.4 (*m*) & 42.9 (*M*) (d), 52.6 (*M*) & 55.2 (*m*) (d), 109.2 (*m*) & 109.3 (*M*) (t), 113.1 (*M*) & 113.4 (*m*) (s), 144.7 (*M*) & 145.5 (*m*) (s), 148.4 (*M*) & 148.7 (*m*) (s), 212.9 (*m*) & 214.1 (*M*) (s). HRMS: M^+, found 334.2333. $C_{20}H_{34}O_2Si$ requires 334.2328. MS *m/e* (%): 334 (M^+, 9), 319 (3), 181 (10), 75 (6), 73 (32).

Product Domino Mukaiyama reactions: 9-acetyl-8a-hydroxy-3-isopropenyl-8,10a-dimethyldodecahydro-1(2*H*)-phenanthrenone

Yield: 24% (2 isomers, 6:1). *Main isomer*. ^1H NMR ($CDCl_3$) 0.96 (d, *J* = 7.3, 3H), 1.14 (s, 3H), 1.20-1.69 (m, 7H), 1.69 (s, 3H), 1.70-2.20 (m, 6H), 2.21 (s, 3H), 2.45-2.95 (m, 4H), 3.77 (s, 1H), 4.66 (s, 1H), 4.81 (s, 1H); ^{13}C NMR ($CDCl_3$) 15.6 (q), 16.8 (q), 19.8 (t), 21.5 (q), 24.2 (t), 25.4 (t), 27.7 (t), 30.8 (q), 32.2 (t), 36.2 (d), 36.5 (d), 36.6 (d), 39.4 (d), 40.7 (t), 47.1 (s), 49.1 (d), 73.8 (s), 111.9 (t), 146.8 (s), 215.5 (s), 215.7 (s). HRMS: M^+, found 332.2346. $C_{21}H_{32}O_3$ requires 332.2351. MS *m/e* (%): 332 (M^+, 20), 314 (25), 271 (58), 262 (26), 112 (88), 43 (100).

Addition reactions with 2-43

For general procedures see syntheses of **2-25** and **2-28**.

Product first Mukaiyama addition: 2-{(5*R*)-5-isopropenyl-2-methyl-3[{trimethyl-silyl)oxy]-2-cyclohexen-1-yl}-5-cyclohexenone

Yield: 44% (2 isomers: 2:1). ^1H NMR (C_6D_6) 0.21 (s, 9H), 1.30-3.45 (m, 17H), 4.84 (s, 1H), 4.89 (s, 1H), 5.96-6.17 (m, 1H), 6.21-6.29 (m, 1H).

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79. The *syn* and *anti* terminology used for the intermediates **2-25** and **2-30** refers to the conformation as depicted in scheme 5.
80. This one-pot procedure is termed a domino reaction although not all reagents are present in the reaction mixture from the start. On the other hand, the reaction conditions remain the same during the whole reaction time and for this reason, we estimate this term appropriate for the situation.
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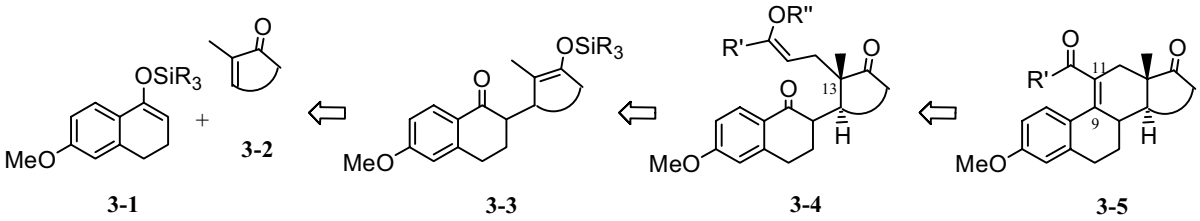
New approach towards *trans*-fused steroid and D-homo steroid skeletons

Chapter 3

3.1. Introduction

In chapter 2 was shown that a short route to steroid skeletons using a double Mukaiyama-Michael addition followed by aldol cyclisation could not be achieved. Nevertheless product **3-3** of the first Mukaiyama-Michael addition of the silyl enol ether of 6-methoxytetralone and an appropriate ring D-precursor, such as 2-methyl-2-cyclopentenone or R-(-)-carvone (see scheme 1 and chapter 2, schemes 8-10), still offers good possibilities for new short steroid syntheses. Prerequisites are however the development of good methods for the introduction of an appropriately functionalised substituent at C13 and to secure the *trans*-fusion of the CD ring system as the second step. The construction of the C9-C11 bond is then the last step for the closure of ring C (see scheme 1).

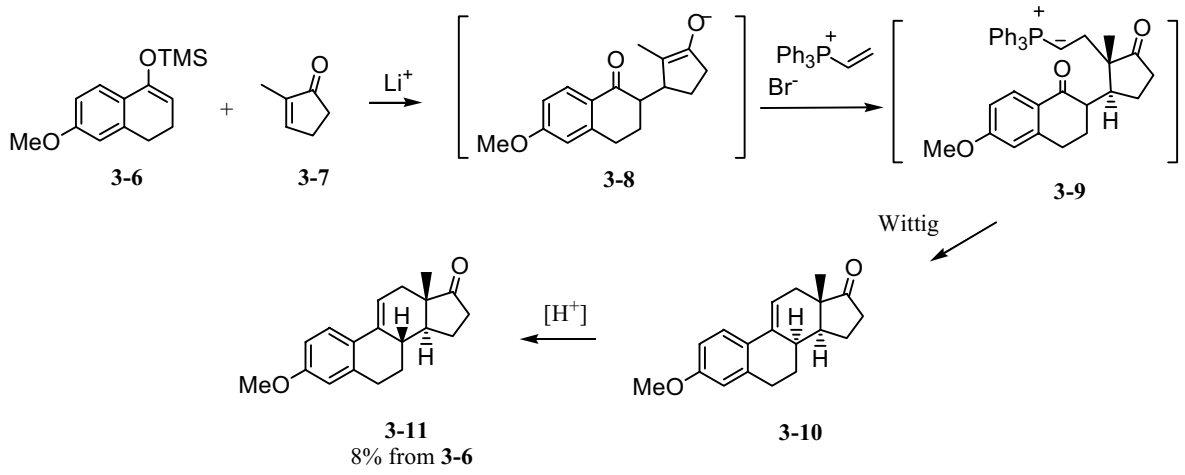
Scheme 1



Similar approaches, also having the C9-C11 bond formation as the last step in a reaction sequence using the methoxytetralone moiety for the AB-ring system, have been reported in literature (see chapter 1). The methods most concurring with the here proposed chemistry were either making use of a Wittig reaction[1,2] or a McMurry reductive cyclisation[3-7] as the final ring C closing step.

Posner published a one-pot synthesis for racemic 9,11-dehydroestrone methyl ether **3-11**[1], which is somewhat similar to the sequence envisaged by us. The reaction starts using a silyl enol ether of methoxytetralone which is added to a cyclopentenone ring, followed by addition of an alkyl chain which enables closure of ring C (scheme 2). The difference however is that the consecutive addition

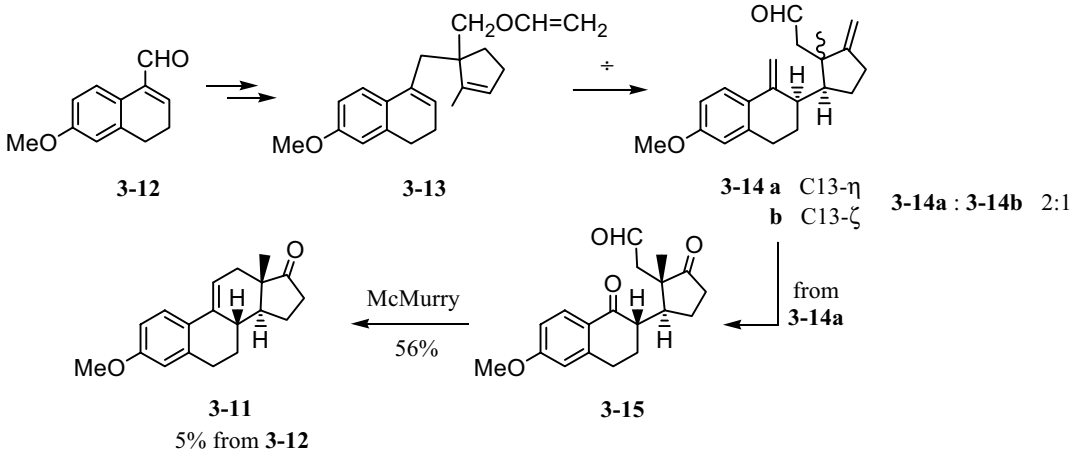
Scheme 2



steps are performed using lithium enolate intermediates and that the ring closure relies on a Wittig reaction. The route yielded a steroid system **3-10** with *trans* fusion around C13-C14 and *cis*-fusion around C8-C9, which could easily be isomerised to the trans-fused system of the estrone skeletons. Although this reaction sequence to the racemic estrone methyl ether **3-11** was short, the overall yield of the reaction sequence was only 8%.

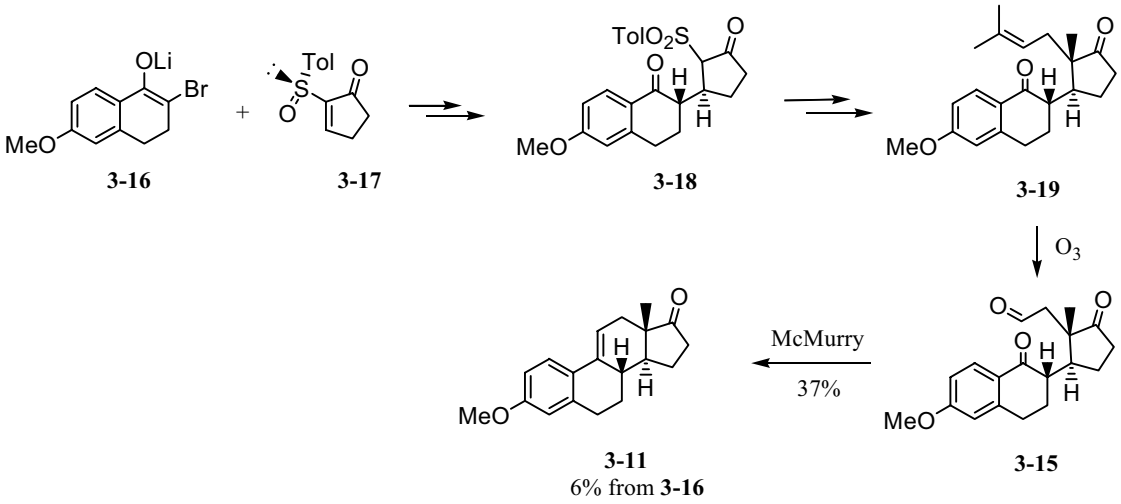
Shortly after this, Ziegler published a synthesis of the same compound (again as a racemic mixture) relying on a Cope-Claisen rearrangement (scheme 3)[4]. After this rearrangement, the obtained aldehyde was subjected to a McMurry radical reaction to close ring C in 56% yield. Again the overall yield of the reaction sequence was low (5%), now due to the low stereoselectivity of the thermal rearrangement, giving an almost 1:1 mixture of *cis* and *trans* fusion around C13-C14.

Scheme 3



In his asymmetric synthesis of natural (+)-estrone methyl ether **3-11** Posner also applied the McMurry cyclisation[5]. This sequence used a stereoselective Michael addition with an enantiomerically pure cyclopentenone sulfoxide to steer the reaction (scheme 4). The cyclisation

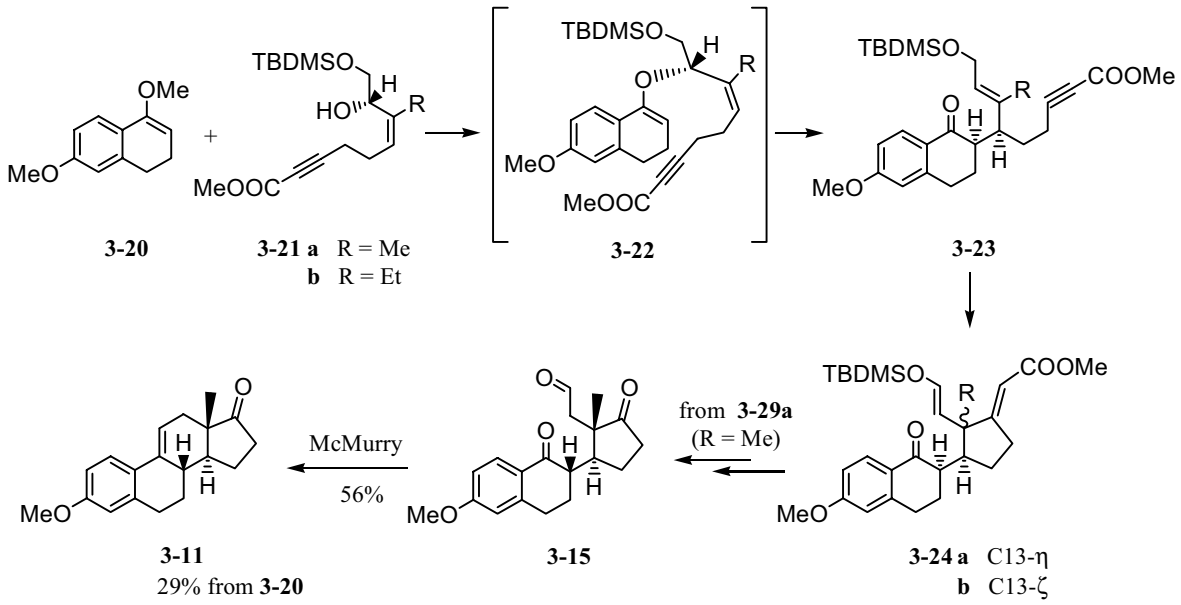
Scheme 4



under McMurry conditions in this case gave a lower yield (37%) but the reaction sequence was highly stereoselective, yielding optically pure (+)-estrone methyl ether **3-11** in 6% overall yield.

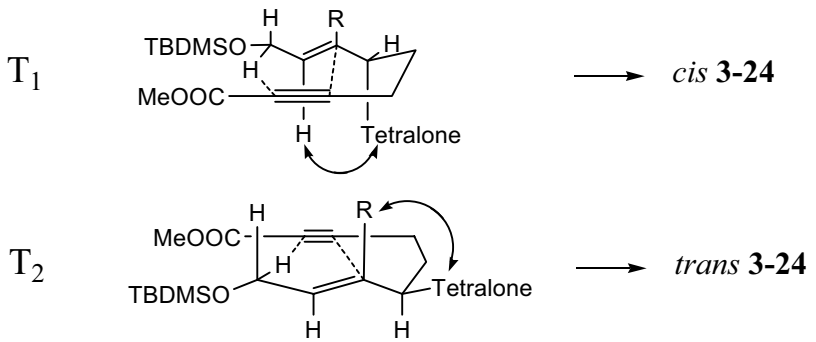
Mikami[6,7] and Groen[2] both used a route based on a tandem Claisen-ene reaction to obtain the seco steroid compound in which ring C closure at C9-C11 had to be performed as the last step to complete the steroid skeleton (schemes 5 and 6).

Scheme 5



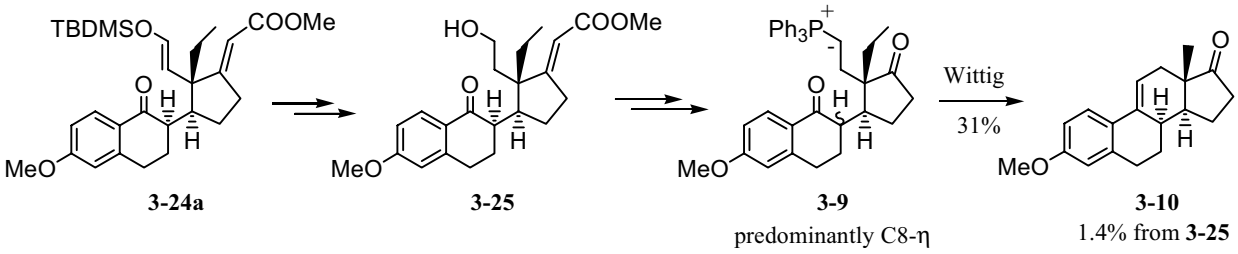
These routes led both to optically pure compounds, starting from R-(+)-glyceraldehyde which is easily accessible from D-mannitol. While Mikami reported the exclusive formation of the *trans* stereochemistry around the C13-C14 bond in the tandem reaction, Groen obtained an approximately 1:1 mixture of this isomer together with the 13ζ-isomer. This difference can be attributed to the replacement of the methyl substituent on C13, in the route of Mikami, with an ethyl group in the compound synthesised by Groen. This ethyl group enhances the steric strain in the transition state of the ring D closure to such an extend that the conformation leading to the unwanted *cis* configuration (T_1) became as probable as the one leading to the *trans* product (T_2) (see figure 1).

Figure 1



After a few more steps, Mikami then cyclised the obtained aldehyde **3-15** *via* the McMurry reaction previously published by Ziegler[4], again in 56% yield. Groen further transformed the aldehyde to a phosphonium salt and closed ring C using the Wittig reaction (scheme 6).

Scheme 6

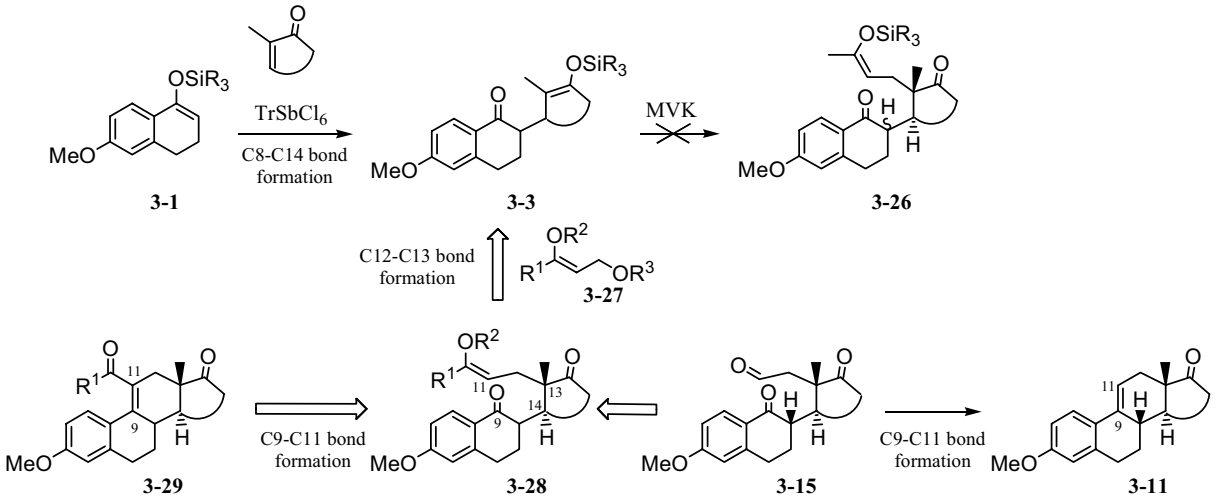


The yield of the ring closing reaction could however not be enhanced and was unfortunately even lower than the yield reported using the McMurry reaction. The only product being isolated after the cyclisation reaction having the C8-ζ configuration, this low yield could be due to the fact that the ring closure seems only to take place when the seco steroid has this ζ-configuration around C8, while compound **3-9** is mainly present as the C8-η isomer. The exact reason for this behaviour was not explained[2] but Posner reported similar results when performing his Wittig ring closing reaction[1]. Surprisingly the McMurry cyclisation, on the other hand, gave significantly higher yields when performed on the 8η-isomer[4], leading directly to the natural all-*trans* configuration around the steroid ring system.

3.2 Construction of the C12-C13 bond

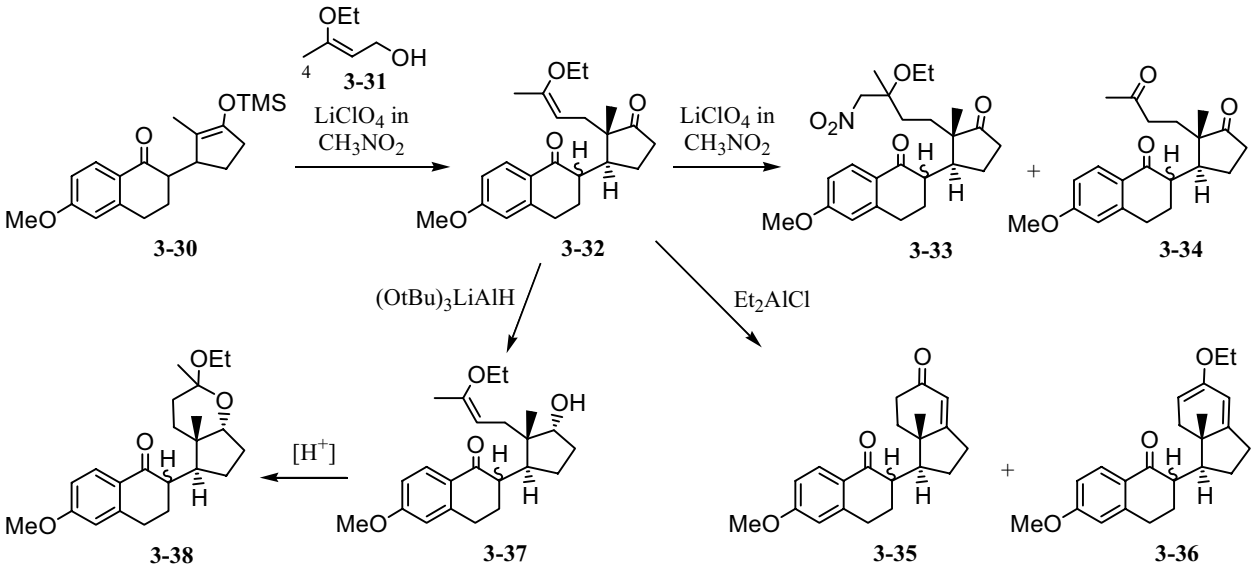
Although, in our case, it appeared not to be possible to add methyl vinyl ketone *via* a Mukaiyama-Michael addition to intermediate **3-3** (see chapter 2), alkylations of silyl enol ethers derived from 2-methyl-2-cyclopentanones with carbocation precursors are known in literature[8,9] and seemed to offer good prospective. For our purpose a congener of 3-methoxy-2-butenol, a reagent developed by Duhamel[10-12], seemed most appropriate (schemes 7 and 8). From the latter reagent a carbocation can be generated under mild Lewis acid conditions, compatible with the presence of a silyl enol ether in ring D. The enol ether in the introduced moiety in adduct **3-28** is located in the correct position for the closure of ring C by an aldol type cyclisation. In this way a suitable functional group would be introduced at C11 as an additional advantage. Ozonolysis of the double bond in adduct **3-28** can be carried out as an alternative leading to Ziegler's triketone **3-15**, the intermediate in the steroid synthesis routes using the McMurry reaction for cyclisation[4-7].

Scheme 7



While the attempted MVK addition to compounds **3-3** only gave desilylation products of the starting materials, it was found that the more reactive allylic alcohol **3-31**[13] did react with silyl enol ether **3-30** under $LiClO_4$ catalysis (scheme 8)[14]. Concentrated solutions of $LiClO_4$ in organic solvents (4-5M in diethyl ether or nitromethane) have been reported previously to catalyse additions of allylic alcohols and esters to silyl enol ethers in high yields[15-17]. Although these high concentrations did not give any result in our case, a lower concentration (0.05 – 0.7 M) in nitromethane did afford the desired product in reasonable 52% yield. Noteworthy in this addition reaction is that the product only became visible after one hour of reaction time. At that moment GC analysis showed the absence of the free allyl alcohol **3-31** in the reaction mixture but further additions of this compound to the reaction mixture did not improve the yield.

Scheme 8

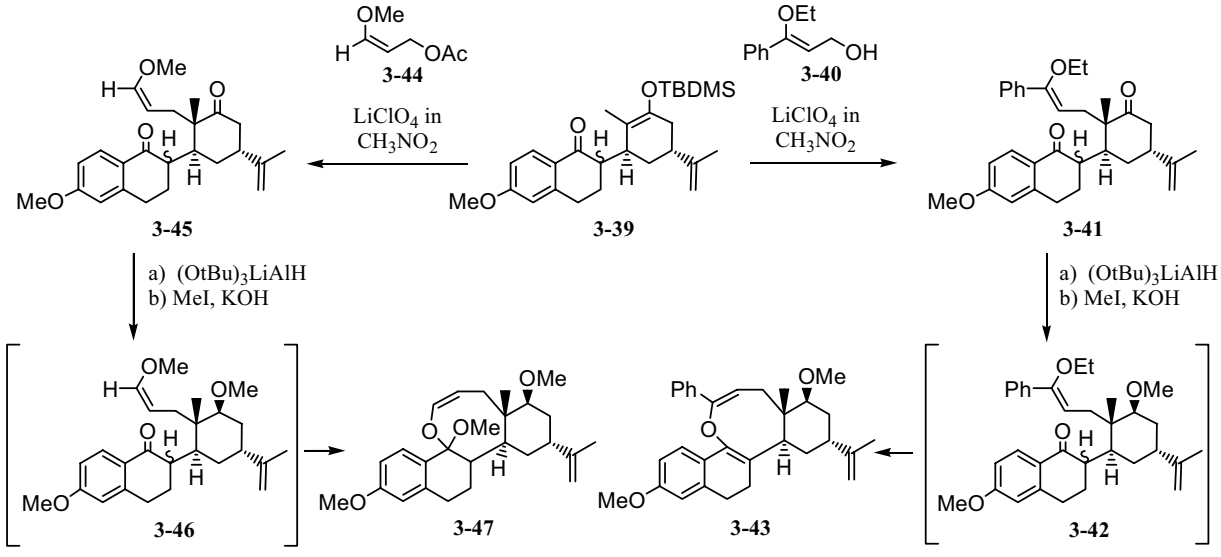


The fact that addition of allylic alcohol **3-31** to compound **3-30** could be achieved indicates that steric hindrance in the MVK addition with **3-3** is probably not the reason for the failure of this reaction, but that the lower reactivity of the carbonyl group in the tetralone part of the molecule is the main obstacle, as was already concluded in chapter 2: the addition of MVK to compound **3-3** does take place, but is immediately followed by the retro reaction. This was confirmed by the failure of other attempts to construct the C9-C11 bond *via* aldol type reactions (scheme 8).

Prolonged reaction time in a more concentrated $LiClO_4$ solution (4M) did consume the addition product **3-32** but no cyclisation was observed and the major product that was isolated was compound **3-33**, next to compound **3-34**, in which hydrolysis of the enol ether function had occurred. Cyclisation under mild Lewis acidic conditions did lead to an aldol type reaction but with the carbonyl group of ring D, giving compound **3-35**, which partially enolised in the reaction mixture to compound **3-36**. An attempt to perform a radical cyclisation using Bu_3SnH/AIBN failed to give any product formation and was stopped after 24 hrs. Selective reduction of the ring D carbonyl to compound **3-37**, followed by application of mild acidic cyclisation conditions, rapidly led to acetal formation, again with the oxygen of ring D, giving compound **3-38**. The configuration of C17 in compounds **3-37** and **3-38** is assumed to be as depicted in scheme 8.

Also with R-carvone as potential ring D precursor we have not been successful in the construction of the C9-C11 carbon bond. To rule out aldol condensation with the carbonyl group in ring D, position 4 in compound **3-31** (see scheme 8 for numbering) was blocked by replacing the methyl group by a phenyl in compound **3-40**, or by a hydrogen in compound **3-44**[18], the latter also to minimize the steric hindrance. To prevent acetal formation, the carbonyl group in ring D was selectively reduced and protected as the methyl ethers **3-42** and **3-46** (scheme 9). Finally, the more

Scheme 9



stable *tert*-butyl dimethylsilyl (TBDMS) enol ether, instead of the trimethylsilyl (TMS) enol ether, was used in the addition step to enhance the yield of this reaction in favour of desilylation.

Although desilylation in the addition with compound **3-40** could indeed be averted using the TBDMS enol ether under optimised conditions (see entry 2, table 1), improvement of the yield of 20% was not obtained, the remaining being unreacted compound **3-39** in the best of cases. The addition product **3-41** was obtained as a mixture of two main isomers that could be separated, together with two more isomers in an inseparable mixture (ratio 26.6:22:4:1). The reason why the reaction stops after 20% conversion, although compound **3-40** is still present in the reaction mixture, is not known. Renewed addition of the catalyst over the reaction period did not help and also a higher reaction temperature only managed to destroy the silyl enol ether, without giving any addition product. Work-up of the reaction and renewed addition of catalyst was not attempted, as further reaction with the compound did not give the desired end product (see below).

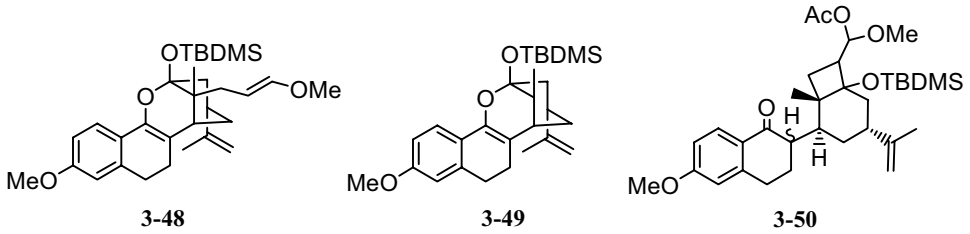
Table 1

	Reaction conditions	**Temperature**	**Reaction time**	**Yield product (absolute)**	**Recovered starting material**	**Yield product (relative)**
1a	∉ Solution of **3-39** and **3-40** in CH_3NO_2 ∉ $LiClO_4$ added in one portion (0.7 M)	Room temp.	24 hrs	23%	57%	53%
1b		Room temp.	72 hrs	22%	35%	34%
1c		40 °C	2 hrs	-	35%	-
2	∉ Solution of **3-39** and $LiClO_4$ in CH_3NO_2 (0.7 M) ∉ **3-40** added dropwise (over 2 hrs)	Room temp.	24 hrs	18%	77%	78%
3	∉ Solution of **3-39** and **3-40** in CH_3NO_2 $LiClO_4$ (10 eq.) added in portions of 1 eq. (0,15 M Ÿ 1,5 M)	Room temp.	72 hrs	-	-	-

When the addition reaction was performed with compound **3-44** desilylation of **3-39** did still stake place during reaction time and only 10% of the desired addition product could be isolated, next to 8% of acetylised compound **3-48**, 3.5% of compound **3-49**, in which addition of **3-44** had not taken place, and 9.5% of a compound with a mass of 570 (= M[**3-44** + **3-39**]), which was tentatively assigned structure **3-50**.

Although the yields of the addition reactions of carbocation precursors **3-40** and **3-44** with silyl enol ether **3-39** were low, we did isolate enough of both products **3-41** and **3-45** to proceed with the reaction sequence. In both compounds, the carbonyl group in ring D was reduced and the free

Figure 2



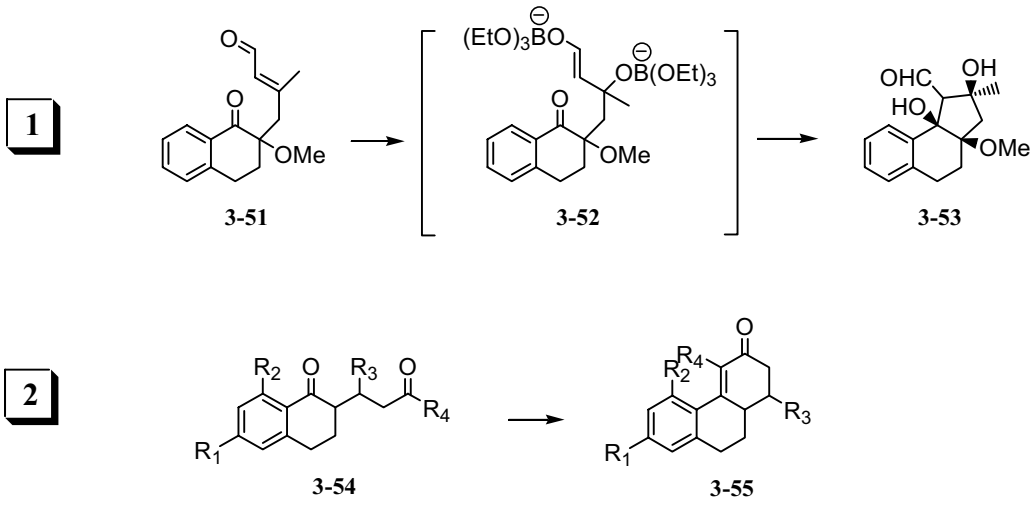
3-48 **3-49** **3-50**

alcohol that was obtained was not isolated but immediately protected as the methyl ether. When isolation of the free alcohols was attempted, acetal formation similar to compound **3-38** quickly took place.

After having performed the addition, reduction and protection steps, the consecutive aldol type cyclisation with formation of the C9-C11 carbon-carbon bond could again not be achieved. Instead, compounds **3-42** and **3-46** appeared to be very unstable and rapidly cyclised to ethers **3-43** and **3-47** when isolation was attempted. Apparently, enolisation of the carbonyl in the tetralone moiety is easy, leading to alternative reactions and not to the desired aldol type cyclisation. Why cyclisation to the ether rings does not happen in compounds **3-41** and **3-45** is not clear.

That enolisation may prevent the carbonyl in the tetralone moiety to undergo an aldol cyclisation is confirmed by the fact that an aldol cyclisation can be performed when enolisation can not take place due to blocking of the C-8 position with an additional substituent[19] (scheme 10, entry 1). It has been shown also that, when the ketone is put under strong basic conditions (KOH/EtOH or NaH), the

Scheme 10



3-51 **3-52** **3-53**

3-54 **3-55**

R_1 = H; R_2 = H; R_3 = H; R_4 = Me
R_1 = OMe; R_2 = H; R_3 = Me; R_4 = Me
R_1 = OMe; R_2 = H; R_3 = H; R_4 = $(CH_2)_3COOMe$
R_1 = OMe; R_2 = OBz; R_3 = H; R_4 = Me

aldol reaction can be forced, even without the extra substituent on C-8[10,20-22]. Note has to be made of the fact that in the products **3-55**, formed in entry 2, the ketone involved in the aldol reaction ends up in the newly formed ring after cyclisation (scheme 10, entry 2), and not in the side chain as would have been the case in our compound.

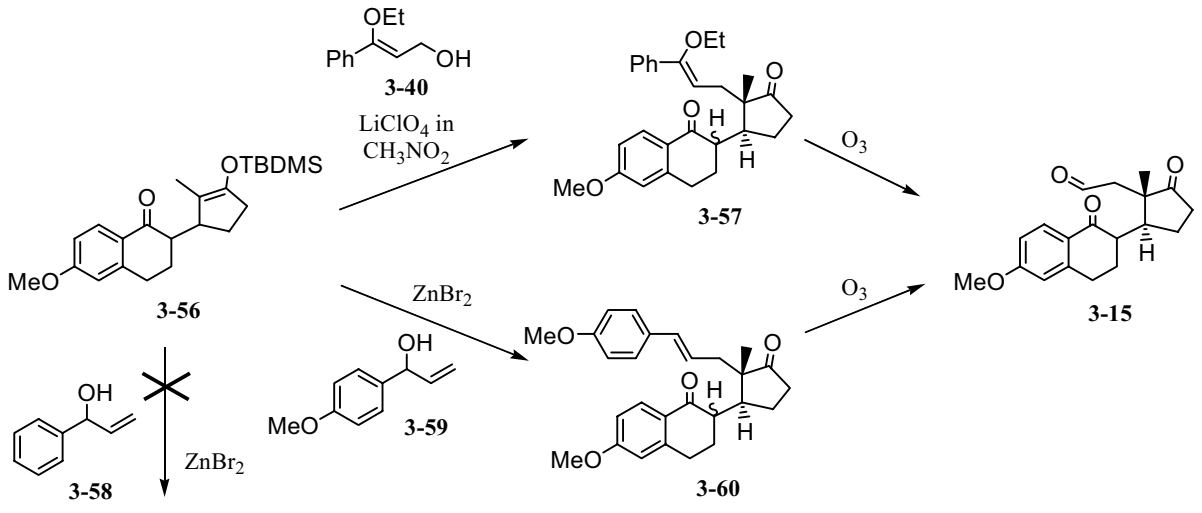
As our focus was to develop short and efficient reaction sequences towards (D-homo) steroid skeletons, longer reaction sequences to achieve the aldol cyclisation were not tried, since a better alternative seemed to be offered by constructing the C9-C11 bond *via* a McMurry cyclisation reaction like with Ziegler's triketone **3-15**[4-7].

3.3 A short synthesis of Ziegler's triketone

The experiments in the former paragraph showed that substituents could be introduced at C13 *via* reaction of carbocation precursors with the silyl enol ether of ring D. In this way, compounds can be obtained with a double bond in the introduced side chain, which can be ozonolysed to a carbonyl group and a short synthesis of steroid precursors like **3-15** should become available. Moreover, when the addition reaction of compound **3-40** was performed with five-membered D-ring compound **3-56**, a good 93% yield of the desired product **3-57** was now obtained (see scheme 11). The divergence in yields obtained when reacting a carbocation with silyl enol ethers derived either from five- or six-membered rings concurs with results obtained in chapter 5, and is in our opinion mainly due to steric factors (see chapter 5 for a discussion of these results).

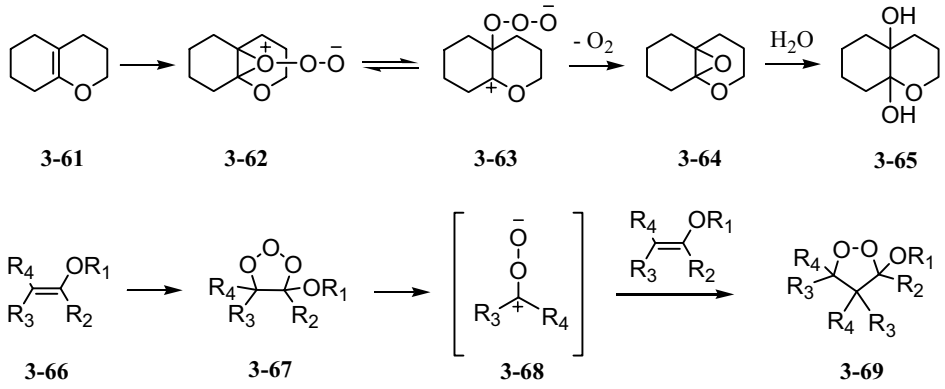
To enhance the yield of the carbocation addition reaction, several other Lewis acid catalysts ($BF_3.Et_2O$, $TrSbCl_6$, Tf_2O, MgI_2, TMSOTf, $ZnBr_2$) were compared with our results of the $LiClO_4$ reaction but did not give yield improvement ($ZnBr_2$ -comparable-, $TrSbCl_6$ -lower yield-), or did not

Scheme 11



yield the desired addition product ($BF_3.Et_2O$, Tf_2O, MgI_2, TMSOTf). In the latter case compounds like either triketone **3-34** ($BF_3.Et_2O$) or compound **3-49** (Tf_2O, TMSOTf), in which intramolecular acetal formation had taken place, could be identified as major products (see scheme 8 and figure 2). Finally, the use of $LiClO_4$ as catalyst in combination with the TBDMS group offered the best yield, giving the abovementioned 93% yield in the addition of **3-56** with **3-40** (scheme 11). The ozonolysis of compound **3-57** did however not give a very high yield, although 10% of the desired triketone could be isolated. Problems in ozonolysis reactions of enol ethers have been reported in literature and formation of different side products were mentioned[23-25]. Borowitz and Rapp, for example, mentioned the isolation of dihydroxy ethers due to formation of epoxy ether **3-64**, instead of the expected ozonide (scheme 12)[25]. This was attributed to the stabilising effect of the ether oxygen on the intermediate positive charge in **3-63**, leading to elimination of an oxygen molecule and formation of the epoxide ring. The neighbouring phenyl ring in our compound would even enhance this stabilising effect on the intermediate cation. Keul and co-workers mentioned the formation of side products due to intermolecular coupling of a peroxidic intermediate with free enol ether leading to 3-alkoxy-[1,2]-dioxolanes **3-69** (scheme 12)[24].

Scheme 12



We theorised then that a more rapid and easier synthesis of compound **3-15** might be possible *via* the addition of a carbocation derived from alcohol **3-58**, which can be synthesised easily by the Grignard addition of vinyl magnesium bromide and benzaldehyde[26]. Addition of such a carbocation to silyl enol ether **3-56**, followed by ozonolysis of the adduct should lead to **3-15** in a very short way.

Surprisingly when the reaction of **3-58** with **3-56** was tried, no addition could be observed and only hydrolysis of the silyl enol ether took place. Evaluating the differences between compounds **3-58** and **3-40** our attention was attracted to the presence of the ethoxy group in compound **3-40**. In the literature a successful addition of a similar reagent with an extra methoxy group in the phenyl ring

has also been reported[9]. To investigate the importance of the presence of an alkoxy group for the stabilisation of the carbocation intermediate in the reaction, compound **3-59**, obtained from *para*-anisaldehyde[27], was reacted with silyl enol ether **3-56**. This time a good 87% yield of the addition product was obtained. This result clearly outlines the importance of a good stabilisation in the carbocation intermediate when performing additions with silyl enol ethers.
Ozonolysis of compound **3-60** now led to steroid precursor **3-15** in 70% yield and in this way a short and efficient synthesis of Ziegler's triketone could be achieved in 61% overall yield from 6-methoxytetralone in only four steps.

In conclusion a short route to CD-*trans*-fused steroid and D-homo steroid skeletons has been developed. The key feature in this approach is the Mukaiyama-Michael reaction with transfer of the silyl group of the starting silyl enol ether to the enol of the product. This enables a second selective addition of a carbocation on the new enol ether. Although ring C could not be closed by aldol type reaction, ozonolysis of a suitably placed double bond in the intermediate gives access to Ziegler's triketone, which has been cyclised previously in literature in reasonable yield.

Experimental

General procedure for cationic addition catalysed by $LiClO_4$ (products 3-32, 3-41, 3-45 and 3-57).

2-[2-(3-Ethoxy-but-2-enyl)-2-methyl-3-oxo-cyclopentyl]-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (3-32)

A solution of silyl enol ether **3-30** (415 mg, 1.2 mmol) and $LiClO_4$ (370 mg, 3.5 mmol, which was previously dried at 90° C/20mm for 1h), in nitromethane (5 ml) was cooled to 5 °C and allyl alcohol **3-31**[13] (183 mg, 1.54 mmol) was added dropwise over a period of 2 hrs. The resulting solution was stirred for 3 hrs at room temperature, then water was added and organic phase was extracted with EtOAc, washed with brine, dried and evaporated. Separation by column chromatography on silica gel (PE:EtOAc 4:1, with 2% of pyridine) gave **3-32** (234 mg, 52%) as a colourless oil (mixture of 2 isomers 2:1). IR (film): 2975, 1738, 1668, 1601, 1252, 734; ^{1}H NMR ($CDCl_3$): 0.93 (*M*) & 0.97 (*m*)(s, 3H), 1.08 (*m*) & 1.18 (*M*) (t, J = 7.0, 3H), 1.54 (*m*) & 1.71 (*M*) (s, 3H), 1.50-2.40 (m, 9H), 2.45-3.05 (m, 3H), 3.30 (*m*) & 3.55 (*M*) (q, J = 7.0, 2H), 3.77 (s, 3H), 3.87 (*m*) & 4.13 (*M*) (t, J = 7.4, 1H), 6.61 (d, J = 2.4, 1H), 6.73 (dd, J_1 = 2.4 & J_2 = 8.8, 1H), 7.88 (*M*) & (7.91 (*m*) (d, J = 8.8, 1H); ^{13}C NMR ($CDCl_3$): 14.6 (q), 16.4 (*m*) & 16.6 (*M*) (q), 18.0 (q), 22.6 (*m*) & 23.1 (*M*) (t), 26.2 (*m*) & 27.9 (*M*) (t), 28.1 (t), 34.2 (*m*) & 36.3 (*M*) (t), 36.8 (*M*) & 37.1 (*m)* (t),

39.6 (*m*) & 42.6 (*M*) (d), 47.7 (*m*) & 48.9 (*M*) (d), 52.4 (*m*) & 53.0 (*M*) (s), 55.4 (q), 61.7 (*m*) & 62.0 (*M*) (t), 91.9 (*m*) & 92.2 (*M*) (d), 112.4 (d), 113.2 (d), 126.2 (*m*) & 126.4 (*M*) (s), 129.8 (*M*) & 130.2 (*m*) (d), 145.6 (*m*) & 145.9 (*M*) (s), 154.5 (s), 163.5 (s), 198.5 (s), 222.0 (*M*) & 222.9 (*m*) (s). HRMS: M^+, found 370.2141. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 3), 342 (8), 285 (5), 272 (25), 271 (9), 176 (97), 117 (16), 99 (100), 71 (34), 73 (13).

2-[2-(3-Ethoxy-3-phenyl-allyl)-5-isopropenyl-2-methyl-3-oxo-cyclohexyl]-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (3-41)

Yield: 18% (78% relative to reacted **3-39**), as two separate main isomers **3-41a** and **3-41b** and a small amount of an inseparable mixture of two minor isomers **3-41c** and **3-41d** (isomeric ratio **a:b:c:d** = 26.5:22:4:1). Next to the desired product were isolated: 77% of compound **3-39** and about 25% of unreacted **3-40,** together with approximately 2% of desilylated **3-39** and small amounts of unidentified products.

Isomer **3-41a**. IR (CCl_4 sol.) cm^{-1}: 2962, 2931, 2871, 1711, 1675, 1601, 1250; ^1H NMR ($CDCl_3$) ι: 0.76-3.15 (m, 13H), 1.01 (s, 3H), 1.30 (t, J = 7.0, 3H), 1.59 (s, 3H), 3.81 (dq obsc., J_1 = 2.3 & J_2 = 7.0, 2H), 3.84 (s obsc., 3H), 4.62 (s, 1H), 4.71 (dd, J_1 = 5.7 & J_2 = 8.3, 1H), 4.77 (s, 1H), 6.60 (d, J = 2.5, 1H), 6.82 (dd, J_1 = 2.5 & J_2 = 8.8, 1H), 7.10-7.43 (m, 5H), 8.01 (d, J = 8.8, 1H); ^{13}C NMR ($CDCl_3$) ι: 14.7 (q), 17.2 (q), 21.6 (q), 25.3 (t), 26.7 (t), 28.8 (t), 31.0 (t), 40.5 (d), 41.3 (d), 43.4 (t), 47.5 (d), 51.0 (s), 55.5 (q), 63.0 (d), 94.4 (d), 110.9 (t), 112.2 (d), 113.5 (d), 125.4 (s), 128.0 (2d), 128.1 (d), 128.7 (2d), 130.8 (d), 136.1 (s), 144.4 (s), 147.3 (s), 155.6 (s), 163.4 (s), 198.5 (s), 214.8 (s). HRMS: M^+, found 486.2771. $C_{32}H_{38}O_4$ requires 486.2770. MS *m/e* (%) 486 (M^+, 8), 457 (10), 440 (2), 336 (40), 335 (39), 308 (23), 179 (34), 161 (100), 133 (30), 105 (33), 55 (20).

Isomer **3-41b**. White crystals (mp. 119-123 ^oC, from hexane/ethyl acetate). IR (CCl_4 sol.) cm^{-1}: 2976, 2938, 2875, 1704, 1679, 1602, 1249; ^1H NMR ($CDCl_3$) ι: 1.06 (s, 3H), 1.26 (d, J = 7.2, 1H), 1.32 (t, J = 6.9, 3H), 1.62 (s, 3H), 1.60-3.25 (m, 12H), 3.80 (q obsc., J = 6.9, 2H), 3.84 (s obsc., 3H), 4.51 (dd, J_1 = 5.9 & J_2 = 9.3, 1H), 4.62 (s, 1H), 4.77 (s, 1H), 6.60 (d, J = 2.5, 1H), 6.82 (dd, J = 2.5 & J = 8.7, 1H), 7.05-7.55 (m, 5H), 7.99 (d, J = 8.7, 1H); ^{13}C NMR ($CDCl_3$) ι: 14.8 (q), 20.7 (q), 20.8 (q), 26.4 (t), 27.0 (t), 30.5 (t), 35.6 (t), 37.1 (d), 42.3 (d), 42.5 (t), 49.1 (d), 52.1 (s), 55.5 (q), 63.1 (d), 95.2 (d), 111.0 (t), 112.3 (d), 113.0 (d), 126.6 (s), 127.8 (2d), 127.9 (d), 129.0 (2d), 129.9 (d), 136.1 (s),145.8 (s), 147.5 (s), 156.4 (s), 163.2 (s), 197.3 (s), 216.0 (s). HRMS: M^+, found 486.2773. $C_{32}H_{38}O_4$ requires 486.2770. MS *m/e* (%) 486 (M^+, 2), 457 (1), 440 (1), 326 (4), 176 (100), 161 (26), 150 (10), 105 (8).

Mixture of isomers **3-41c** *and* **3-41d**. ^1H NMR ($CDCl_3$) ι: 0.77-3.30 (m, …H), 1.05 (*M*) & 1.32 (*m*) (t, J = 7.1, 3H), 1.17 (*m*) & 1.21 (*M*) (s, 3H), 1.61 (*m*) & 1.76 (*M*) (s, 3H), 3.56 (*M*, dq, J_1 = 5.3 & J_2

= 7.1) & (3.79 (*m*, q, *J* = 7.1) (2H), 3.83 (s, 3H), 4.50 (*m*, dd, J_1 = 5.7 & J_2 = 9.3) & 5.00 (*M*, t, *J* = 8.7) (1H), 4.61 (*m*) & 4.72 (*M*) (s, 1H), 4.80 (bs, 1H), 6.60 (*m*) & 6.66 (*M*) (d, *J* = 2.6, 1H), 6.80 (dd, *J* = 2.6 & *J* = 8.7, 1H), 7.03-7.65 (m, 5H), 7.97 (*M*) & 7.99 (*m*) (d, *J* = 8.7, 1H); ^{13}C NMR ($CDCl_3$) ι: 14.8 (*m*) & 15.4 (*M*) (q), 20.4 (*M*) & 20.7 (*m*) (q), 20.8 (q), 27.1 (t), 27.4 (t), 30.7 (t), 34.4 (*M*) & 35.4 (*m*) (t), 37.2 (*m*) & 38.8 (*M*) (d), 42.2 (*m*) & 42.5 (*M*) (d), 42.6 (t), 49.1 (*m*) & 49.7 (*M*) (d), 51.4 (*M*) & 52.0 (*m*) (s), 55.5 (q), 63.1 (*m*) & 65.6 (*M*) (t), 108.8 (d), 110.8 (t), 112.3 (d), 113.1 (d), 126.5 (s), 126.6 (d), 127.9 (d), 128.2 (2d), 128.9 (d), 130.0 (d), 136.2 (s), 145.9 (s), 147.5 (s), 155.7 (s), 163.3 (s), 197.5 (s), 216.3 (s).

2-[5-Isopropenyl-2-(3-methoxy-allyl)-2-methyl-3-oxo-cyclohexyl]-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (3-45)

Yield: 10.5% (13% relative to reacted **3-39**), as a mixture of 2 isomers (2:3). Next to the desired product **3-45** a few other compounds could be isolated and identified: 8% of compound **3-48**, 3.5% of compound **3-49** and 9.5% of compound **3-50**, 29% desilylated **3-39** and 20% **3-39**.

3-45. IR (CCl_4 sol.) cm^{-1}: 2956, 2938, 2869, 2839, 1707, 1678, 1601, 1250; ^{1}H NMR (C_6D_6) ι: 0.85-3.02 (m, 10H), 0.94 (s, 3H), 1.13 (d, *J* = 6.7, 2H), 1.45 (*m*) & 1.63 (*M*) (s, 3H), 3.23 (s, 3H), 3.26 (s, 3H), 3.38-3.54 (m, 1H), 4.75 (dt, J_1 = 7.8 & J_2 = 12.6, 1H), 4.86 (s, 1H), 4.89 (*M*) & 4.94 (*m*) (s, 1H), 6.35 (d, *J* = 12.6, 1H), 6.40-6.69 (m, 3H), 8.25 (d, *J* = 8.6, 1H); ^{13}C NMR (C_6D_6) ι: 13.0 (*M*) & 21.8 (*m*) (q), 20.8 (*M*) & 20.9 (*m*) (q), 26.5 (*M*) & 26.7 (*m*) (t), 27.0 (*M*) & 29.4 (*m*) (t), 29.4 (*m*) & 30.1 (*M*) (t), 35.1 (*M*) & 40.5 (*m*) (d), 35.6 (t), 41.6 (*M*) & 47.8 (*m*) (d), 42.5 (*M*) & 44.0 (*m*) (t), 48.4 (*m*) & 48.7 (*M*) (d), 51.8 (s), 54.6 (q), 55.1 (q), 97.1 (d), 111.4 (*M*) & 112.6 (*m*) (t), 112.7 (2d), 129.8 (*m*) & 130.1 (*M*) (d), 130.1 (s), 145.7 (s), 146.5 (s), 147.1 (s), 149.7 (d), 163.3 (s), 196.0 (*M*) & 196.8 (*m*) (s), 210.4 (*m*) & 213.1 (*M*) (s). HRMS: M^+, found 396.2307. $C_{25}H_{32}O_4$ requires 396.2301. MS *m/e* (%) 396 (M^+, 2), 364 (2), 326 (6), 325 (5), 176 (100), 161 (6), 150 (15), 71 (13).

3-48. ^{1}H NMR (C_6D_6) ι: 0.41 (s, 3H), 0.46 (s, 3H), 1.04 (s, 9H), 1.15 (s, 3H), 1.57 (s, 3H), 1.40-2.80 (m, 12H), 3.22 (s, 3H), 3.34 (s, 3H), 4.65-4.85 (m, 3H), 6.38 (m, 1H), 6.67-6.77 (m, 2H), 7.75 (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: -2.4 (2q), 18.1 (s), 18.9 (q), 20.7 (q), 25.9 (3q), 26.6 (t), 28.6 (t), 28.9 (t), 31.9 (t), 38.1 (d), 39.7 (s), 41.5 (t), 42.8 (d), 54.6 (q), 55.4 (q), 97.3 (d), 104.4 (s), 106.3 (s), 109.3 (t), 110.7 (d), 114.2 (d), 122.3 (d), 124.2 (s), 138.0 (s), 144.5 (S), 148.2 (s), 149.2 (d), 159.2 (s). MS *m/e* (%) 510 (22), 495 (8), 453 (10), 437 (94), 335 (19), 263 (70), 237 (30), 202 (24), 176 (17), 73 (88), 71 (100).

3-49 (see below for data).

3-50. 2 isomers (2:1); ^{1}H NMR (C_6D_6) ι: 0.19 (s, 3H), 0.31 (*m*) & 0.35 (*M*) (s, 3H), 0.75-2.40 (m,

18H), 0.92 (*m*) & 0.95 (*M*) (s, 3H), 1.04 (*m*) & 1.07 (*M*) (s, 3H), 1.59 (*m*) & 1.63 (*M*) (s, 3H), 1.71 (*M*) & 1.76 (*m*) (s, 3H), 2.50-2.80 (m, 1H), 3.28 (s, 3H), 3.31 (*M*) & 3.40 (*m*) (s, 3H), 3.65-3.87 (m, 1H), 4.67 (*m*) & 4.74 (*M*) (s, 1H), 4.79 (*m*) & 4.83 (*M*) (s, 1H), 6.38-6.53 (m, 2H), 6.59 (dd, J_1 = 2.5 & J_2 = 8.7, 1H), 8.18 (*M*) & 8.19 (*m*) (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: -1.3 (q), -1.2 (q), 14.3 (q), 18.6 (s), 19.8 (*m*) & 20.4 (*M*) (q), 20.5 (*M*) & 20.6 (*m*) (q), 25.2 (*m*) & 25.4 (*M*) (t), 25.7 (*M*) & 25.9 (*m*) (t), 26.1 (3q), 28.2 (*M*) & 28.6 (*m*) (t), 32.2 (*m*) & 32.3 (*M*) (t), 33.9 (*m*) & 34.2 (*M*) (t), 38.4 (2d), 38.4 (*M*) & 38.6 (*m*) (d), 47.6 (s), 50.7 (*m*) & 51.1 (*M*) (d), 54.7 (q), 56.0 (*M*) & 56.6 (*m*) (q), 77.6 (*m*) & 77.9 (*M*) (s), 96.9 (*m*) & 97.8 (*M*) (d), 108.4 (*M*) & 109.0 (*m*) (t), 112.8 (d), 112.9 (d), 126.2 (*m*) & 126.4 (*M*) (s), 130.7 (d), 144.3 (*M*) & 144.4 (*m*) (s), 149.4 (*m*) & 149.9 (*M*) (s), 163.2 (s), 169.7 (*M*) & 170.4 (*m*) (s), 198.7 (*M*) & 198.8 (*m*) (s). HRMS: $[M\text{-}t\text{Bu}]^+$, found 513.2672. $C_{29}H_{41}SiO_6$ requires 513.2672. MS *m/e* (%) 539 ($[M\text{-MeO}]^+$, 0.6), 513 ($[M\text{-}t\text{Bu}]^+$, 14), 510 ($[M\text{-HOAc}]^+$, 4), 485 ($[M\text{-}t\text{Bu-CO}]^+$, 4), 453 ($[M\text{-}t\text{Bu-HOAc}]^+$, 16), 439 (20), 379 (98), 267 (100), 239 (59), 117 (57), 60 (5), 43 (10).

2-[2-(3-Ethoxy-3-phenyl-allyl)-2-methyl-3-oxo-cyclopentyl]-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (3-57)

Yield: 93%, as a mixture of isomers (5:1, NMR determination). IR (CCl_4 sol.) cm^{-1}: 2976, 2937, 2840, 1737, 1679, 1602, 1249; ^{1}H NMR (C_6D_6) ι: 0.91 (*M*) & 0.97 (*m*) (s, 3H), 1.09 (t, *J* = 6.9, 3H), 1.10-2.65 (m, 12H), 3.24 (*m*) & 3.26 (*M*) (s, 3H), 3.61 (q, *J* = 6.9, 2H), 4.75 (*M*) & 5.21 (*m*) (t, *J* = 7.5, 1H), 6.45 (*M*) & 6.49 (*m*) (d, *J* = 2.5, 1H), 6.57 (*m*) & 6.61 (*M*) (dd, J_1 = 2.5 & J_2 = 8.7, 1H), 6.95-7.25 (m, 3H), 7.35-7.55 (m, 2H), 8.17 (*m*) & 8.20 (*M*) (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 14.6 (*M*) & 15.3 (*m*) (q), 17.6 (*M*) & 17.8 (*m*) (q), 21.3 (*M*) & 23.3 (*m*) (t), 26.0 (*M*) & 27.4 (*m*) (t), 27.9 (*m*) & 28.8 (*M*) (t), 34.9 (t), 36.4 (*M*) & 36.7 (*m*) (t), 40.3 (*M*) & 42.9 (*m*) (d), 47.9 (*M*) & 49.0 (*m*) (d), 51.9 (*M*) & 52.4 (*m*) (s), 54.7 (q), 62.9 (*M*) & 63.0 (*m*) (t), 95.6 (M) & 96.6 (*m*) (d), 112.7 (d), 112.8 (d), 126.5 (*m*) & 127.9 (*M*) (2d), 126.8 (*M*) & 127.1 (*m*) (s), 128.1 (*M*) & 128.3 (*m*) (d), 129.2 (d), 129.4 (d), 129.9 (*m*) & 130.1 (*M*) (d), 136.8 (s), 145.6 (*M*) & 145.7 (*m*) (s), 156.7 (*m*) & 157.2 (*M*) (s), 163.3 (s), 163.5 (s), 196.6 (*M*) & 197.3 (*m*) (s), 219.7 (*m*) & 220.2 (*M*) (s). HRMS: M^+, found 432.2309. $C_{28}H_{32}O_4$ requires 432.2301. MS *m/e* (%) 432 (M^+, 2.5), 403 (1), 271 (3), 176 (8), 161 (100), 133 (25), 105 (9), 55 (10).

2-(2'-(3''-ethoxy-3''-methyl-4''-nitrobutyl)-2'-methyl-3'-oxocyclopentyl)-6-methoxy-3,4-dihydro-2*H*naphalene-1-one (3-33)

To a solution of ethyl enol ether **3-32** (140 mg, 0.38 mmol) in nitromethane (5 ml) at –5 °C was added $LiClO_4$ (2.13 g, 20 mmol, previously dried for 1 hr at 90 °C/20mm). The reaction mixture

was stirred for 48 hrs at room temperature, then water (5 ml) and EtOAc (20 ml) were added and the layers separated. The water phase was extracted once with EtOAc (10 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 6:4) yielding **3-33** as a clear oil in 33% yield (54 mg), next to compound **3-34** (28%, 36 mg).

3-32. IR (film): 2977, 1731 (CO), 1672 (CO), 1650, 1600, 1551, 1252, 732; ^{1}H NMR: 0.99 (s, 3H), 1.00-1.12 (m, 4H), 1.27 (s, 3H), 1.30-2.50 (m, 10H), 2.55-2.73 (m, 1H), 2.85-3.05 (m, 2H), 3.37 (q, J = 7.0, 2H), 3.82 (s, 3H), 4.42 (m, 2H), 6.66 (d, J = 2.6, 1H), 6.78 (dd, J_1 = 2.6 & J_2 = 8.6, 1H), 7.91 (d, J = 8.6, 1H); ^{13}C NMR: 15.5 (q), 17.8 and 18.0 (q), 21.4 and 21.6 (q), 23.0 (t), 27.7 (t), 27.9 (t), 28.1 and 28.3 (t), 31.4 and 31.6 (t), 36.6 (t), 42.7 and 43.1 (d), 48.7 (d), 51.5 (s), 55.4 (q), 57.3 (t), 75.4 and 75.6 (s), 80.3 and 80.7 (d), 112.3 (d), 113.4 (d), 126.2 (s), 129.8 (d), 145.9 (s), 163.6 (s), 198.3 and 198.4 (s), 221.7 and 221.8 (s).

2-(2'-methyl-3'-oxo-2'-(3''-oxobutyl)-cyclopentyl)-6-methoxy-3,4-dihydro-2*H*naphalene-1-one (3-34) IR (film): 2941, 1732 (CO), 1714 (CO), 1667 (CO), 1600, 1252; ^{1}H NMR: 0.92 (s, 3H), 2.06 (s, 3H), 2.92 (t, J = 6, 2H), 3.77 (s, 3H), 6.61 (d, J = 2.4, 1H), 6.73 (dd, J = 2.4 & J = 8.3, 1H), 7.88 (d, J = 8.3, 1H); ^{13}C NMR: 17.2 (q), 22.6 (t), 28.0 (t), 28.4 (t), 30.1 (q), 32.0 (t), 36.3 (t), 38.5 (t), 44.7 (d), 49.0 (d), 50.9 (s), 55.4 (q), 112.4 (d), 113.3 (d), 126.3 (s), 129.8 (d), 145.9 (s), 163.6 (s), 198.3 (s), 208.2 (s), 221.4 (s).

2-(7'a-methyl-5'-oxo-1',2',3',6',7',7'a-hexahydroindenyl)-6-methoxy-3,4 -dihydro-2*H*-naphalene-1-one (3-35)

The main isomer of ethyl enol ether **3-32** (229 mg, 0.62 mmol) was dissolved in dichloromethane (6 ml) and a 1M solution of Et_2AlCl in hexane (0.7 ml) was added at -70 ^{o}C. The solution was stirred for 30 min at indicated temperature and then for another 30 min at room temperature. 1M HCl solution was added and the reaction mixture was diluted with Et_2O, washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated. Column chromatography (PE:EtOAc 4:1, with 2% of pyridine) afforded 95 mg **3-35** (47%) and 43 mg of **3-36** (20%),

3-35. IR (KBr) cm^{-1}: 2960, 2940, 2879, 2863, 1669, 1598, 1348, 1256; ^{1}H NMR ($CDCl_3$): 1.18 (s, 3H), 2.85 (dt, J_1 = 4.5 & J_2 = 17.5, 2H), 3.12 (m, 2H), 3.82 (s, 3H), 5.72 (s, 1H), 6.66 (d, J = 2.4, 1H), 6.80 (dd, J_1 = 2.4 & J_2 = 8.8, 1H), 7.91 (d, J = 8.8, 1H); ^{13}C NMR ($CDCl_3$): 16.4 (q), 26.1 (t), 26.6 (t), 26.9 (t), 29.0 (t), 33.5 (t), 36.6 (t), 45.3 (s), 47.0 (d), 47.9 (d), 55.5 (q), 112.4 (d), 113.4 (d), 121.8 (d), 125.9 (s), 130.0 (d), 145.4 (s), 157.3 (s), 163.5 (s), 178.8 (s), 198.7 (s), 198.8 (s). HRMS: M^+, found 324.1723. $C_{21}H_{24}O_3$ requires 324.1725. MS *m/e* (%) 324 (M^+, 10), 202 (5), 176 (100), 175 (13), 161 (7), 148 (15), 121 (8), 91 (7).

2-(5-Ethoxy-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-1-yl)-6-methoxy-3,4-dihydro-2H-

naphthalen-1-one (3-36). IR (film): 2964, 2939, 1668, 1600, 1259, 732; ^{1}H NMR ($CDCl_3$): 0.98 (s, 3H), 1.30 (t, J = 7, 3H), 1.66 (dt, J_1 = 5.8 & J_2 = 12.2, 2H), 2.40 (m, 2H), 2.78 (m, 2H), 3.15 (m, 1H), 3.76 (m, 2H), 3.82 (s, 3H), 5.11 (br s, 1H), 5.26 (d, J = 1.4, 1H), 6.66 (d, J = 2.4, 1H), 6.78 (dd, J_1 = 2.4 & J_2 = 8.6, 1H), 7.91 (d, J 8.6, 1H); ^{13}C NMR ($CDCl_3$): 14.6 (q), 15.5 (q), 25.7 (t), 26.2 (t), 26.4 (t), 35.6 (t), 35.9 (t), 45.9 (s), 46.7 (d), 47.8 (d), 55.4 (q), 62.4 (t), 93.7 (d), 112.4 (d), 113.2 (d), 116.5 (d), 126.1 (s), 129.9 (d), 145.7 (s), 147.5 (s), 157.3 (s), 163.3 (s), 199.9 (s).

_E_-2-(3'-hydroxy-2'-(3''-ethoxybut-2''-enyl)-2'-methylcyclopentyl)-6-methoxy-3,4 -dihydro-2_H_-naphalene-1-one (3-37)

The main isomer of ethyl enol ether **3-32** (117 mg, 0.31 mmol) was dissolved in THF (7 ml) and the solution was refluxed for 36 hrs. During this period (tBuO)$_3$LiAlH (190 mg, 0.75 mmol) was added in two portions. Then the solution was cooled on ice, treated with EtOAc (2ml), a saturated solution of K_2CO_3 (0.5 ml) and filtered over a short plug of Na_2SO_4. After removal of the solvent, column chromatography (PE:EtOAc 4:1, with 5% of Et_3N) afforded alcohol **3-37** as essentially one isomer (92 mg, 79%). IR (film): 3400 (OH), 2940, 1650, 1585, 1264, 740; ^{1}H NMR: 0.92 (s, 3H), 1.18 (t, J = 7.0, 3H), 1.73 (s, 3H), 2.56 (m, 1H), 2.92 (m, 2H), 3.55 (q, J = 7.0, 2H), 3.77 (m, 1H), 3.77 (obsc. s, 3H), 4.38 (t, J = 7.8, 1H), 6.60 (d, J = 2.4, 1H), 6.73 (dd, J_1 = 2.4 & J_2 = 8.8, 1H), 7.89 (d, J = 8.8, 1H); ^{13}C NMR: 14.6 (q), 15.2 (q), 16.5 (q), 25.0 (t), 28.5 (t), 29.8 (t), 31.0 (t), 39.7 (t), 46.0 (d), 48.3 (d), 48.6 (s), 55.3 (q), 61.8 (t), 79.5 (d), 93.0 (d), 112.2 (d), 113.0 (d), 126.6 (s), 129.9 (d), 146.0 (s), 154.0 (s), 163.4 (s), 200.0 (s). HRMS: M^+, found 372.2296. $C_{23}H_{32}O_4$ requires 372.2301. MS *m/e* (%) 372 (M^+, 5), 326 (14), 178 (28), 176 (100), 99 (46), 71 (20), 43 (13).

2-(2-Ethoxy-2,4a-dimethyl-octahydro-cyclopenta[b]pyran-5-yl)-6-methoxy-3,4-dihydro-2_H_-naphthalen-1-one (3-38)

Compound **3-37** (82 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (20 ml) and 1M solution of Et_2AlCl in hexane (0.24 ml) was added at -70 ^{o}C. The reaction mixture was stirred for 1 hr at this temperature and then 1M HCl solution was added and the reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (PE:EtOAc 4:1) afforded **3-38** (46 mg, 56%) as a thick oil. IR (film) cm^{-1}: 2948, 1673, 1600, 1271. ^{1}H NMR ($CDCl_3$) ι: 0.87 (s, 3H), 1.12 (t, J = 7.2, 3H), 1.10-3.23 (m, 14H), 3.40 (q, J = 7.2, 2H), 3.55 (d, J = 5.5, 1H), 3.83 (s, 3H), 6.64 (d, J = 2.5, 1H), 6.79 (dd, J_1 = 2.5 & J_2 = 8.7, 1H), 7.87 (d, J = 8.7, 1H); ^{13}C NMR ($CDCl_3$) ι: 11.4 (q), 15.9 (q), 21.3 (t), 21.8 (q), 24.1 (t), 24.8 (t), 29.3 (t), 29.4 (t), 36.1 (t), 39.6 (s), 42.6 (d), 44.8 (d), 55.2 (q), 56.1 (t), 80.6 (d), 101.2 (s), 112.4 (d), 113.1 (d), 131.2 (s), 131.2 (d), 142.5 (s), 163.6 (s), 205.9 (s).

HRMS: M^+, found 372.2310. $C_{23}H_{32}O_4$ requires 372.2301. MS *m/e* (%) 372 (M^+, 0.5), 344 (1), 326 (42), 189 (8), 176 (100), 175 (16), 148 (9), 137 (8), 109 (7).

3-Ethoxy-3-phenyl-prop-2-en-1-ol (3-40)

Ethylbenzoylacetate (19.2 g, 100 mmol) en triethylorthoformate (14.8 g, 100 mmol) were stirred at room temperature and 5 drops of conc. H_2SO_4 were added. The reaction mixture was left to stir overnight after which ethanol and ethylformate were removed under reduced pressure. The residue was purified by distillation (135 ^oC, 2 Torr), yielding 17.9 g of a colourless oil. This product was dissolved in Et_2O (50 ml) and added dropwise, at 0 ^oC, to a suspension of lithium aluminum hydride ($LiAlH_4$, 2.94 g, 77.5 mmol) in Et_2O (300 ml). The reaction mixture was stirred for 5 hrs at room temperature, until TLC showed no remaining starting material. The excess of $LiAlH_4$ was destroyed by addition of water (3.9 ml), 4M NaOH solution (3.9 ml) and again water (11.7 ml). The white precipitate was filtered off and washed carefully with Et_2O (100 ml). The filtrate was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (PE:Et_2O 2:1) yielded **3-40** as a colourless oil in 37% overall yield (6.66 g, mixture of 2 isomers *E:Z*[28] 3:2). IR (CCl_4 sol.) cm^{-1}: 3621, 3479 (br), 3062, 3028, 2981, 2932, 2881, 1645, 1231, 1134, 989; ^1H NMR ($CDCl_3$) ι: 1.26 (*m*, t, *J* = 7.0) & 1.36 (*M*, t, *J* = 6.9) (3H), 1.88 (*M*) & 2.30 (*m*) (bs, 1H), 3.73 (*m*, q, *J* = 7.0) & 3.87 (*M*, q, *J* = 6.9) (2H), 4.13 (*M*, d, *J* = 7.7) & 4.38 (*m*, d, *J* = 6.7) (2H), 4.98 (*M*, t, *J* = 7.7) & 5.49 (*m*, t, *J* = 6.7) (1H), 7.10-7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) ι: 14.6 (*M*) & 15.2 (*m*) (q), 57.6 (*m*) & 59.6 (*M*) (t), 63.2 (*M*) & 66.3 (*m*) (t), 99.1 (*M*) & 113.1 (*m*) (d), 126.3 (d), 127.1 (d), 128.0 (d), 128.4 (d), 128.6 (d), 135.5 (s), 155.7 (*m*) & 158.7 (*M*) (s). HRMS: M^+, found 178.0987. $C_{11}H_{14}O_2$ requires 178.0994. MS *m/e* (%) 178 (M^+, 19), 177 (6), 149 (13), 135 (28), 105 (100), 103 (14), 91 (12), 77 (29).

Reaction sequence to ether 3-43 and acetal 3-47

Ether 3-43

Compound **3-41b** (100 mg, 0.21 mmol) was dissolved in THF (7 ml) and $Li(tBuO)_3AlH$ (104 mg, 0.42 mmol) was added in two portions (2nd portion after 1 hr reaction time). The reaction mixture was refluxed during 3 hrs and then the solution was cooled on ice, treated with EtOAc (2ml), 1M $NaHSO_4$ solution (0.5 ml) and filtered over a short plug of Na_2SO_4. The solvent was evaporated and the residue was dissolved in DMSO (2 ml) and cooled on ice before pulverised KOH (47 mg, 0.84 mmol) was added. After stirring for 5 min, MeI (26 σl, 0.42 mmol) was added and stirring was continued for 2 hrs at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and solvent removed under reduced

pressure. Column chromatography (PE:EtOAc 3:1) afforded compound **3-43** (22 mg, 23%) and compound **3-42** (48 mg, 46%), which rapidly isomerised to **3-43** upon evaporation of the solvent, next to some remaining starting material **3-41b**. ^{1}H NMR (C_6D_6) ι: 1.01 (s, 3H), 1.50-2.70 (m, 10H), 1.65 (s, 3H), 3.15-3.30 (m, 1H), 3.43 (s, 6H), 4.18 (dd, J_1= 4.2 & J_2= 11.9, 1H), 5.02 (s, 1H), 5.07 (s, 1H), 5.35 (dd, J_1= 2.4 & J_2= 5.7, 1H), 6.77 (dd, J_1= 2.6 & J_2= 8.4, 1H), 6.85 (d, J= 2.6,1H), 7.05-7.35 (m, 3H), 7.43 (d, J_1= 8.4, 1H), 7.79 (d, J_1= 9.7, 2H); ^{13}C NMR (C_6D_6) ι: 12.9 (q), 22.6 (q), 26.9 (t), 28.5 (t), 29.3 (2t), 36.5 (t), 37.0 (s), 38.9 (d), 39.0 (d), 54.6 (q), 58.8 (q), 77.4 (d), 97.0 (d), 111.1 (d), 111.3 (t), 113.8 (d), 122.4 (s), 123.8 (d), 124.5 (2d), 127.5 (2d), 128.4 (d), 136.3 (s), 139.4 (s), 146.1 (2s), 149.9 (s),150.6 (s), 159.1 (s). HRMS: M^+, found 456.2658. $C_{31}H_{36}O_3$ requires 456.2664. MS *m/e* (%) 456 (M^+, 100), 441 (26), 308 (23), 269 (17), 216 (28), 105 (35).

Acetal 3-47

Yield: 37%. IR (CCl_4 sol.) cm^{-1}: 2937, 2833, 1649, 1607, 1496, 1449, 1252, 1039; ^{1}H NMR (C_6D_6) ι: 0.93 (s, 3H), 1.70 (s, 3H), 1.34-2.62 (m, 12H), 3.10-3.35 (m, 1H), 3.24 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.92 (dd, J_1 = 3.9 & J_2 = 11.7, 1H), 5.03 (s, 1H), 5.08 (s, 1H), 5.24 (dt, J_1 = 7.8 & J_2 = 12.7, 1H), 6.31 (d, J = 12.6, 1H), 6.69 (dd, J_1 = 2.5 & J_2 = 8.4, 1H), 6.77 (d, J = 2.5, 1H), 7.33 (d, J = 8.4, 1H); ^{13}C NMR (C_6D_6) ι: 13.8 (q), 22.7 (q), 25.1 (t), 29.2 (t), 29.4 (t), 32.5 (t), 36.5 (d), 37.8 (t), 39.0 (d), 43.5 (s), 54.6 (q), 55.2 (q), 58.7 (q), 70.8 (d), 100.1 (d), 110.7 (t), 111.1 (d), 113.6 (d), 123.7 (d), 124.3 (s), 124.6 (s), 139.3 (s), 147.1 (s), 148.4 (d), 149.6 (s), 159.0 (s). HRMS: M^+, found 412.2612. $C_{26}H_{36}O_4$ requires 412.2614. MS *m/e* (%) 412 (M^+, 100), 380 (17), 269 (40), 216 (48), 203 (64), 190 (64), 75 (33), 71 (25).

Ether 3-49

Silyl enol ether **3-39** (883 mg, 2 mmol) and allyl alcohol **3-40** (356 mg, 2 mmol) were dissolved in CH_2Cl_2 (10 ml) and cooled to –78 ^{o}C. Trifluoromethanesulfonic anhydride (Tf_2O, 0.17 ml, 1 mmol) was added and the reaction mixture was stirred for 15 min at –78 ^{o}C. Pyridine was added to quench the catalyst and the reaction mixture was warmed to room temperature. Et_2O (20 ml) was added and the reaction mixture was washed with a saturated $NaHCO_3$ solution (15 ml) and brine (15 ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 4:1) yielding **3-49** as a colourless oil (60%, 531 mg). ^{1}H NMR: 0.20 (s, 3H), 0.33 (s, 3H), 0.96 (s, 9H), 1.18 (d, J = 7.1, 3H), 1.20-2.92 (m, 11H), 1.86 (s, 3H), 3.82 (s, 3H), 4.72 (s, 2H), 6.68 (d, J = 2.6, 1H), 6.72 (dd, J_1 = 2.6 & J_2 = 8.7, 1H), 7.45 (d, J = 8.7, 1H); ^{13}C NMR: -2.6 (q), -2.2 (q), 13.4 (q), 18.1 (s), 21.0 (q), 26.0 (3q), 26.3 (t), 27.1 (t), 28.9

(t), 38.0 (d), 38.9 9d), 40.3 (t), 40.8 (d), 55.2 (q), 103.3 (s), 109.0 (t), 109.2 (s), 110.6 (d), 113.6 (d), 122.2 (d), 124.4 (s), 138.1 (s), 144.3 (s), 148.9 (s), 158.6 (s). HRMS: M^+, found 440.2742. $C_{27}H_{40}O_3Si$ requires 440.2747. MS *m/e* (%) 440 (M^+, 43), 383 (53), 264 (100), 202 (18), 176 (14), 75 (18), 73 (27).

6-Methoxy-2-[2-methyl-3-oxo-2-(3-phenyl-allyl)-cyclopentyl]-3,4-dihydro-2H-naphthalen-1-one (3-60)

Silyl enol ether **3-56** (774 mg, 2 mmol) and 1-(4-methoxy-phenyl)-prop-2-en-1-ol **3-59**[27] (164 mg, 1 mmol) were dissolved in CH_2Cl_2 (10 ml) and cooled to –5 °C. $ZnBr_2$ (a few crystals, appr. 60 mg) was added as the catalyst and the reaction mixture was stirred for 5 hrs at –5 to 0 °C, and then left to stand overnight at 4 °C. EtOAc (10 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution (10 ml) and brine (10 ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 9:1) yielding compound **3-60** as a clear oil in 87% (363 mg), which crystallised upon standing. IR (KBr) cm^{-1}: 2952, 2931, 2839, 1737, 1672, 1599, 1511, 1248, 1028; ^1H NMR (C_6D_6) ι: 0.75-1.15 (m, 1H), 1.17 (s, 3H), 1.50-2.95 (m, 11H), 3.31 (s, 3H), 3.35 (s, 3H), 5.80-6.10 (m, 2H), 6.50 (d, J = 2.5, 1H), 6.67 (dd, J_1 = 2.5 & J_2 = 8.7, 1H), 6.72 (d, J = 8.8, 2H), 7.03 (d, J = 8.8, 2H), 8.32 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 18.2 (q), 23.3 (t), 25.6 (t), 26.3 (t), 36.6 (t), 38.9 (d), 39.7 (t), 47.4 (d), 52.0 (s), 54.5 (q), 54.7 (q), 112.9 (d), 113.0 (d), 113.9 (2d), 123.5 (d), 126.7 (s), 127.3 92d), 130.4 (d), 130.5 (s), 133.3 (d), 145.5 (s), 159.2 (s), 163.5 (s), 197.8 (s), 220.3 (s). HRMS: M^+, found 418.2148. $C_{27}H_{30}O_4$ requires 418.2144. MS *m/e* (%) 418 (M^+, 16), 271 (5), 176 (16), 147 (100), 121 (5), 91 (4).

[2-(6-Methoxy-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-1-methyl-5-oxo-cyclopentyl]-acetaldehyde (3-15)

A solution of **3-60** (210 mg, 0.502 mmol) in 6.5 ml of CH_2Cl_2 and 26 ml of MeOH was cooled to –78 °C, and ozone was bubbled through the reaction mixture until the solution turned blue (15 min). The mixture was then purged with nitrogen for 15 min at –78 °C and treated with 0.6 eq. of thiourea (23 mg). The cold bath was removed and the reaction mixture was allowed to stir at room temperature for 1 hr. The solvents were evaporated and the crude mixture was purified by column chromatography, yielding 110 mg of **3-15** (70%) as white crystals which were recrystallised from tBuOMe (mp. 110-112 °C; lit.[5] 108-110 °C from Et_2O). IR (KBr) cm^{-1}: 2934, 2818, 2718, 1739, 1718, 1668, 1597, 1263; ^1H NMR (C_6D_6) ι: 1.07 (s, 3H), 1.50-1.75 (m, 2H), 1.95-3.15 (m, 10H), 3.82 (s, 3H), 6.64 (d, J = 2.5, 1H), 6.79 (dd, J = 2.5 & J = 8.7, 1H), 7.89 (d, J = 8.7, 1H), 9.33 (s,

1H); ^{13}C NMR (C_6D_6) ι: 17.7 (q), 24.1 (t), 26.1 (t), 26.7 (t), 35.7 (t), 39.6 (d), 46.9 (d), 48.6 (s), 50.3 (t), 55.4 (q), 112.4 (d), 113.5 (d), 125.6 (s), 129.7 (d), 145.6 (s), 163.6 (s), 200.0 (s), 200.0 (s), 221.4 (s). HRMS: M^+, found 314.1521. $C_{19}H_{22}O_4$ requires 314.1518. MS *m/e* (%) 314 (M^+, 13), 286 (8), 271 (8), 242 (5), 229 (17), 202 (4), 176 (100), 161 (6), 148 (13). Data are in accordance with literature values[5].

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28. Assignment according to 1H-NMR shifts of allylic proton due to influence of adjacent phenyl group.

A new and short synthesis of C,D-*cis* fused steroid and D-homosteroid skeletons

Chapter 4

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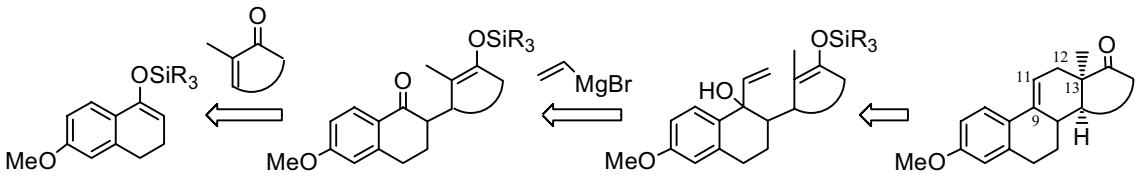
4.1 Introduction

In the preceding chapters an efficient Mukaiyama addition reaction[1-4] has been described, which led to selectively protected compounds **4-2** in high yields. This chemistry involved a Mukaiyama-Michael reaction, accompanied by transfer of the silyl group of the enol ether of 6-methoxytetralone to the carbonyl group of the receiving enone, i.e. (*R*)-(-)-carvone or 2-methyl-2-cyclopentenone (scheme 1)[5-14]. In these chapters, we have investigated the possibilities of using these compounds for the total synthesis of steroids *via* carbocation addition to the silyl enol ether function, forming the C12-C13 bond first, and closure of the C9-C11 bond in ring C as the final step. This research led to a short and efficient synthesis of a known intermediate for the synthesis of *trans*-fused steroid skeletons (see chapter 3, scheme 11)[15-18].

Owing to the selective protection of its carbonyl groups, compound **4-2** could however also lend itself for another approach. Instead of a reaction on the enol ether moiety a selective reaction on the free ketone can also be carried out. In this way the C9-C11 bond is formed first and C12-C13 bond formation would become the final step in closure of ring C.

The conceived strategy relies on a selective Grignard reaction of vinyl magnesium bromide with the unprotected carbonyl group of 6-methoxytetralone, leading to a Torgov type intermediate. This compound should then be converted into a carbocation, which in turn should react *intramolecularly* with the silyl enol ether moiety, closing ring C and thus completing the synthesis of the (homo) steroid skeleton (scheme 1).

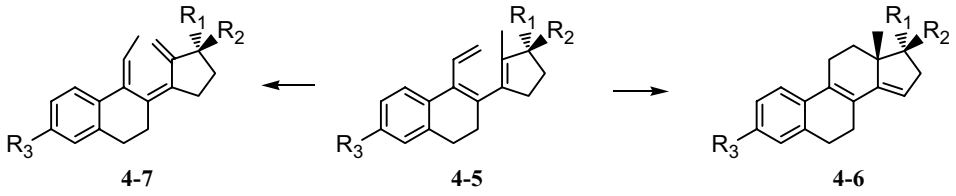
Scheme 1



4-1 **4-2** **4-3** **4-4**

To the best of our knowledge only one method has been published on steroid total synthesis in which the construction the C12-C13 bond is the final step in the closure of ring C. As was also mentioned in chapter 1, Gilchrist and co-workers used an electrocyclic ring closure to construct ring C (scheme 2 and chapter 1, scheme 20)[19-22]. After cyclisation and isomerisation of the double bonds under acidic conditions steroidal diene **4-6** was obtained which led to known estrone derivatives upon further oxidation or deprotection to the ketone on C17 and reduction of the double bonds. When, in the cyclisation reaction, the compound was used in which R_1R_2 was the unprotected ketone, which should lead directly to the estrone derivatives, the electrocyclic ring closure did not take place and instead compound **4-7** was isolated as the result of a [1,7] hydrogen shift.

Scheme 2



4-7 R_1R_2 = =O; R_3 = H

4-5 R_1R_2 = =O; R_3 = H; R_1R_2 = SCH_2CH_2S; R_3 = H; R_1R_2 = OH, H; R_3 = H; R_1R_2 = OH, H; R_3 = OMe

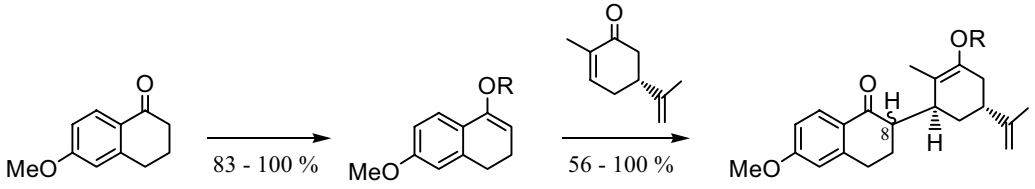
4-6 R_1R_2 = SCH_2CH_2S; R_3 = H; R_1R_2 = OH, H (diast. mix.); R_3 = H or OMe

In our approach, stereoselectivity can be introduced using carvone as starting material. D-homo steroids will then be obtained as end products but handles are available in ring D for ring-contraction to a normal steroid skeleton. Moreover, the D-homo steroids may also have interesting biological properties. Since both enantiomers of carvone are available from nature, it is possible to determine the configuration of C14 by choosing the correct enantiomer as starting material, thus making the normal *14ζ*-D-homo steroids and their *14η*-isomers accessible. The $\div^{9,11}$ double bond in the ring-closed products allows an easy functionalisation of C11.

4.2 Synthesis of D-homo steroid skeletons with CD-*cis* fusion

In chapter 2 was shown that the Mukaiyama-Michael reaction of 6-methoxy-1-tetralone with (*R*)-(-)-carvone led to diastereomeric mixtures of adducts, which differ in configuration at C8, and in which the stereoselectivity was dependent on the nature of the starting silyl enol ether (see scheme 3 and chapter 2, scheme 9).

Scheme 3



4-8

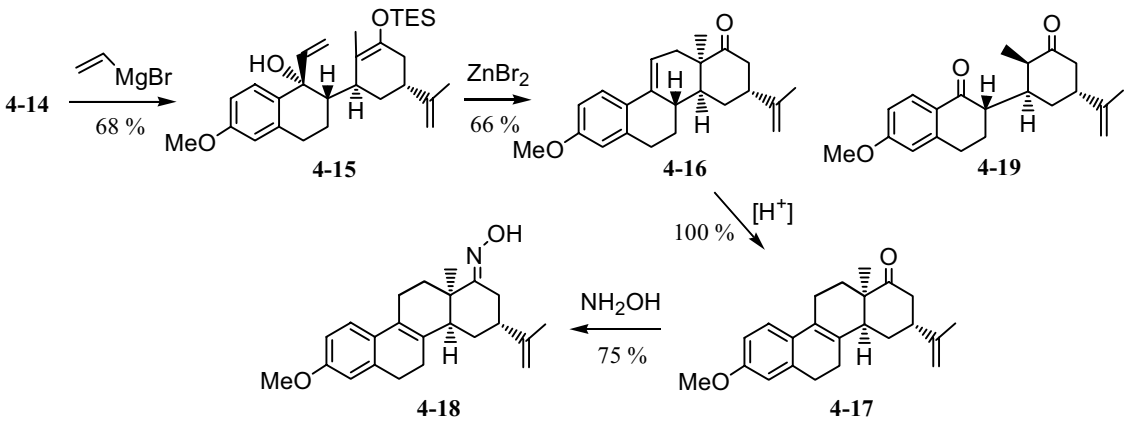
4-9 R = TMS
4-10 R = TBDMS
4-11 R = TES

R = TMS **4-12a : 4-12b** = 3 : 2
R = TBDMS **4-13a : 4-13b** = 4 : 1
R = TES **4-14a : 4-14b** = 7 : 1

Since the diastereomeric mixtures of the TMS and TBDMS enol ether products **4-12** and **4-13** could be separated only with difficulties or not at all, further reactions were first carried out with the pure major diastereomer of TES enol ether **4-14** (see scheme 4). The addition of vinyl magnesium bromide to **4-14** proceeded in a reasonable 70 % yield to give only one stereoisomer of the adduct **4-15**, which tentatively was assigned the indicated configuration[20]. About 10% of non-converted

starting material could be recovered. Complete conversion of **4-14** proved to be difficult to achieve, probably because of competing enolisation. Unfortunately enol ether **4-14** and adduct **4-15** could not be separated by column chromatography in our hands. Therefore cyclisation of the mixture of **4-15** and **4-14** with $ZnBr_2$[23,24] was undertaken and went smoothly to give **4-16** in good yield, together with the desilylated diketone **4-19**. In a separate reaction it was shown that desilylation of **4-14** to **4-19** indeed takes place with $ZnBr_2$ under the applied reaction conditions.

Scheme 4

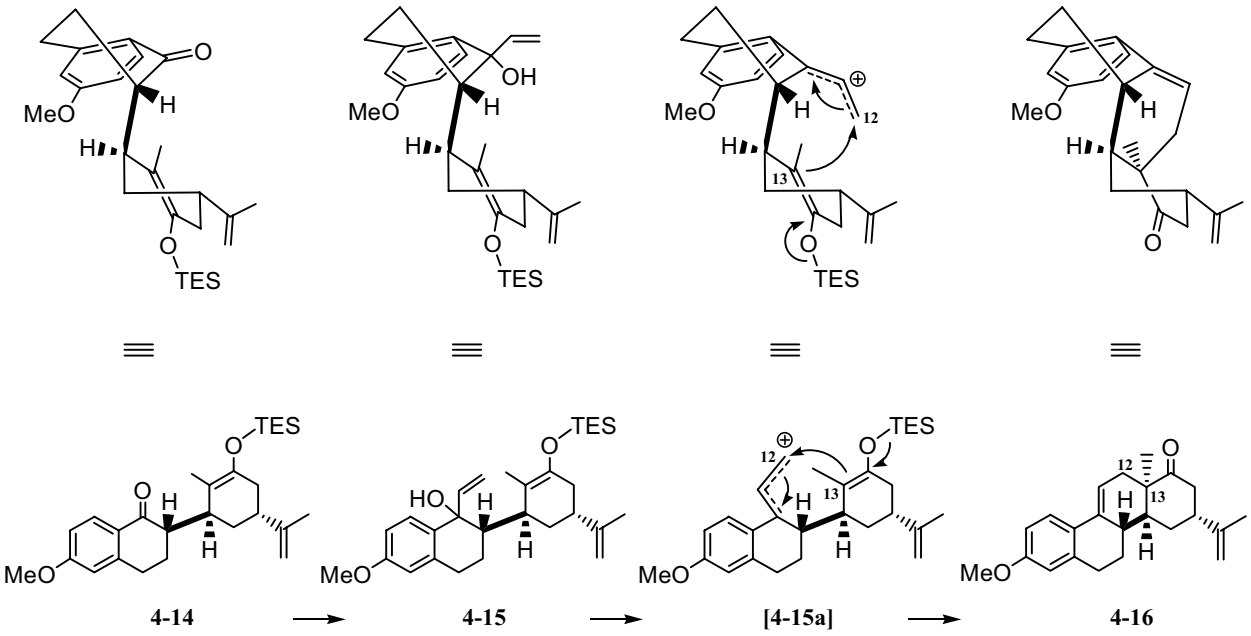


The yield of the vinyl magnesium bromide addition could be improved by repeating the addition twice or three times after workup and drying of the mixture of **4-14** and **4-15**. This worked well for the TES and TBDMS silyl enol ethers because these are stable compounds. The TMS silyl enol ether is less stable and some decomposition leading to desilylated product **4-19** and its stereoisomers, was observed.

The cyclisation of pure **4-15** with $ZnBr_2$ proceeded in 66% yield, and in this way D-homo steroid **4-16** was obtained as an enantiopure product in just four steps starting from 6-methoxytetralone in 40% overall yield. It is known that the $\div^{9,11}$ double bond in steroids like **4-16** can be isomerised easily by treatment with mild acid[25]. This indeed proved to be the case and also **4-16** could be converted smoothly into its $\div^{8,9}$ isomer **4-17** by treatment with hydrochloric acid at room temperature in quantitative yield. All compounds were obtained as oils, but the oxime **4-18**, derived from **4-17**, could be obtained in crystalline form, so an X-ray became possible (see appendix for crystal structure)[26]. In this way the stereochemistry of **4-18** was determined unambiguously, and turned out to be as indicated in scheme 4. This stereochemistry can be explained by a selective approach of the bulky TES enol ether **4-11** to (*R*)-(-)-carvone from the top face, opposite to the isopropenyl group. The carvone substituent ends up in the favourable axial position next to the carbonyl group in the tetralone portion of the molecule and consequently the addition of vinyl

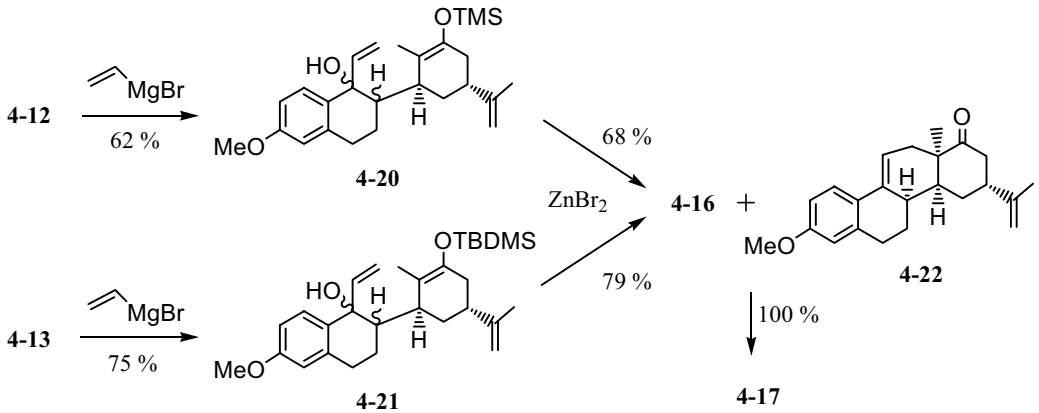
magnesium bromide occurs from the top face[20]. Closure of ring C in this system is then only possible *via* approach of the carbocation from the side leading to *cis* fusion between rings C and D in the steroid skeleton (see figure 1). This is also in accordance with results mentioned in literature on annelation reactions using a carbocation addition to a silyl enol ether and leading to *cis* fusion of the rings[27].

Figure 1



The reaction of the mixture of TMS enol ethers **4-12** with vinyl magnesium bromide gave again a mixture of two diastereomers of adduct **4-20** in reasonable yield, and in a similar way the mixture of **4-13** could be converted into **4-21** in a good 75% yield (see scheme 5). The ratio of the diastereomers varied slightly with the enol ether that was used, and again the reaction was not

Scheme 5



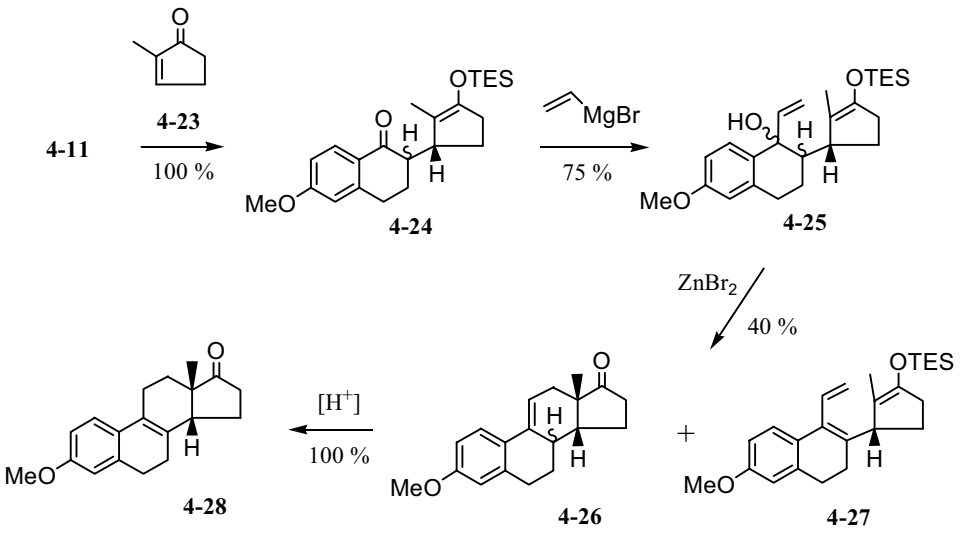
complete after one run but also here a good yield could be achieved by performing several repetitions of the reaction without purification of the intermediate mixtures. The ratio of the recovered silyl enol ethers **4-12** and **4-13** and the ratio of the corresponding adducts **4-20** and **4-21**, respectively, differed from that of the starting mixture of silyl enol ethers **4-12** and **4-13**, which can be explained either by different rates of enolisation and reprotonation of the enols, or by different rates of adduct formation.

The adducts **4-20** and **4-21** could be cyclised to a mixture of **4-16** and its C8 epimer **4-22** with $ZnBr_2$. The fact that the two compounds in the mixture were epimeric at C8 was proven by acid catalysed isomerisation of the mixture to single compound **4-17**.

4.3 Synthesis of a natural steroid skeleton with unnatural CD-*cis* fusion

To obtain a steroid skeleton with a five-membered D-ring, the reaction sequence was repeated using 2-methyl-2-cyclopentenone as the accepting enone in the Mukaiyama reaction. The reactions were performed with silyl enol ether **4-11** and also here the Mukaiyama-Michael reaction gave diastereomeric mixtures of the new silyl enol ether **4-24**. The addition of vinyl magnesium bromide went smoothly and again the reaction was not complete after one run. A good yield could be achieved by performing several repetitions of the reaction without purification of the intermediate mixtures.

Scheme 6



The cyclisation of the adduct **4-25** with $ZnBr_2$ gave a lower yield of the cyclised diastereomeric mixture of the steroid skeleton **4-26**, dehydration to compound **4-27** being a major side reaction. Finally acid catalysed isomerisation of the mixture of **4-26** gave known racemic **4-28**[28] in about 30% overall yield starting from **4-10**.

Experimental

(1*R*)-6-methoxy-2-{2-methyl-3-[(triethylsilyl)oxy]-2cyclopenten-1-yl}-3,4-dihydro-1(2H)-naphthalenone (4-24)

To a solution of triethylsilylenol ether **4-11** (2.03 g, 7 mmol) and 2-methyl-2-cyclopentenone (0.5 g, 5.25 mmol) in CH_2C1_2 (30 ml), at –78 ^oC, was added $TrSbC1_6$ (0.03 g, 0.07 mmol). After 1 hr some drops of pyridine were added to destroy the catalyst, and the yellow colour of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. Compound **4-24** was obtained as a mixture of two diastereomers in a 3:2 ratio in 100% yield (2.02 g, colourless oil). IR (CCl_4) cm^{-1}: 2957, 2877, 1679, 1601, 1250; ^{1}H NMR ι: 0.62 (m, 6H), 0.94 (m, 9H), 1.29 (*m*) & 1.51 (*M*) (s, 3H), 1.30 – 2.35 (m, 6H), 2.53 – 2.65 (m, 1H), 2.86 –2.92 (m, 2H), 3.43 – 3.70 (m, 1H), 3.81 (s, 3H), 6.65 (d, J = 2.2, 1H), 6.77 (dd, J_1 = 8.8 & J_2 = 2.2, 1H), 7.98 (dd, J_1 = 8.8 & J_2 = 2.2, 1H); ^{13}C NMR (*main isomer*) ι: 5.4 (3t), 6.7 (3q), 10.0 (q), 22.4 (t), 22.9 (t), 29.9 (t), 33.2 (t), 43.9 (d), 49.7 (d), 55.3 (q), 112.3 (d), 112.8 (s), 112.9 (d), 127.0 (s), 129.6 (d), 146.8 (s), 148.1 (s), 163.3 (s), 198.9 (s); (*minor isomer*): 5.4 (3t), 6.7 (3q), 11.7 (q), 23.6 (t), 25.0 (t), 29.8 (t), 32.9 (t), 43.3 (d), 52.1 (d), 55.3 (q), 112.4 (d), 113.0 (d), 113.9 (s), 126.5 (s), 129.9 (d), 146.5 (s), 148.3 (s), 163.3 (s), 197.8 (s). HRMS: M^+, found 386.2273. $C_{23}H_{34}O_3Si$ requires 386.2277. MS *m/e* (%) 386 (M^+, 8), 290 (10), 270 (12), 211 (100), 176 (27), 87 (15).

General reaction procedure for the addition of vinyl magnesium bromide (1*R*,2*S*)-2-{(1*R*,5*S*)-5-isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (4-15)

To a solution of vinylmagnesium bromide in THF (1M, 15 mmol), at 0 ^oC, was added slowly a solution of the diastereomeric mixture of **4-14** (1.16 g, 3 mmol) in THF (15 ml). The reaction mixture was stirred under these conditions for 1hr and at the room temperature for 4-5 hrs. Then saturated NH_4Cl solution (25 ml) was added and the mixture was extracted with EtOAc (3 x 75ml). The organic extracts were dried (Na_2SO_4) and the solvent was evaporated. This residue was treated again with vinyl magnesium bromide (1M, 10 mmol) as described above and worked up in a similar way. This procedure was repeated once more and then the residue was purified by column chromatography (PE: EtOAc grad.) to give 0.95 g of **4-15** (68%) as a colourless oil. IR (CCl_4) cm^{-1}: 3616, 2957, 2914, 2878, 1677, 1604, 1575, 1498, 1460, 1245, 1177; ^{1}H NMR ι: 0.69 (q, J = 7.9, 6H), 1.00 (t, J = 7.8, 9H), 1.56 (s, 3H), 1.72 (s, 3H), 1.50-2.85 (m, 11H), 3.77 (s, 3H), 4.69 (d, J = 5.2, 2H), 5.40 (dd, J_1 = 10.2 & J_2 = 2.3, 1H), 5.62 (dd, J_1 = 17.1 & J_2 = 2.4, 1H), 5.84 (dd, J_1 = 17.1

& J_2 = 10.2, 1H), 6.61 (d, J = 2.4, 1H), 6.71 (dd, J_1 = 8.7 & J_2 = 2.4, 1H), 7.29 (d, J = 8.7, 1H); ^{13}C NMR ι: 5.4 (3t), 6.6 (3q), 14.2 (q), 19.9 (t), 20.8 (q), 28.9 (t), 31.0 (t), 34.3 (t), 37.5 (d), 38.3 (d), 43.7 (d), 55.0 (q), 104.8 (s), 108.3 (t), 112.2 (d), 112.6 (d), 113.1 (s), 113.6 (t), 129.2 (d), 133.8 (s), 137.9 (s), 143.6 (d), 144.5 (s), 148.9 (s), 158.6 (s). HRMS: M^+, found 468.3062. $C_{29}H_{44}O_3Si$ requires 468.3060. MS *m/e* (%) 468 (M^+, 4.5); 450 (10); 336 (10); 265 (100); 115 (6); 87 (17).

2-{(1*R*,5*S*)-5-isopropenyl-2-methyl-3-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (4-20)

Yield: 62%, as a mixture of 2 isomers in a 3:2 ratio. IR (CCl_4) cm^{-1}: 3617, 2936, 1678, 1643, 1607, 1499, 1277, 1175; ^{1}H NMR ι: 0.20 (s, 9H), 1.63 (*M*) & 1.64 (*m*) (s, 3H), 1.70 (*M*) & 1.72 (*m*) (s, 3H), 1.40-2.85 (m, 11H), 3.77 (s, 3H), 4.69 (d, J = 5.6, 2H), 5.35 (*M,* dd, J_1 = 10.3 & J_2 = 2.4) & 5.39 (*m*, dd, J = 9.8, 2.4) (1H), 5.62 (dd, J_1 = 17.1 & J_1 = 2.4, 1H); 5.81 (*M*, dd, J_1 = 17.1 & J_2 = 10.3) & 5.84 (*m*, dd, J_1 = 17.1 & J_2 = 9.8, 1H), 6.62 (br s, 1H), 6.72 (dd, J_1 = 8.6 & J_2 = 2.4, 1H), 7.29 (m, 1H); ^{13}C NMR (*main isomer*) ι: 0.9 (3q), 14.6 (q), 20.0 (t), 21.1 (q), 29.1 (t),31.3 (t), 34.6 (t), 37.7 (d), 38.8 (d), 43.9 (d), 55.2 (q), 76.8 (s), 108.6 (t), 112.5 (d), 113.4 (d), 113.8 (t), 114.4 (s), 129.5 (d), 134.1 (s), 138.2 (s), 143.8 (d), 144.7 (s), 149.0 (s), 158.9 (s); (*minor isomer*) 0.8 (3q), 17.4 (q), 20.4 (q), 23.4 (t), 31.3 (t), 35.5 (t), 37.1 (d), 37.9 (t), 38.0 (d), 49.8 (d), 55.2 (q), 75.3 (s), 108.9 (t), 112.6 (d), 113.1 (d), 113.4 (s), 113.5 (t), 130.4 (d), 132.6 (s), 138.4 (s), 143.5 (d), 144.5 (s), 149.5 (s), 158.9 (s). HRMS: M^+, found 426.2590. $C_{26}H_{38}O_3Si$ requires 426.2590. MS *m/e* (%) 426 (M^+, 51), 411 (5), 408 (10), 281 (24), 223 (100), 186 (31), 73 (28).

2-{(1*R*,5*S*)-5-isopropenyl-2-methyl-3-[(dimethyl-*tert*-butylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (4-21)

Yield: 75%, as a mixture of 2 isomers in a 5:1 ratio. IR (CCl_4) cm^{-1}: 3617, 2931, 2859, 1676, 1607, 1558, 1256, 1167; ^{1}H NMR ι: 0.15 (s, 6H), 0.97 (s, 9H), 1.55 (*m*) & 1.58 (*M*) (s, 3H), 1.71 (*m*) & 1.74 (*M*) (s, 3H), 1.80 – 2.95 (m, 11H), 3.77 (s, 3H), 4.68 (*m*) & 4.72 (*M*) (d, J = 6.3, 2H), 5.35 (*m*) & 5.41 (*M*) (dd, J_1 = 10.2 & J_2 = 2.2, 1H), 5.63 (dd, J_1 = 17.1 & J_2 = 2.2, 1H), 5.82 (*m*) & 5.85 (*M*) (dd, J_1 = 17.1 & J_2 = 10.2, 1H), 6.61 (d, J = 2.6, 1H), 6.72 (dd, J_1 = 8.6 & J_2 = 2.6, 1H), 7.27 (*M*) & 7.30 (*m*) (d, J = 8.6, 1H); ^{13}C NMR (*main isomer*) ι: -3.6 (2q), 14.7 (q), 18.3 (s), 20.0 (t), 21.1 (q), 25.9 (3q), 29.1 (t), 31.3 (t), 34.8 (t), 37.8 (d), 38.9 (d), 43.9 (d), 55.2 (q), 76.8 (s), 108.6 (t), 112.5 (d), 112.9 (s), 113.3 (d), 113.8 (t), 129.5 (d), 134.1 (s), 138.2 (s), 143.8 (d), 144.7 (s), 149.1 (s), 158.8 (s); (*minor isomer*): -4.3 (s), 17.2 (q), 17.5 (s), 22.1 (q), 23.4 (t), 25.9 (3q), 27.8 (t), 31.3 (t), 35.6 (t), 37.3 (d), 38.1 (d), 43.6 (d), 55.4 (q), 75.3 (s), 108.9 (t), 111.9 (t), 112.6 (d), 113.2 (d), 130.4 (d), 132.7 (s), 138.4 (s), 143.6 (d), 148.8 (s), 149.5 (s), 155.0 (s). HRMS: M^+, found 468.3066.

$C_{29}H_{44}O_3Si$ requires 468.3060. MS *m/e* (%) 468 (M^+, 3), 450 (11), 336 (12), 265 (100), 263 (27), 223 (7), 186 (11), 75 (14), 73 (48).

(1*R*)-6-methoxy-2-{(1R)-2-methyl-3-[(triethylsilyl)oxy]-2-cyclopenten-1-yl}-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (4-25)

Yield: 75%, as a diastereomeric mixture (ratio 10:1). IR (CCl_4) cm^{-1}: 3617, 2956, 2876, 1609, 1498, 1240; (*main isomer*) ^{1}H NMR ι: 0.68 (q, *J* = 7.9, 6H), 1.00 (t, *J* = 7.9, 9H), 1.47 (s, 3H), 1.50 – 1.91 (m, 4H), 2.21 – 2.26 (m, 2H), 2.7 – 2.95 (m, 4H), 3.76 (s, 3H), 5,35 (dd, J_1 = 10.4 & J_2 = 2.2, 1H), 5.58 (dd, J_1 = 17.1 & J_2 = 2.2, 1H), 5.80 (dd, J_1 = 17.1 & J_1 = 10.4, 1H), 6.60 (d, *J* = 2.2, 1H), 6.71 (dd, J_1 = 8.6 & J_2 = 2.2, 1H), 7.28 (d, *J* = 8.6, 1H). ^{13}C NMR ι: 5.4 (3t), 6.7 (3q), 10.1 (q), 18.1 (t), 22.6 (t), 31.0 (t), 33.7 (t), 44.0 (d), 44.1 (d), 55.2 (q), 76.4 (s), 112.5 (d), 113.2 (d), 113.4 (t), 114.4 (s), 130.1 (d), 133.3 (s), 138.6 (s), 144.4 (d), 147.7 (s), 158.7 (s); (*minor isomer*) ^{1}H NMR ι: 0.65 (q, *J* = 7.9, 6H), 0.99 (t, *J* = 8.0, 9H), 1.63 (s, 3H), 1.40–2.9 (m, 10H), 3.77 (s, 3H), 5.30 (dd, J_1 = 10.4 & J_2 = 1.8, 1H), 5.50 (dd, J_1 = 17.1 & J_2 = 10.4, 1H), 5.84 (dd, J_1 = 17.1 & J_2 = 10.4, 1H), 6.60 (d, *J* = 2.6, 1H), 6.71 (dd, J_1 = 8.6 & J_2 = 2.6, 1H), 7.30 (d, *J* = 8.6, 1H); ^{13}C NMR ι: 6.3 (3t), 7.1 (3q), 13.1 (q), 21.5 (t), 25.3 (t), 31.1 (t), 32.5 (t), 43.9 (d), 50.4 (d), 55.2 (q), 75.4 (s), 111.6 (d), 112.6 (d), 113.0 (t), 115.5 (s), 130.2 (d), 133.0 (s), 138.4 (s), 144.7 (d), 149.0 (s), 158.7 (s). HRMS: M^+, found 414.2590. $C_{25}H_{38}O_3Si$ requires 414.2590. MS *m/e* (%) 414 (M^+, 8), 385 (7), 300 (8), 227 (11), 211 (16), 186 (100), 176 (11), 171 (6).

General procedure for closure of ring C

(3*R*,4a*S*,4b*S*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (4-16)

To a solution of compound **4-15** (0.47 g, 1 mmol) in dry CH_2C1_2 (20 ml), under nitrogen and at –78 ^oC, was added $ZnBr_2$ (0.22 g, 1 mmol). The reaction mixture was stirred for 1 hr at this temperature and then allowed to warm to room temperature. The solution became clear and green. After 2 hrs the mixture was poured into 50 ml of saturated $NaHCO_3$ solution. The layers were separated and the aqueous solution was washed with CH_2Cl_2 (3 x 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed over silica gel (PE: EtOAc 9:1) to give 0.22 g of **4-16** *(*66%) as a colourless oil. IR (CCl_4) cm^{-1}: 2935, 2837, 1711, 1644, 1608, 1571, 1234, 1177; ^{1}H NMR ι: 1.35 (s, 3H), 1.82 (s, 3H), 1.65-2.85 (m, 13H), 3.76 (s, 3H), 4.81 (s, 2H), 6.11 (m, 1H), 6.56 (d, *J* = 2.6, 1H), 6.71 (dd, J_1 = 8.6 & J_2 = 2.4, 1H), 7.50 (d, *J* = 8.6, 1H); ^{13}C NMR ι: 20.6 (q), 26.8 (t), 27.1 (q), 29.2 (t), 30.4 (t), 33.2 (t), 36.0 (d), 41.3 (d), 41.7

(t), 46.7 (d), 47.1 (s), 55.2 (q), 109.9 (t), 112.5 (d), 112.9 (d), 116.6 (d), 125.2 (d), 127.9 (s), 133.5 (s), 136.8 (s), 147.6 (s), 158.4 (s), 213.3 (s). HRMS: M^+, found 336.2096. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100), 321 (11), 239 (14), 225 (29), 187 (17), 186 (44), 174 (14).

(3*R*,4a*S*,4b*S*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (4-16) and (3*R*,4a*S*,4b*R*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (4-22)

Yield from **4-20**: 68%, as a 1:1 mixture of **4-16** and **4-22**.

Yield from **4-21**: 72%, as a 5:3 mixture of **4-16** and **4-22**.^{1}H NMR ι (**4-16** + **4-22**): 1.15 & 1.35 (s, 3H), 1.74 & 1.78 (s, 3H), 1.68 – 2.90 (m, 13H), 3.76 & 3.78 (s, 3H), 4.68 & 4.88 (s, 1H), 4.80 (s, 2H), 6.09 & 6.17 (m, 1H), 6.58 (dd, J_1 = 10.0 & J_2 = 2.6, 1H), 6.69 & 6.73 (dd, J_1 = 8.6 & J_2 = 2.6, 1H), 7.48 & 7.59 (d, J = 8.6, 1H); ^{13}C NMR ι:(**4-22**) 19.6 (q), 22.1 (q), 23.8 (t), 27.4 (t), 31.2 (t), 32.7 (t), 35.3 (d), 39.9 (d), 39.9 (d), 40.6 (t), 47.7 (s), 55.2 (q), 112.5 (t), 112.8 (d), 113.4 (d), 123.2 (d), 124.3 (d), 126.6 (s), 131.9 (s), 138.1 (s), 146.9 (s), 158.4 (s), 215.5 (s). HRMS: M^+, found 336.2083. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100), 239 (18), 225 (30), 224 (19), 187 (33), 186 (57), 171 (16).

3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (4-26)

Yield: 40%, as a diastereomeric mixture (ratio 4:1), white crystals (mp 94-95^{0}C from EtOAc/ pentane). IR (CCl_4) cm^{-1}: 2961, 2934, 2836, 1742, 1608, 1499, 1252; ^{1}H NMR ι: 1.09 (s, 3H), 1.4 – 2.4 (m, 10H), 2.84 (m, 2H), 3.77 (*M*) & 3.79 (*m*) (s, 3H), 6.06 (*M*) & 6.11 (*m*) (m, 1H), 6.60 (d, J = 2.1, 1H), 6.70 (dd, J_1 = 8.6 & J_2 = 2.7, 1H), 7.45 (*M*) & 7.55 (*m*) (d, J = 8.6, 1 H); ^{13}C NMR ι: 23.0 (q), 25.1 (t), 29.7 (t), 29.8 (t), 30.6 (t), 34.7 (t), 37.9 (d), 47.2 (s), 47.9 (d), 55.2 (q), 112.6 (d), 113.1 (d), 115.5 (d), 124.9 (d), 128.2 (s), 135.2 (s), 137.5 (s), 158.6 (s), 221.7 (s). HRMS: M^+, found 282.1618. $C_{19}H_{22}O_2$ requires 282.1620. MS *m/e* (%) 282 (M^+, 100), 267 (16), 225 (24), 186 (51).

General procedure for migration of double bond in ring C

(3*R*,4a*S*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,5,6,11,12,12a-octahydro-1(2H)-chrysenone (4-17)

Compound **4-16** (0.08 g, 0.24 mmol) was stirred in a 5:1 solution of MeOH/ 10N HCl (12 ml) for 1hr. The MeOH was removed and the remaining aqueous suspension was diluted with 12 ml NaH_2PO_4 buffer (pH = 4) and extracted with EtOAc (3 x 30 ml). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to give 0.08 g (100%) of **4-17** as a colourless oil.

For mixtures of compounds **4-16** and **4-22** (5:3 or 1:1) a similar procedure was followed leading to pure **4-17** in 100% yield.

IR (CCl_4) cm^{-1}: 2937, 2834, 1705, 1608, 1500, 1283; ^1H NMR ι: 1.19 (s, 3H), 1.74 (s, 3H), 2.05-2.73 (m, 14H), 3.78 (s, 3H), 4.68 (s, 1H), 4.80 (s, 1H), 6.69 (s, 1H), 6.73 (d, *J* = 8.2, 1H), 7.10 (d, *J* = 8.1, 1H); ^{13}C NMR ι: 21.1 (q), 22.9 (t), 24.5 (q), 26.6 (t), 28.9 (t), 30.3 (t), 40.1 (d), 43.1 (t), 45.9 (d), 47.1 (s), 55.3 (q), 110.6 (t), 110.9 (d), 113.2 (d), 123.2 (d), 128.2 (s), 129.5 (s), 131.5 (s), 136.9 (s), 147.3 (s), 158.1 (s), 215.6 (s). HRMS: M^+, found 336.2090. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100), 321 (16), 240 (18), 239 (16), 226 (36), 225 (43), 211 (14), 150 (10).

3-methoxyestra-1(10),2,4,8-tetraen-17-one (4-28)[25]

Yield: 100% of the racemic mixture of **4-28** as white crystals, mp 85-87 ^oC (from EtOAc/ pentane), lit.[25] mp 88-90^{0}C (from Et_2O/ hexane). IR (CCl_4) cm^{-1}: 2935, 2835, 1740, 1608, 1500, 1251; ^1H NMR ι: 1.07 (s, 3H), 1.51 (m, 1H), 1.77 (m, 2H), 2.05 – 2.39 (m, 8H), 2.71 (t, *J* = 8.2, 2H), 3.79 (s, 3H), 6.69 (s, 1H), 6.71 (d, *J* = 7.4, 1H), 7.10 (d, *J* = 7.4, 1H); ^{13}C NMR ι: 20.6 (q), 21.9 (t), 25.5 (t), 26.9 (t), 27.5 (t), 28.9 (t), 36.8 (t), 47.2 (s), 48.6 (d), 55.3 (q), 110.9 (d), 113.5 (d), 123.1 (d), 126.4 (s), 129.0 (s), 131.8 (s), 137.1 (s), 158.1 (s), 223.4 (s). HRMS: M^+, found 282.1620. $C_{19}H_{22}O_2$ requires 282.1620. MS *m/e* (%) 282 (M^+, 100), 254 (7), 226 (25), 225 (20), 211 (9).

(1*E*,3*R*,4a*S*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,5,6,11,12,12a-octahydro-1(2H)-chrysenone oxime (4-18)

To a stirred solution of **4-17** (0.67 g, 2.0 mmol) in EtOH was added hydroxylamine hydrohloride (1.39 g, 20 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol) in several portions. The suspension was refluxed until TLC showed the reaction to be complete (30 min). The mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (100 ml) and washed with water (3 x 30 ml). Drying (Na_2SO_4), removal of the solvent under reduced pressure, and column chromatography (PE: EtOAc 9:1) provided 0.53 g (75%) of **4-18** as white crystals, mp 112 ∀C (from hexane/ Et_2O). IR (CCl_4) cm^{-1}: 3602, 3267, 3086, 2936, 2833, 1645, 1608, 1573, 1500, 1284; ^1H NMR ι: 1.24 (s, 3H), 1.55 (m, 1H), 1.77 (s, 3H), 1.93 (t, *J* = 5.8, 2H), 2.23 (m, 6H), 2.74 (m, 5H), 3.81 (s, 3H), 4.80 (s, 2H), 6.73 (m, 2H), 7.15 (d, *J* = 8.0, 1H), 9.20 (br s, 1H); ^{13}C NMR ι: 21.4 (q), 22.9 (t), 25.5 (t), 25.9 (q), 26.8 (t), 28.9 (t), 29.3 (t), 31.4 (t), 38.6 (d), 39.1 (s), 45.2 (d), 55.2 (q), 110.2 (t), 110.9 (d), 113.2 (d), 123.0 (d), 127.0 (s), 129.4 (s), 132.1 (s), 136.9 (s), 147.3 (s), 157.9 (s), 163.9 (s). HRMS: M^+, found 351.2191. $C_{23}H_{29}NO_2$ requires 351.2198. MS *m/e* (%) 351 (M^+, 100), 334 (57), 306 (4), 226 (12), 225 (19), 143 (16).

(2*S*)-2-[(1*R*,5*R*)-isopropenyl-2-methyl-3-oxocyclohexyl]-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (4-19)

A suspension of enol ether **4-14** (0.22 g, 0.5 mmol) and $ZnBr_2$ (0.11 g, 0.5 mmol) in dry CH_2C1_2 (15 ml), under nitrogen and at –78°C, was stirred for 1 hr. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 2.5 hrs the mixture was poured into 25 ml of saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was washed with CH_2Cl_2 (3 x 30 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed over silica gel (PE: EtOAc 4:1) to give 0.168 g (100%) of diketone **4-19** as 2 isomers in 15:1 ratio (white crystals, mp 118-119 °C, from hexane/Et_2O, *main isomer*). *Main isomer*: IR (CCl_4) cm^{-1}: 2938, 1712, 1678, 1601, 1476, 1252, 1177; ^1H NMR ι: 1.02 (d, *J* = 6.5, 3H), 1.50-1.72 (m, 1H), 1.80 (s, 3H), 1.82-2.71 (m, 9H), 2.93-2.98 (m, 2H), 3.81 (s, 3H), 4.73 (s, 1H), 4.89 (s, 1H), 6.66 (d, *J* = 2.4, 1H), 6.77 (dd, *J* = 8.6, 2.4, 1H), 7.96 (d, *J* = 8.6, 1H); ^{13}C NMR ι: 11.7 (q), 22.0 (q), 22.8 (t), 28.9 (t), 29.9 (t), 37.5 (d), 40.7 (d), 44.6 (t), 46.7 (d), 48.7 (d), 55.4 (q), 112.4 (d), 112.5 (t), 113.1 (d), 126.7 (s), 129.8 (d), 146.1 (s), 146.5 (s), 163.5 (s), 197.4 (s), 212.5 (s). HRMS: M^+, found 326.1879. $C_{21}H_{26}O_3$ requires 326.1882. MS *m/e* (%) 326 (M^+, 6), 176 (100), 161 (4), 150 (15), 135 (3).

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A second new and short synthesis of trans-fused steroid skeletons

Chapter 5

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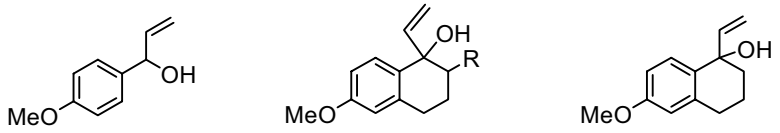
5.1. Introduction

In the preceding chapters 3 and 4 it was shown that stabilised carbocations derived from precursors **5-1** and **5-2** (figure 1) can be generated under conditions that are compatible with the presence of silyl enol ethers.

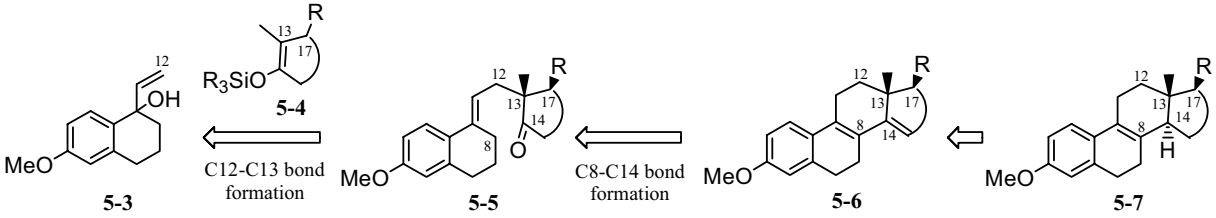
Figure 1



5-1 **5-2** **5-3**

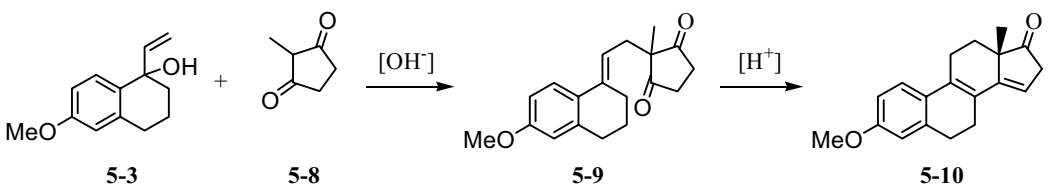
Based on this experience it was anticipated that a second approach to CD-*trans*-fused (D-homo) steroid skeletons could be developed using a Lewis acid catalysed reaction of the Torgov reagent **5-3** with silyl enol ether containing ring D precursors **5-4** (scheme1). In this way the C12-C13 bond would be formed, leading to seco steroids **5-5**, and a cyclisation reaction would then close ring C *via* the C8-C14 bond as the last step, giving steroids **5-6**. This method was expected to give a quick access to a wide variety of C17-substituted steroids in which selective catalytic reduction would lead to the CD-*trans*-fused (D-homo) steroid skeletons **5-7**.

Scheme 1



This approach is an *intermolecular* variation of the chemistry described in chapter 4, and resembles a route published by Torgov and co-workers in the late fifties (scheme 2)[1,2]. Later on, this route has been extensively used in steroid synthesis due to its good results[3-20], including the technical synthesis of the commercially important levonorgestrel[7].

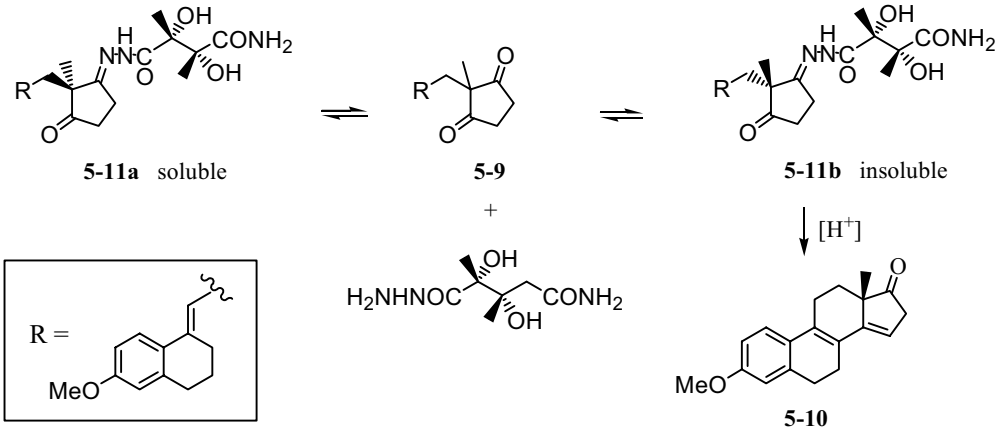
Scheme 2



To our knowledge five different routes leading to enantiomerically pure steroid compounds have been published using Torgov type chemistry, two of them using chemical resolution[10,12] and the other three using either enzymatic resolution[7-9], a chiral ring D precursor[15] or a chiral Lewis catalyst[19] for the introduction of asymmetry in the molecule.

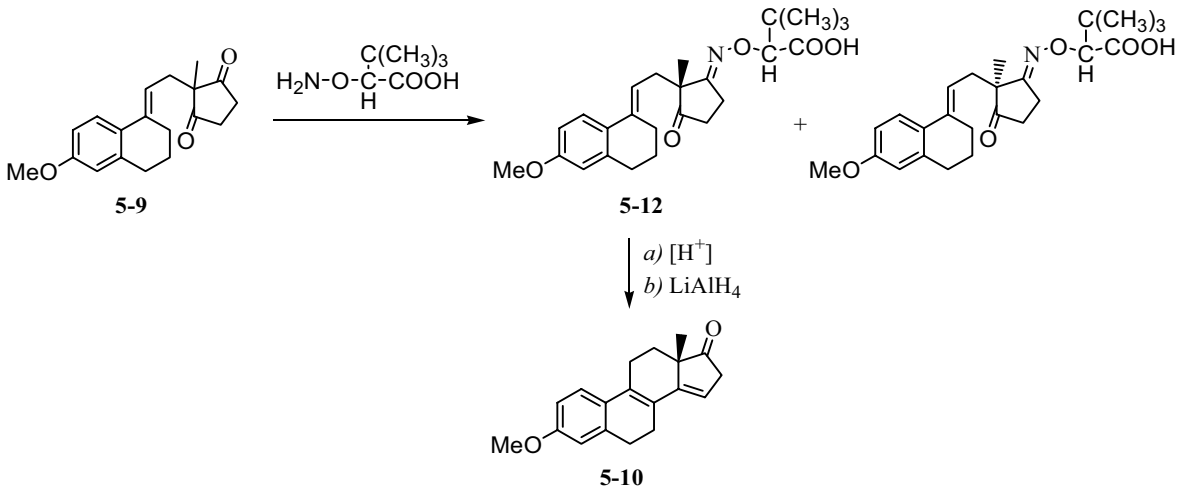
The first chemical asymmetric synthesis was published by Bucourt and coworkers[10] and used L-tartaric amide hydrazide to form the steroidal monohydrazones which could then be separated (see scheme 2). In a suitably chosen solvent system, selective crystallisation of the monohydrazone with the η-configuration on C13 could be achieved and over 75% yield of the pure product could be obtained. Consecutive treatment with acid gave the cyclised diene **5-10** in 80% yield.

Scheme 3



A few years later a second method using chemical resolution was published by Pappo and coworkers[12]. They derivatised the intermediate seco steroids to the oxime ethers using chiral amino oxycarboxylic acids and could selectively form mainly one of the two diastereomers on C13 via variation of the chemical environment (reaction conditions, used amine, etc.). In this way

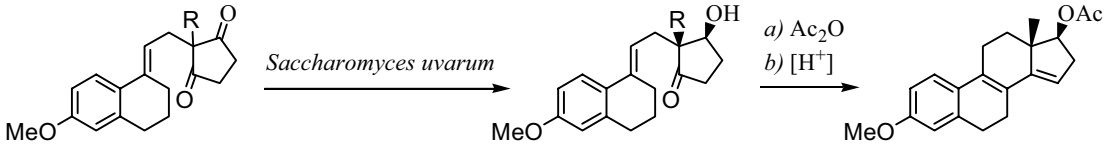
Scheme 4



compound **5-10** was obtained in high optical purity with an overall yield of 36% (scheme 3).

Gibian and co-workers[7-9] made use of enzymatic resolution of the seco steroidal intermediates from the Torgov route. Selective reduction of the ketone using *Saccharomyces uvarum* gave compounds **5-13**, in 53% to 74% yield, having both a η-standing alcohol on C17 and a η-standing methyl or ethyl on C13. After acetylation, they could then cyclise these products in high yields and further transform them to known compounds.

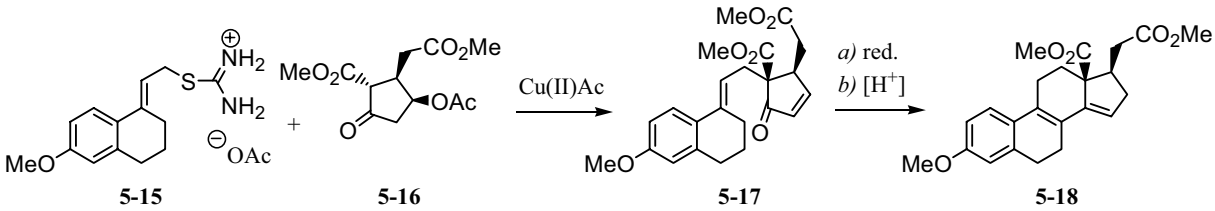
Scheme 5



5-9 R = Et, Me **5-13** **5-14**

Johnson and Magriotis[15] used a synthesis in which the diketone that served as ring D precursor in the traditional Torgov route was replaced by chiral cyclopentanone **5-16**, derived from S-malic acid. This compound was coupled with modified Torgov steroid precursor **5-15**. They obtained in this way seco steroid **5-17** as an 8:1 diastereomeric mixture on C13, out of which the C13-η isomer could be isolated in 95% optical purity and with a yield of about 40%. Subsequent cyclisation to compound **5-18** and further transformation enabled them to synthesise optically active (+)-18-hydroxyestrone.

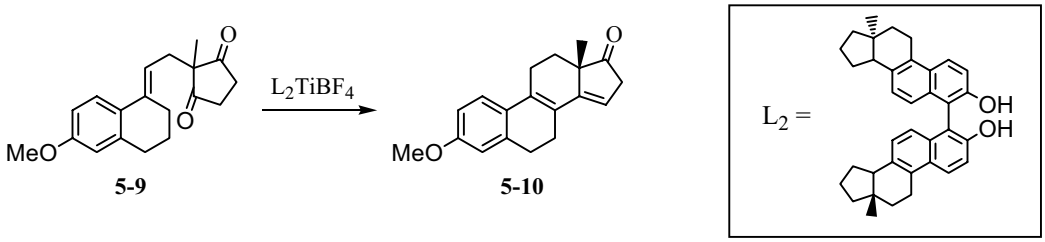
Scheme 6



5-15 **5-16** **5-17** **5-18**

Finally, Enev and coworkers[19] used a chiral Lewis acid to perform the cyclisation step of ring C. Using a chirally modified Ti complex in combination with a bis-steroidal ligand they were able to achieve a yield of 72% in combination with an *ee* of 70%, and in this way synthesise optically

Scheme 7



5-9 **5-10**

active estrone derivative **5-10**.

Silyl enol ether ring D precursors have been used previously in other routes to steroids by the groups of Magnus[21] and Wicha[22-25], and once a chiral ring D precursor has been used[24]. However, no publication has mentioned their use in combination with the Torgov approach to steroids for the introduction of enantioselectivity and variety in the C17 substitution. An application of chiral ring D precursors, using the silyl enol ether approach to steroids presented here, will be discussed in chapter 6.

5.2. Synthesis of the seco steroid skeletons

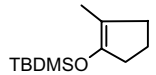
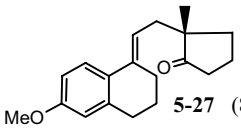
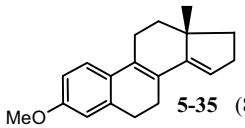
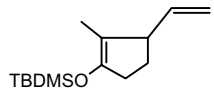
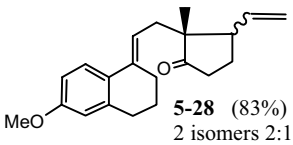
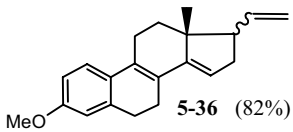
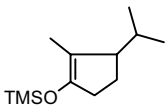
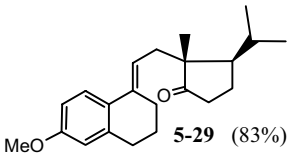
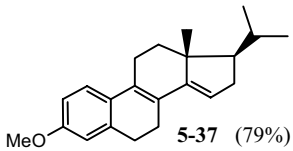
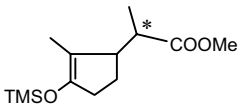
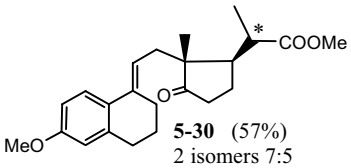
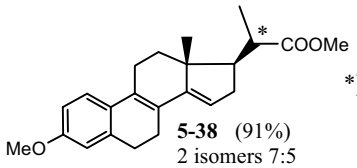
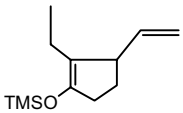
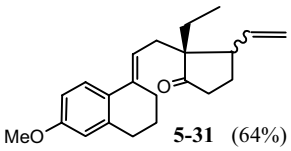
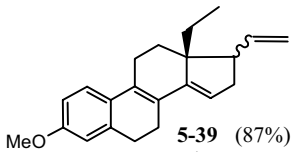
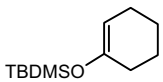
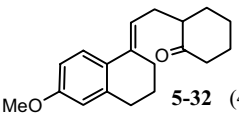
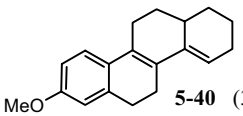
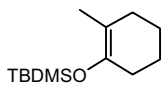
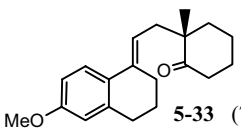
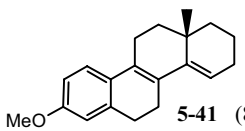
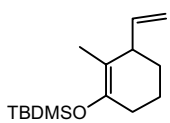
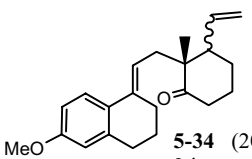
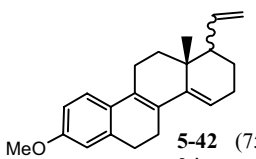
A large flexibility of our approach can be realised because several methods are available for the synthesis of silyl enol ether containing ring D precursors. In our hands they were obtained by conjugate addition followed by capture of the enolate with a silylating agent (compounds **5-20**, **5-21**, **5-23**, **5-26**, **5-43**, **5-44** and **5-45**), *via* Mukaiyama-Michael reactions on enones with transfer of the silyl group from the starting enol ether to the enol of the adduct (**5-22** and **5-47**), or by direct silylation of ketones (**5-19**, **5-24**, **5-25** and **5-48**). In the case of silyl enol ether **5-46** Kharash conditions[26] were used to form the dienol ether from R-(-)-carvone. In our experience, the TBDMS enol ethers are often the best compromise between stability and reactivity in Lewis acid catalysed reactions[27], but sometimes the more reactive trimethylsilyl (TMS) enol ethers were used. $ZnBr_2$ was chosen as Lewis acid catalyst and was usually used in a 5 – 10 mol% amount, as the use of stoichiometric amounts did not change the reaction rates or yields dramatically. All reactions were performed between -20 and 0 ^oC, in CH_2Cl_2 as a solvent.

Under these conditions the reactions of the Torgov reagent **5-3** with silyl enol ethers of the cyclopentanones **5-19** - **5-23** to seco steroids **5-27 - 5-31** proceeded in good yields, as can be seen in table 1. Steric hindrance did not hamper the yields and improved the stereoselectivity from good to complete as shown by the results with compounds **5-28** and **5-29**. Even when the silyl enol ether had an ethyl group at C2, as in **5-23**, a good yield of its coupling with the Torgov reagent could be achieved, leading to seco steroid **5-31** with an angular ethyl group. The 2-ethyl substituted cyclopentanone derivatives often show a lower reactivity than their 2-methyl congeners[28].

Similar reactions with silyl enol ethers derived from cyclohexanones, leading to D-homo steroid skeletons, gave more diverse results. The reaction of the 2-methyl cyclohexanone derivative **5-25** with the Torgov reagent proceeded in good yield, but higher substitution, as in compounds **5-26** and **5-43** - **5-47**, quickly lowered the yield, although the increase in stereoselectivity noticed in the reactions with the five-membered rings was maintained. One explanation for the low yields in substituted six-membered silyl enol ethers could be that the stability of the intermediate carbocation that is formed after the addition reaction has a larger stability in the five-membered ring than in the

six-membered ring and that the first one is therefore more easily formed. Another reason could be the difference in steric hindrance of the substituents in the two ring systems. To get an impression of the ease of formation of the carbocationic intermediate, molecular orbital calculations using the quantum chemistry program Gaussian 03[29] to predict the formation enthalpy were performed[30].

Tabel 1

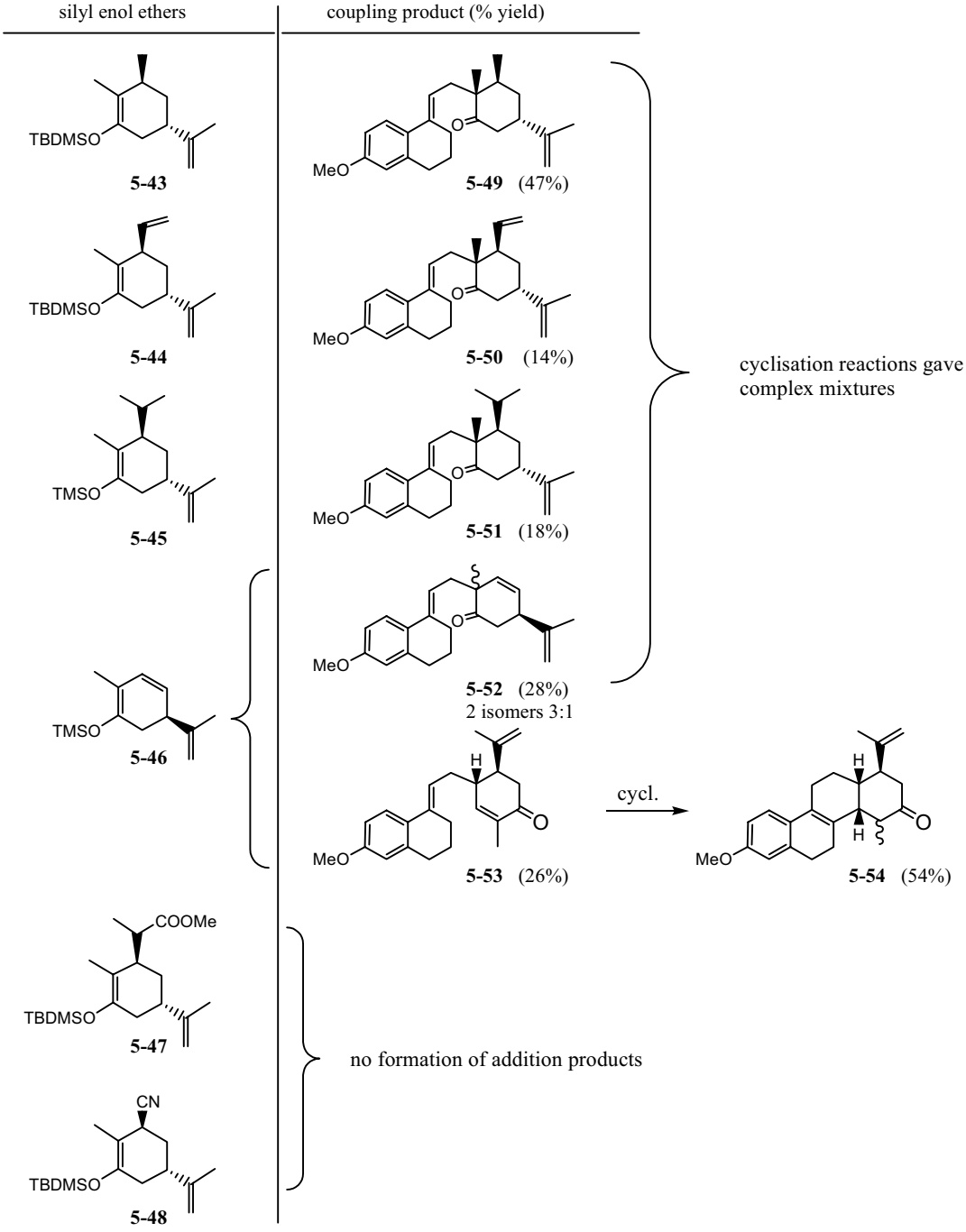
silyl enol ethers	coupling product (% yield)	cyclisation product (% yield)
 **5-19**	 **5-27** (84%)	 **5-35** (87%)
 **5-20**	 **5-28** (83%) 2 isomers 2:1	 **5-36** (82%)
 **5-21**	 **5-29** (83%)	 **5-37** (79%)
 **5-22**	 **5-30** (57%) 2 isomers 7:5	 **5-38** (91%) 2 isomers 7:5 *)
 **5-23**	 **5-31** (64%) 2 isomers 2:1	 **5-39** (87%) 2 isomers 2:1
 **5-24**	 **5-32** (42%)	 **5-40** (33%) **)
 **5-25**	 **5-33** (72%)	 **5-41** (88%) ***)
 **5-26**	 **5-34** (20%) 2 isomers 2:1	 **5-42** (75%) 2 isomers 2:1

*) for both isomers of **5-38** the depicted stereochemistry was confirmed using NOE experiments.

) yield of **5-40 obtained by addition of P_2O_5 to the reaction mixture of the addition reaction, after complete disappearance of **5-3**.

***) using P_2O_5 as a catalyst

Tabel 2



These calculations were performed on simple, OTMS substituted rings bearing no extra groups. Optimisation was done using B3LYP/6-31G(d,p)[31], after which single point calculations were performed with B3LYP/6-311+G(d,p) (gas phase) or B3LYP/6-311G(d,p) (CH2Cl2)[3233,34]. The difference between the calculated enthalpies was smaller than 0.01 kcal/mol in the gas phase and 0.78 kcal/mol in a model for CH_2Cl_2. The calculated enthalpies are therefore identical within the accuracy limits of the theoretical methods used and apparently there is no real difference in the ease of formation of the cationic intermediates. This indicates that steric hindrance is probably the main

factor influencing the yields to a larger extend in the six-membered rings than in the corresponding five-membered rings.

The addition reaction of **5-3** with the silyl enol ether of cyclohexanone **5-24** gave, together with **5-32**, next to small amounts of several other side products, one major unidentified additional product in 32% yield with a mass of 470, which, according to the NMR data, seems to include two tetralone moieties and, according to exact mass mesurements and isotope peak analysis, should have the bruto formula of $C_{32}H_{38}O_3$.

The silyl dienol ether derivative of carvone (**5-46**) reacted on the ζ and on the ν positions with respect to the ether function in approximately a 1:1 ratio, yielding compounds **5-52** and **5-53** respectively. The absence of reactivity of **5-48** probably has to be attributed to the lower nucleophilicity of the silyl enol ether due to the negative inductive effect of the cyano group[35]. Whereas compound **5-22** did react with the Torgov reagent **5-3**, compound **5-47** did not. Possibly again a negative inductive effect, although probably less pronounced than in compound **5-48**, but here in combination with steric hindrance, could explain the absence of reactivity in the six-membered ring compound **5-47**.

5.3. Ring closures of the seco steroids

Ring closures of seco steroids like **5-27** – **5-31** have been reported in literature and, when catalytic conditions are used, *p*-TsOH tends to be the reagent of choice, giving consistently high yields[4,9,36-38].

The ring closure of the seco steroids having a five-membered ring D to the unsaturated steroid skeletons **5-35** - **5-39** all gave very good results under these mildly acidic conditions (catalytic *p*-TsOH in benzene at 40 ^oC). However, when *p*-TsOH was used with the D-homo seco steroid **5-33** the reaction yielded next to a low amount of the wanted cyclised product **5-41** also a certain amount of the $\div_{9,11}$-14-hydroxycompound in which dehydration after the cyclisation step had not taken place. Therefore cyclisation reactions of these D-homo seco steroids were performed using P_2O_5 as catalyst (in CH_2Cl_2). Similar problems with the cyclisation step have been reported previously in literature for compounds with a carbonyl on C17a[3] although good cyclisation results of these compounds using *p*-TsOH have also been reported[39]. With compound **5-32** complex mixtures were obtained upon treatment with *p*-TsOH. Best results were obtained when P_2O_5 was added to the reaction mixture of the addition reaction after complete disappearance of **5-3**, giving 33% of cyclised compound **5-40**.

Compound **5-34** could be cyclised using *p*-TsOH in reasonable yield but the higher substituted D-homo seco steroids all gave complex mixtures upon cyclisation, both with *p*-TsOH and P_2O_5. The double bond of the isopropenyl group probably migrates during or after cyclisation and causes

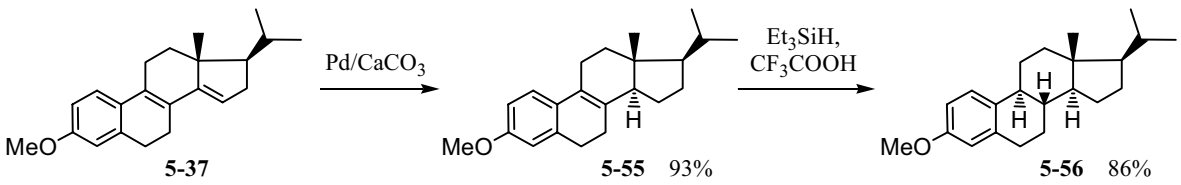
formation of isomers and maybe even aromatisation of ring B, leading to inseparable mixtures of several similar but not identical compounds.

Only with compound **5-53** a cyclised product could be obtained pure in reasonable yield. The assigned configuration around the ring system for the product **5-54** is tentative and could not be established unambiguously using 2D-NMR techniques. Since **5-54** was isolated as an oil, X-ray crystallography could not be used.

5.4. Reduction of the diene system to the all-*trans* configuration

The double bonds in the C and D rings in the steroid and D-homo steroid skeletons can be reduced catalytically to a C,D-*trans* fused steroid skeleton according to well known literature procedures[15,37,38,40,41]. As a trial this reduction was tested on compound **5-37** using $Pd/CaCO_3$ as catalyst, which gave the 13,14-trans reduced compound **5-55** in 93% yield (scheme 8). Further reduction to an all-*trans* ring system has also been extensively reported in literature. Usually a basic reduction in liquid ammonia is used for the *trans* reduction of the ÷[8,9] double bond. The Birch reduction conditions were used when reduction of ring A to an enone is desired, but a strong variation in yields is reported under these conditions[14,15,37,38,40-46]. Ionic reduction using triethylsilane and trifluoroacetic acid[40] also appeared effective and more reliable in our hands giving the all-*trans* steroid skeleton **5-56** in 86% yield[47].

Scheme 8



5-37 **5-55** 93% **5-56** 86%

In conclusion a short and flexible route to C,D-*trans* fused steroid and D-homo steroid skeletons has been developed, which, especially with five-membered ring D precursors, enables a quick access to a wide variety of C17 substituted steroid skeletons. Substituted silyl enol ethers can be prepared easily in various ways and the coupling under Lewis acid catalysed conditions with a Torgov reagent is performed in good to high yields. These addition products are rapidly cyclised and then selectively reduced to a C,D-*trans* fused ring system, making this approach high yielding, easy and attractive. Moreover, when appropriate chiral ring D precursors could be obtained, this route can give a quick access to enantiomerically pure steroid skeletons.

Experimental

(*1*RS)- 6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (5-3)

To an ice-cooled solution of vinyl magnesium bromide (65 ml, 1M in THF) a solution of 6-methoxy-1-tetralone (3.0 g, 17 mmol) in THF (30 ml) was added dropwise over a period of 30 min. After complete addition the ice-bath was removed and the reaction mixture was stirred at 40 ^{o}C for 1 hr. The reaction mixture was then cooled on ice again and a saturated water solution of NH_4Cl (25 ml) was carefully added, followed by EtOAc (25 ml). The layers were separated and the water layer was extracted with EtOAc (2 x 25 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc 9:1) yielding 3.2 g (92%) of pure **5-3** as a slightly yellow oil. IR (CCl_4 sol.) cm^{-1}: 3617, 3021, 2940, 2869, 2837, 1608, 1575, 1499, 1277, 1243; ^{1}H NMR ($CDCl_3$) ι: 1.72-2.07 (m, 5H), 2.62-2.91 (m, 2H), 3.78 (s, 3H), 5.18 (dd, J_1 = 10.5, J_2 = 1.5, 1H), 5.29 (dd, J_1 = 17.1, J_2 = 1.5, 1H), 6.02 (dd, J_1 = 10.5, J_2 = 17.1, 1H), 6.62 (d, J = 2.7, 1H), 6.74 (dd, J_1 = 8.6, J_2 = 2.7, 1H), 7.30 (d, J = 8.6, 1H); ^{13}C NMR (C_6D_6) ι: 19.32 (t), 30.12 (t), 37.91 (t), 55.215 (q), 73.03 (s), 112.58 (d), 112.88 (t), 113.18 (d), 129.43 (d), 132.19 (s), 138.62 (s), 145.08 (d), 158.73 (s). HRMS: M^+, found 204.1150. $C_{13}H_{16}O_2$ requires 204.1150. MS *m/e* (%) 204 (M^+, 46), 187 (13), 177 (100), 175 (32), 161 (17), 121 (12), 91 (6).

General procedure for silyl-compounds 5-19, 5-24, 5-25 and 5-48.

tert-Butyl-dimethyl-(2-methyl-cyclopent-1-enyloxy)-silane (5-19)

To a solution of 2-methylcyclopentanone (5.2 g, 53.0 mmol) in acetonitrile (100 ml) were added triethyl amine (Et_3N, 11 ml, 80 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl, 12 g, 80 mmol) and NaI (12 g, 80 mmol) in this order. The reaction mixture was stirred overnight at room temperature, after which PE (50 ml) and saturated $NaHCO_3$ solution (50 ml) were added. The layers were separated and the combined acetonitrile-water phases were extracted with PE (3 x 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc:pyridine 98:1:1) and yielded compound **5-19** as a colourless oil in 95% yield (10.68 g). IR (CCl_4 sol.) cm^{-1}: 2956, 2931, 2361, 1690, 1550, 1472, 1333, 1253; ^{1}H NMR (C_6D_6) ι: 0.14 (s, 6 H), 1.04 (s, 9H), 1.63-1.68 (m, 3H), 1.69-1.85 (m, 2H), 2.12-2.38 (m, 4H); ^{13}C NMR (C_6D_6) ι: -4.2 (q), -4.1 (q), 11.8 (q), 18.0 (s), 19.8 (t), 25.6 (3q), 33.5 (t), 33.7 (t), 111.9 (s), 146.6 (s). HRMS: M^+, found 212.1592. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%) 212 (M^+, 13), 197 (3), 155 (71), 75 (100), 59 (9).

***tert*-Butyl-(cyclohex-1-enyloxy)-dimethyl-silane (5-24)**

Yield: 83%. IR (CCl_4 sol.) cm^{-1}: 2931, 2859, 1668, 1549, 1254; ^1H NMR ($CDCl_3$) ι: 0.01 (9H, s), 0.12 (6H ,s), 1.45-1.59 (2H, m), 1.59-1.72 (2H, m), 1.94-2.08 (4H, m), 4.85-4.90 (1H, m); ^{13}C NMR ($CDCl_3$) ι: -4.39 (2q), 18.01 (s), 22.37 (t), 23.17 (t), 23.83 (t), 25.71 (3q), 29.88 (t), 104.3 (d), 150.5 (s). HRMS: M^+, found 212.1598. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%) 212 (M^+, 22), 75 (80), 73 (19).

***tert*-Butyl-dimethyl-(2-methyl-cyclohex-1-enyloxy)-silane (5-25)**

Yield: quantitative. IR (CCl_4 sol.) cm^{-1}: 2931, 2858, 1686, 1550, 1254; ^1H NMR ($CDCl_3$) ι: 0.09 (s, 6H), 0.92 (s, 9H), 1.43-1.72 (m, 4H), 1.56 (s, 3H), 1.85-2.09 (m, 4H); ^{13}C NMR ($CDCl_3$) ι: -3.8 (2q), 16.4 (q), 18.1 (s), 22.9 (t), 23.8 (t), 25.7 (3q), 30.3 (t), 30.4 (t), 111.5 (s), 142.9 (s). HRMS: M^+, found 226.1759. $C_{13}H_{26}OSi$ requires 226.1753. MS *m/e* (%) 226 (M^+, 34), 221 (3), 169 (70), 84 (22), 75 (100).

3-(*tert*-Butyl-dimethyl-silanyloxy)-5-isopropenyl-2-methyl-cyclohex-2-enecarbonitrile (5-48)

Yield: 70%, from cyanocarvone[48]. IR (CCl_4 sol.) cm^{-1}: 2960, 2932, 2885, 2860, 2235, 1686, 1647, 1550, 1256, 1210; ^1H NMR (C_6D_6) ι: -0.01 (s, 6H), 0.92 (s, 9H), 1.11 (dt, J_1 = 5.6, J_2 = 12.8, 1H), 1.46 (s, 3H), 1.64 (s, 3H), 1.69-1.94 (m, 2H), 1.85 (dt, J_1 = 2.0, J_2 = 11.0, 1H), 2.04 (dd, J_1 = 5.2, J_2 = 16.5, 1H), 2.37-2.45 (m, 1H), 2.53 (dd, J_1 = 4.4, J_2 = 14.6, 1H); ^{13}C NMR (C_6D_6) ι: -4.0 (q), -3.9 (q), 14.7 (q), 18.0 (s), 20.3 (q), 25.6 (3 x q), 30.8 (t), 32.0 (d), 35.2 (t), 38.8 (d), 104.9 (s), 109.8 (t), 120.9 (s), 146.7 (s), 146.9 (s); HRMS: M^+, found 291.2017. $C_{17}H_{29}NOSi$ requires 291.2018. MS *m/e* (%) 291 (M^+, 6), 248 (10), 234 (100), 179 (8), 166 (14), 165 (20), 75 (26), 73 (26).

General procedure for silyl-compounds 5-20, 5-21, 5-23, 5-26, 5-43, 5-44 and 5-45

2-Methyl-3-ethenyl-*tert*-butyldimethylsilyloxy-cyclopent-1-ene (5-20).

To a cooled (-40°C) solution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 3.84 g, 30 mmol) in THF (15 ml) cuprous bromide-dimethyl sulfide ($CuBr.Me_2S$, 0.155 g, 0.75 mmol) was added, after which 22,5 ml of a 1M solution of vinyl magnesium bromide in THF was added dropwise over a period of 1 hr. The reaction mixture was stirred for a further 15 min and a mixture of 2-methyl-1-cyclopenten-1-one (1.40 g, 15 mmol) and TBDMSCl (3.40 g, 22.5 mmol) in THF (15 ml) was added dropwise over 30 min. The reaction mixture was stirred for 1 hr, during which the temperature rose to –20 °C. Et_3N (4.15 ml, 30 mmol) was added and stirring was continued overnight at room temperature. A saturated NH_4Cl solution (75 ml) was added and the reaction

mixture was extracted with *tert*-butyl dimethylether (*t*BuOMe, 3 x 75 ml). The organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by rapid column chromatography (PE:EtOAc:pyridine 98:1:1), yielding 1.93 g of **5-20** as a colourless oil (54%). IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2858, 2290, 1686, 1550, 1254; ^1H NMR (C_6D_6) ι: 0.13 (s, 6H), 0.89-1.00 (m, 1H), 1.03 (s, 9H)1.48-1.66 (m, 1 H), 1.67 (s, 3H), 1.90-2.45 (m, 3H), 2.93-3.14 (m, 1H), 4.79 (dd, J_1 = 2.0 Hz, J_2 = 9.8 Hz, 1H), 4.86 (dd, J_1 = 2.0 Hz, J_2 = 17.0 Hz, 1H), 5.51 (ddd, J_1 = 9.0 Hz, J_2 = 9.8 Hz, J_3 = 17.0 Hz, 1H); ^{13}C NMR (C_6D_6) ι: -4.3 (q), -4.2 (q), 10.4 (q), 17.9 (s), 25.6 (3q), 27.5 (t), 32.7 (t), 50.2 (d), 113.2 (t), 114.2 (s), 142.8 (d), 147.9 (s). HRMS: M^+, found 238.1746. $C_{14}H_{26}OSi$ requires 238.1753. MS *m/e* (%) 238 (M^+, 51), 223 (20), 211 (21), 182 (32), 181 (30), 75 (100), 73 (57).

(3-Isopropyl-2-methyl-cyclopent-1-enyloxy)-trimethyl-silane (5-21)

Yield: 69%. IR (CCl_4 sol.) cm^{-1}: 2959, 2925, 2862, 2825, 1688, 1549, 1328, 1252, 1214; ^1H NMR (C_6D_6) ι: 0.13 (s, 9H), 0.73 (d, J = 6.8, 3H), 0.88 (d, J = 8.6, 3H), 1.36-2.05 (m, 3H), 1.56 (s, 3H), 2.13-2.29 (m, 2H), 2.35-2.52 (m, 1H); ^{13}C NMR (C_6D_6) ι: 0.3 (3q), 10.5 (q), 15.7 (q), 20.1 (t), 20.5 (q), 28.9 (d), 33.2 (t), 50.6 (d), 114.8 (s), 147.4 (s). HRMS: M^+, found 212.1597. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%) 212 (M^+, 4), 197 (3), 169 (100), 84 (16), 75 (25), 73 (50).

(2-Ethyl-3-vinyl-cyclopent-1-enyloxy)-trimethyl-silane (5-23)

Yield: 77%. IR (CCl_4 sol.) cm^{-1}: 2963, 2940, 2851, 1678, 1549, 1344, 1252, 1204; ^1H NMR (C_6D_6) ι: 0.12 (s, 9H), 1.03 (t, J = 7.5, 3H), 1.31-2.51 (m, 6H), 3.08-3.27 (m, 1H), 4.93 (dd, J_1 = 9.8, J_2 = 2.1, 1H), 5.02 (dd, J_1 = 16.9, J_2 = 2.1, 1H), 5.65 (ddd, J_1 = 9.0, J_2 = 9.8, J_3 = 16.9, 1H); ^{13}C NMR (C_6D_6) ι: 0.2 (3q), 12.2 (q), 18.1 (t), 27.6 (t), 32.7 (t), 47.8 (d), 113.1 (t), 120.3 (s), 143.0 (d), 147.1 (s). HRMS: M^+, found 210.1440. $C_{12}H_{22}OSi$ requires 210.1440. MS *m/e* (%) 210 (M^+, 59), 195 (42), 181 (90), 129 (11), 75 (28), 73 (100).

***tert*-Butyl-dimethyl-(2-methyl-3-vinyl-cyclohex-1-enyloxy)-silane (5-26)**

Yield: 51%. IR (CCl_4 sol.) cm^{-1}: 2932, 2858, 1678, 1549, 1256, 1193; ^1H NMR (C_6D_6) ι: 0.12 (s, 6H), 1.03 (s, 9H), 1.29-1.68 (m, 4H), 1.71 (s, 3H), 1.91-2.05 (m, 2H), 2.54-2.69 (m, 1H), 4.97 (m, 1H), 5.04 (s, 1H), 5.68 (m, 1H); ^{13}C NMR ($CDCl_3$) ι: -3.8 (2q), 14.9 (q), 18.2 (s), 20.0 (t), 25.9 (3q), 29.1 (t), 30.5 (t), 44.3 (d), 112.6 (s), 114.3 (t), 142.1 (d), 144.7 (s). HRMS: M^+, found 252.1912. $C_{15}H_{28}OSi$ requires 252.1909. MS *m/e* (%) 252 (M^+, 44), 237 (44), 195 (67), 167 (14), 119 (39), 75 (100), 73 (46).

***tert*-Butyl-(5-isopropenyl-2,3-dimethyl-cyclohex-1-enyloxy)-dimethyl-silane (5-43)**

Yield: 64%. IR (CCl_4 sol.) cm^{-1}: 2960, 2930, 2859, 1682, 1645, 1193; ^1H NMR (C_6D_6) ι: 0.00 (s, 6H), 0.88-0.91 (m, 12H), 1.32-1.47 (m, 2H), 1.53 (s, 3H), 1.60 (t, *J* = 1.6, 3H), 1.98-2.05 (m, 3H), 2.29-2.34 (m, 1H), 4.68 (s, 1H), 4.72 (s, 1H). ^{13}C NMR (C_6D_6) ι: -3.9 (q), -3.7 (q), 14.9 (q), 18.2 (s), 19.6 (q), 20.6 (q), 25.8 (3 x q), 33.7 (d), 35.2 (t), 36.1 (t), 37.3 (d), 109.0 (t), 115.0 (s), 142.7 (s), 148.9 (s). HRMS: M^+, found 280.2226. $C_{17}H_{32}OSi$ requires 280.2222. MS *m/e* (%) 280 (M^+, 69), 265 (72), 237 (100), 223 (37), 179 (15), 155 (15), 149 (17), 129 (17), 75 (78), 73 (79).

***tert*-Butyl-(5-isopropenyl-2-methyl-3-vinyl-cyclohex-1-enyloxy)-dimethyl-silane (5-44)**

Yield: 82%. IR (CCl_4 sol.) cm^{-1}: 2959, 2930, 1859, 1682, 1644, 1256, 1192, 1179, 925; ^1H NMR (C_6D_6) ι: 0.01 (s, 6H), 0.89 (s, 9H), 1.23-1.57 (m, 2H), 1.55 (s, 3H), 1.61 (s, 3H), 1.90-2.12 (m, 2H), 2.21-2.45 (m, 1H), 2.48-2.62 (m, 1H), 4.604.70 (m, 2H), 4.80-5.00 (m, 2H), 5.64 (ddd, *J* = 7.1, *J* = 10.4 & *J* = 17.4, 1H); ^{13}C NMR (C_6D_6) ι: -3.8 (2q), 15.2 (q), 18.2 (s), 20.5 (q), 25.7 (3q), 33.4 (t), 35.9 (t), 37.2 (d), 43.8 (d), 109.1 (t), 111.4 (s), 114.6 (t), 141.3 (d), 144.5 (s), 148.7 (s). HRMS: M^+, found 292.2217. $C_{18}H_{32}OSi$ requires 292.2222. MS *m/e* (%) 292 (M^+, 14), 277 (52), 249 (100), 235 (17), 161 (20), 75 (96), 73 (79), 59 (16).

(5-isopropenyl-3-isopropyl-2-methyl-cyclohex-1-enyloxy)-trimethyl-silane (5-45)

Yield: 95%. IR (CCl_4 sol.) cm^{-1}: 2960, 2871, 1677, 1644, 1447, 1252, 1182, 927; ^1H NMR (C_6D_6) ι: 0.17 (s, 9H), 0.82 (d, *J* = 6.6, 3H), 0.93 (d, *J* = 6.6, 3H), 1.31-2.23 (m, 6H), 1.65 (s, 3H), 1.68 (s, 3H), 2.33-2.53 (m, 1H), 4.80 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (C_6D_6) ι: 0.5 (3q), 15.2 (q), 18.5 (q), 20.7 (q), 21.6 (q), 27.6 (t), 29.6 (d), 35.2 (t), 38.8 (d), 43.5 (d), 109.1 (t), 113.5 (s), 144.2 (s), 148.3 (s). HRMS: M^+, found 266.2068. $C_{16}H_{30}OSi$ requires 266.2066. MS *m/e* (%) 266 (M^+, 8), 251 (1.4), 223 (100), 195 (5), 181 (14), 165 (4), 75 (6), 73 (40).

General procedure for Mukaiyama-addition products 5-22 and 5-47.

2-(2-Methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-propionic acid methyl ester (5-22)

2-Methyl-1-cyclopenten-1-one (0.96 g, 10 mmol) and 1-methoxy-1-(trimethylsiloxy) propene[49] (3.2 g, 20 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to –78 °C. A solution of $TrSbCl_6$ (290 mg, 0.5 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred for 3 hrs at –78 °C. When all 2-methyl-1-cyclopenten-1-one had disappeared (TLC), pyridine (1 ml) was added to quench the catalyst and the reaction mixture was warmed to room temperature. *t*BuOMe (50 ml) and saturated

$NaHCO_3$ solution were added, the layers were separated and the organic layer was washed with brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc: pyridine 98:1:1) yielding 96% of **5-22** (2.46 g, colourless oil) as a mixture of two isomers (7:5, GC determination). IR (CCl_4 sol.) cm^{-1}: 2954, 2906, 2850, 1738, 1688, 1549, 1253; ^1H NMR (C_6D_6) ι: 0.10 (s, 9H), 0.99(*M*) & 1.06(*m*) (d, *J* = 7.0, 3H), 1.47(*M*) & 1.64(*m*) (s, 3H), 1.53-2.00 (m, 2 H), 2.04-2.37 (m, 2H), 2.46-2.68 (m, 1H), 2.68-2.82(*m*) & 2.97-3.12(*M*) (m, 1H), 3.34(*m*) & 3.37(*M*) (s, 3H); ^{13}C NMR (C_6D_6) ι: 0.4 (3q), 9.9 (*m*) & 10.3 (*M*) (q), 10.7 (*m*) & 13.7 (*M*) (q), 21.5 (*M*) & 22.8 (*m*) (t), 33.6 (*m*) & 33.0 (*M*) (t), 40.6 (*M*) & 41.7 (*m*) (d), 47.1 (*M*) & 48.8 (*m*) (q), 50.7 (q), 112.9 (*M*) & 113.6 (*m*) (s), 148.5 (s), 175.1 (*m*) & 175.6 (*M*) (s). HRMS: M^+, found 256.1496. $C_{13}H_{24}O_3Si$ requires 256.1495. MS *m/e* (%) 256 (M^+, 5), 169 (100), 89 (28), 84 (31), 75 (63), 73 (62).

2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-5-isopropenyl-2-methyl-cyclohex-2-enyl]-propionic acid methyl ester (5-47)

Yield: 85% (2 isomers 7:1, NMR determination). IR (CCl_4 sol.) cm^{-1}: 2931, 2859, 1737, 1677, 1254, 1195; ^1H NMR ($CDCl_3$) ι: 0.07 (s, 6H), 0.91 (s, 9H), 1.02 (*M*) & 1.15 (*m*) (d, *J* = 7.0, 3H), 1.10-2.90 (m, 7H), 1.52 (s, 3H), 1.63 (*m*) & 1.67 (*M*) (s, 3H), 3.59 (*m*) & 3.64 (*M*) (s, 3H), 4.65 (s, 1H), 4.69 (s, 3H); ^{13}C NMR ($CDCl_3$) ι: -3.8 (2q), 12.9 (*M*) & 16.2 (*m*) (q), 14.5 (*M*) & 16.6 (*m*) (q), 18.1 (s), 20.7 (q), 25.8 (3q), 28.9 (*M*) & 30.8 (*m*) (t), 34.9 (*M*) & 36.2 (*m*) (t), 37.5 (*m*) & 38.2 (*M*), 39.9 (*m*) & 40.7 (*M*) (d), 41.8 (*M*) & 42.8 (*m*) (d), 51.3 (q), 109.0 (t), 111.7 (*M*) & 112.4 (*m*) (s), 145.2 (s), 148.2 (*M*) & 148.5 (*m*) (s), 176.8 (s). HRMS: M^+, found 352.2428. $C_{20}H_{36}O_3Si$ requires 352.2434. MS *m/e* (%) 352 (M^+, 10), 265 (100), 223 (5), 73 (27), 59 (3).

(5-Isopropenyl-2-methyl-cyclohexa-1,3-dienyloxy)-trimethyl-silane (5-46)

A solution of dry $FeCl_3$ in THF (50 ml) was cooled to –20 ^oC and a solution of MeMgBr in THF (75 mmol, 3M in THF) was added dropwise over a period of 1 hr. After complete addition the reaction mixture was stirred for 30 min at –20 ^oC and R-(-)-carvone (10 g, 66.7 mmol) in THF (100 ml) was then added by slow dropping over a period of 2 hrs. The temperature was kept at –20 ^oC during the complete addition and for 30 min more and then warmed to 0 ^oC. TMSCl (8.2 g, 75 mmol) was added, followed by EtN_3 (6 ml) and DMPU (6 ml). The reaction mixture was stirred overnight at room temperature. A saturated solution of $NaHCO_3$ (100 ml) was added and the resulting grey suspension was filtered over a plug of Hyflo and carefully washed with Et_2O. The filtrate layers were separated and the water layer was extracted with Et_2O (3 x 50 ml). The combined organic

layers were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography (PE:EA:pyridine 98:1:1) gave compound **5-46** as a colourless oil in 70% yield (10.3 g). ^{1}H NMR (C_6D_6) ι: 0.17 (s, 9H), 1.67 (s, 3H), 1.71 (s, 3H), 2.00-2.52 (m, 2H), 2.97-3.19 (m, 1H), 4.78 (s, 1H), 4.86 (s, 1H), 5.37 (dd, J_1 = 3.4 & J_2 = 9.8, 1H), 5.86 (dd, J_1 = 2.4 & J_2 = 9.3, 1H); ^{13}C NMR (C_6D_6) ι: 0.3 (s, 3q), 20.4 (q), 20.5 (q), 34.3 (t), 43.7 (d), 110.4 (t), 121.8 (d), 129.8 (d), 145.4 (s), 146.9 (s), 148.8 (s).

General procedure for coupling of 6-methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (5-3) with the different silyl-compounds (5-19 - 5-26 & 5-43 - 5-46)

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (5-27)

6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (**5-3**, 204 mg, 1 mmol) and 2-methyl-*tert*-butyldimethylsilyloxy-cyclopent-1-ene (**5-19**, 636 mg, 3 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to –20 ^{o}C. $ZnBr_2$ (a few crystals, appr. 60 mg) was added as the catalyst and the reaction mixture was stirred for 3 hrs at –15 to –10 ^{o}C. When all of compound **5-3** had disappeared (TLC), EtOAc (25 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 9:1) yielding compound **5-27** as a colourless oil in 84% yield (238 mg), which crystallised upon standing (mp 53-55 ^{o}C, decomp. from tBuOMe). IR (CCl_4 sol.) cm^{-1}: 2959, 1738, 1550, 1255; ^{1}H NMR (C_6D_6) ι: 0.93 (s, 3H), 1.26-1.54 (m, 3H), 1.54-1.83 (m, 3H), 1.87-2.09 (m, 2H), 2.25 (d, J = 7.7, 2H), 2.32 (t, J = 6.1, 2H), 2.54 (t, J = 6.1, 2H), 3.38 (s, 3H), 5.87 (t, J = 7.7, 1H), 6.57 (d, J = 2.5, 1H), 6.71 (dd, J_1 = 2.5, J_2 = 8.7, 1H), 7.51 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 18.8 (t), 21.9 (q), 23.4 (t), 26.8 (t), 30.8 (t), 35.1 (2t), 37.3 (t), 48.7 (s), 54.5 (q), 112.7 (d), 113.2 (d), 117.0 (d), 125.3 (d), 129.2 (s), 136.5 (s), 138.5 (s), 158.9 (s), 220.8 (s). HRMS: M^+, found 284.1779. $C_{19}H_{24}O_2$ requires 284.1776. MS *m/e* (%) 284 (M^+, 10), 187 (100), 148 (4), 146 (4), 128 (4), 115 (3).

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclopentanone (5-28)

Yield: 83%, mixture of 2 isomers (2:1, NMR determination). IR (CCl_4 sol.) cm^{-1}: 2945, 2937, 2836, 1739, 1606, 1496, 1234; ^{1}H NMR (C_6D_6) ι: 0.78(*M*) & 1.06(*m*) (s, 3H), 1.15-2.61 (m, 13H), 3.32 (s, 3H), 4.88-5.07 (m, 2H), 5.52-5.84 (m, 1H), 5.89-6.11 (m, 1H), 6.58 (d, J = 2.6, 1H), 6.70 (dd, J_1 = 2.6, J_2 = 8.7, 1H), 7.53(*M*) & 7.64(*m*) (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 17.9 (*M*) & 20.8 (*m*)

(q), 23.4 (*m*) & 23.5 (*M*) (t), 24.2 (*m*) & 24.6 (*M*) (t), 26.7 (*M*) & 26.8 (*m*) (t), 30.8 (*M*) & 30.9 (*m*) (t), 34.7 (*M*) & 35.7 (*m*) (t), 37.0 (t), 47.5 (*M*) & 51.9 (*m*) (d), 52.3 (s), 54.5 (q), 112.7 (*m*) & 112.7 (*M*) (d), 113.3 (*M*) & 113.4 (*m*) (d), 115.9 (*m*) & 115.9 (*M*) (t), 116.8 (*m*) & 117.3 (*M*) (d), 125.4 (d), 129.2 (s), 135.8 (*m*) & 136.4 (*M*) (s), 137.6 (*m*) &137.9 (*M*) (d), 138.5 (*M*) & 138.5 (*m*) (s), 159.0 (s), 219.0 (*m*) & 219.8 (*M*) (s). HRMS: M^+, found 310.1937. $C_{21}H_{26}O_2$ requires 310.1933. MS *m/e* (%) 310 (M^+, 15), 187 (100), 161 (4), 160 (4), 159 (8), 146 (5).

3-Isopropyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (5-29)

Yield: 83%. IR (CCl_4 sol.) cm^{-1}: 2962, 2940, 2836, 1738, 1606, 1496, 1239; ^1H NMR (C_6D_6) ι: 0.66 (dd, J_1 = 1.8 & J_2 = 6.2, 1H), 0.74 (d, J = 6.5, 3H), 0.85 (s, 3H), 0.90 (d, J = 6.5, 3H), 0.96-2.02 (m, 6H), 2.05 (dd, J_1 = 8.2 & J_2 = 18.4, 1H), 2.29 (dd, J_1 = 8.7 & J_2 = 14.7, 1H), 2.42 (t, J = 6.2, 2H), 2.56 (t, J = 6.2, 2H), 2.71 (dd, J_1 = 6.5 & J_2 = 13.4, 1H), 3.34 (s, 3H), 5.84 (dd, J_1 = 6.5 & J_2 = 8.5, 1H), 6.55 (d, J = 2.7, 1H), 6.67 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.52 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 18.0 (q), 21.0 (q), 22.3 (q), 23.5 (t), 23.6 (t), 26.8 (t), 29.2 (d), 30.7 (t), 36.5 (t), 37.5 (t), 48.5 (d), 52.1 (s), 54.4 (q), 112.6 (d), 113.3 (d), 117.8 (d), 125.2 (d), 129.3 (s), 135.8 (s), 138.5 (s), 158.9 (s), 221.3 (s). HRMS: M^+, found 326.2248. $C_{22}H_{30}O_2$ requires 326.2246. MS *m/e* (%) 326 (M^+, 9), 187 (100), 161 (4), 159 (3), 146 (3), 131 (3), 69 (8).

2-{2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-oxo-cyclopentyl}-propionic acid methyl ester (5-30)

Yield: 57% (isomeric ratio 7:5)

Main isomer. IR ($CHCl_3$ sol.) cm^{-1}: 2974, 2942, 2839, 1732, 1605, 1496, 1464, 1272, 1235, 1198, 1164; ^1H NMR (C_6D_6) ι: 0.84-1.08 (m, 1H), 0.96 (s, 3H), 1.02 (d, J = 6.7, 3H), 1.45-2.82 (m, 12H), 2.84 (dd, J_1 = 8.5 & J_2 = 14.8, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 6.16 (dd, J_1 = 6.9, J_2 = 8.3, 1H), 6.62 (d, J = 2.7, 1H), 6.76 (dd, J_1 = 2.7, J_2 = 8.7, 1H), 7.74 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 15.8 (q), 18.3 (q), 23.0 (t), 23.6 (t), 26.7 (t), 30.8 (t), 34.7 (t), 36.9 (t), 40.3 (d), 44.3 (d), 50.9 (s), 52.1 (q), 54.4 (q), 112.6 (d), 113.2 (d), 117.0 (d), 125.4 (d), 129.5 (s), 136.6 (s), 138.8 (s), 158.9 (s), 175.9 (s), 219.7 (s). HRMS: M^+, found 370.2149. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 11), 339(1.5), 187 (100), 174 (2), 171 (2), 159 (5), 146 (3).

Minor isomer. IR (CCl_4 sol.) cm^{-1}: 2941, 2837, 1740, 1604, 1550, 1496, 1458, 1251, 1156; ^1H NMR (C_6D_6) ι: 0.86 (s, 3H), 0.90-1.04 (m, 1H), 1.19 (d, J = 6.7, 3H), 1.25-2.65 (m, 12H), 2.72 (dd, J_1 = 8.0 & J_2 = 14.8, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 5.93 (dd, J_1 = 6.9, J_2 = 8.4, 1H), 6.62 (d, J = 2.7, 1H), 6.76 (dd, J_1 = 2.7, J_2 = 8.7, 1H), 7.74 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 16.7 (q), 17.7

(q), 23.5 (t), 23.8 (t), 26.8 (t), 30.7 (t), 36.3 (t), 37.2 (t), 41.3 (d), 45.6 (d), 50.7 (q), 51.7 (s), 54.4 (q), 112.6 (d), 113.3 (d), 116.9 (d), 125.3 (d), 129.1 (s), 136.6 (s), 138.5 (s), 159.0 (s), 175.4 (s), 219.9 (s). HRMS: M^+, found 370.2150. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 7), 339 (2), 187 (100), 159 (3), 146 (3).

2-Ethyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-3-vinyl-cyclopentanone (5-31)

Yield: 64% (isomeric ratio 2:1). IR (CCl_4 sol.) cm^{-1}: 2950, 2939, 2836, 1736, 1606, 1570, 1497, 1464, 1237, 1235; ^1H NMR (C_6D_6) ι: 0.78 (M) & 0.85 (m) (t, *J* = 7.3, 3H), 1.23-2.76 (m, 16H), 3.33 (s, 3H), 4.97 (*m*, d, *J* = 11.1) & 5.04 (*M*, d, *J* = 2.9) (2H), 5.66-5.87 (m, 1H), 5.94 (*m*) & 6.07 (*M*) (m, 1H), 6.60 (d, *J* = 2.6, 1H), 6.71 (dd, J_1 = 2.6 & J_2 = 8.7, 1H), 7.55 (*m*) & 7.66 (*M*) (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 8.5 (*m*) & 8.7 (*M*) (q), 23.4 (*M*) & 23.5 (*m*) (t), 24.3 (*m*) & 24.4 (*M*) (t), 24.3 (*m*) & 26.5 (*M*) (t), 26.8 (*M*) & 26.9 (*m*) (t), 30.5 (*m*) & 30.8 (*M*) (t), 30.7 (*M*) & 31.7 (*m*) (t), 36.9 (*m*) & 37.1 (*M*) (t), 47.0 (*M*) & 47.9 (*m*) (d), 54.5 (q), 55.4 (*m*) & 55.7 (*M*) (s), 112.7 (d), 113.3 (*m*) & 113.4 (*M*) (d), 115.7 (*m*) & 115.8 (*M*) (t), 116.8 (*M*) & 117.5 (*m*) (d), 15.4 (d), 129.3 (s), 135.6 (*M*) & 136.3 (*m*) (s), 137.9 (*m*) & 138.0 (*M*) (d), 138.5 (s), 158.9 (s), 218.9 (s)). HRMS: M^+, found 324.2093. $C_{22}H_{28}O_2$ requires 324.2089. MS *m/e* (%) 324 (M^+, 20), 187 (100), 186 (5), 174 (6), 171 (5), 159 (8).

2-[2-(6-Methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-cyclohexanone (5-32)

Yield: 42%. IR (CCl_4 sol.) cm^{-1}: 2936, 2863, 2836, 1713, 1606, 1550, 1497, 1253; ^1H NMR (C_6D_6) ι: 0.47 (s, 1H), 1.00-2.45 (m, 13H), 2.60 (t, *J* = 6.1, 2H), 2.81 (dt, J_1 = 5.4 & J_2 = 14.9, 1H), 3.40 (s, 3H), 6.00 (t, *J* = 7.4, 1H), 6.66 (d, *J* = 2.7, H), 6.82 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.64 (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 23.4 (t), 25.1 (t), 26.8 (t), 27.7 (t), 28.2 (t), 30.9 (t), 33.4 (t), 41.8 (t), 50.8 (d), 54.5 (q), 112.7 (d),113.2 (d), 119.9 (d), 125.3 (d),129.4 (s),135.1 (s), 138.5 (s), 159.0 (s), 210.0 (s). HRMS: M^+, found 284.1774. $C_{19}H_{24}O_2$ requires 284.1776. MS *m/e* (%) 284 (M^+, 28), 187 (100), 174 (18), 159 (7), 146 (5), 115 (3).

Unidentified side-product Yield: 32%. IR (CCl_4 sol.) cm^{-1}: 2935, 2835, 1692, 1610, 1550, 1499, 1259; ^1H NMR (C_6D_6) ι: 1.35-2.75 (m, 26H), 3.39 (s, 3H), 3.40 (s, 3H), 5.93 (t, *J* = 7.4, 1H), 6.64 (d, *J* = 2.7, 1H), 6.70 (d, *J* = 2.7, 1H), 6.83 (dd, *J* = 2.7 & *J* = 8.7, 1H), 6.88 (dd, *J* = 2.7 & *J* = 8.7, 1H), 7.54 (d, *J* = 8.7, 1H), 7.66 (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 19.5 (t), 23.4 (2t), 23.4 (t), 26.7 (2t), 28.0 (t), 28.8 (t), 30.4 (t), 30.5 (t), 30.8 (t), 31.3 (t), 42.7 (d), 54.5 (2q), 77.1 (s), 103.0 (s), 112.7 (d), 112.8 (d), 113.1 (d), 113.2 (d), 120.4 (d), 125.3 (d), 129.0 (d), 129.3 (s), 131.4 (s), 134.6 (s), 138.4 (s), 140.4 (s), 145.3 (s), 158.8 (s), 158.9 (s). HRMS: M^+, found 470.2829. $C_{32}H_{38}O_3$

requires 470.2821. MS *m/e* (%) 470 (M^+, 21), 360 (20), 284 (8), 283 (7), 187 (100), 174 (10), 161 (55).

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone (5-33)

Yield: 72%. IR (CCl_4 sol.) cm^{-1}: 2936, 2866, 2856, 2281, 1708, 1606, 1550, 1496, 1237, 1234; ^1H NMR (C_6D_6) ι: 1.10 (s, 3H), 1.21-1.78 (m, 8H), 2.17-2.54 (m, 6H), 2.60 (t, J = 6.2, 2H), 3.39 (s, 3H), 6.01 (t, J = 7.6, 1H), 6.65 (d, J = 2.7, 1H), 6.74 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.62 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 21.2 (t), 22.8 (q), 23.4 (t), 26.9 (t), 27.2 (t), 30.8 (t), 35.9 (t), 38.4 (t), 38.5 (t), 49.1 (s), 54.5 (q), 112.7 (d), 113.3 (d), 117.1 (d), 125.4 (d), 129.3 (s), 136.2 (s), 138.4 (s), 158.9 (s), 212.7 (s). HRMS: M^+, found 298.1935. $C_{20}H_{26}O_2$ requires 298.1933. MS *m/e* (%) 298 (M^+, 11), 187 (100), 159 (3), 146 (4), 128 (3), 115 (3).

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclohexanone (5-34)

Yield: 20%, mixture of 2 isomers (2:1, NMR determination). IR (CCl_4 sol.) cm^{-1}: 3079, 2936, 2867, 2836, 2360, 1708, 1606, 1550, 1496, 1464, 1233; ^1H NMR (C_6D_6) ι: 0.99 (*M*) & 1.28 (*m*) (s, 3H), 1.28-1.77 (m, 6H), 2.05-2.80 (m, 9H), 3.39 (s, 3H), 4.90-5.10 (m, 2H), 5.59-5.82 (m, 1H), 5.88 (*m*) & 6.19 (*M*) (m, 1H), 6.70 (d, J = 2.4, 1H), 6.79 (dd, J = 2.4 & J = 8.7, 1H), 7.63 (*m*) & 7.69 (*M*) (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 19.6 (*M*) & 20.6 (*m*) (q), 23.4 (*m*) & 23.5 (*M*) (t), 24.1 (*M*) & 25.3 (*m*) (t), 26.9 (*M*) & 27.0 (*m*) (t), 27.0 (*m*) & 27.1 (*M*) (t), 30.7 (*m*) & 30.9 (*M*) (t), 31.3 (*m*) & 34.9 (*M*) (t), 38.1 (*M*) & 38.3 (*m*) (t), 49.1 (*M*) & 52.9 (*m*) (d), 52.1 (s), 54.5 (q), 112.6 (d), 113.3 (*M*) & 113.4 (*m*) (d), 116.0 (t), 116.2 (*m*) & 118.4 (*M*) (d), 125.5 (d), 129.1 (*m*) & 129.5 (*M*) (s), 135.4 (*M*) & 136.3 (*m*) (s), 138.1 (*m*) & 138.2 (*M*) (d), 138.3 (*m*) & 138.4 (*M*) (s), 158.9 (*M*) & 159.0 (*m*) (s), 212.0 (*m*) & 212.3 (*M*) (s). HRMS: M^+, found 324.2090. $C_{22}H_{28}O_2$ requires 324.2089. MS *m/e* (%) 324 (M^+, 14), 213 (3), 187 (100), 174 (6), 161 (4), 159 (4), 146 (4).

5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-2,3-dimethyl-cyclohexanone (5-49)

Yield: 47%. IR (CCl_4 sol.) cm^{-1}: 2936, 2836, 1706, 1606, 1496, 1234; ^1H NMR (C_6D_6) ι: 0.75 (d, J = 7.0, 3H), 1.06 (s, 3H), 1.51 (s, 3H), 1.80-2.10 (m, 6H), 2.25-2.63 (m, 8H), 3.34 (s, 3H), 4.77 (s, 2H), 5.91 (t, J = 7.7, 1H), 6.59 (d, J = 2.6, 1H), 6.68 (dd, J_1 = 2.6 & J_2 = 8.7, 1H), 7.57 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 16.0 (q), 19.3 (q), 20.7 (q), 23.4 (t), 26.9 (t), 30.8 (t), 32.9 (t), 35.8 (t), 36.6 (d), 40.4 (d), 42.7 (d), 52.3 (s), 54.5 (q), 110.3 (t), 112.6 (d), 113.4 (d), 117.0 (d), 125.4 (d), 129.2 (s), 136.6 (s), 138.4 (s), 147.5 (s), 158.9 (s), 212.9 (s). HRMS: M^+, found 352.2403. $C_{24}H_{32}O_2$

requires 352.2402. MS *m/e* (%) 352 (M^+, 4), 187 (100), 186 (11), 174 (6), 171 (3), 159 (5), 146 (4).

5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclohexanone (5-50)

Yield: 14%. IR (CCl_4 sol.) cm^{-1}: 3080, 2937, 2836, 1707, 1606, 1496, 1234; ^1H NMR (C_6D_6) ι: 0.88-1.12 (m, 1H), 1.08 (s, 3H), 1.49 (s, 3H), 1.50-1.98 (m, 4H), 2.32-2.61 (m, 9H), 3.34 (s, 3H), 4.79 (s, 2H), 4.84-4.92 (m, 1H), 5.03 (s, 1H), 5.55-5.78 (m, 1H), 5.96 (t, J = 7.2, 1H), 6.60 (d, J = 2.7, 1H), 6.69 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.60 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 20.3 (q), 20.8 (q), 23.4 (t), 27.0 (t), 30.8 (t), 31.5 (t), 35.7 (t), 40.6 (d), 42.6 (t), 47.2 (d), 51.4 (s), 54.5 (q), 110.7 (t), 112.6 (d), 113.4 (d), 116.0 (t), 116.9 (d), 125.4 (d), 129.2 (s), 136.0 (s), 138.4 (s), 138.5 (d), 147.3 (s), 158.9 (s), 212.3 (s). HRMS: M^+, found 364.2403. $C_{25}H_{32}O_2$ requires 364.2402. MS *m/e* (%) 364 (M^+, 3), 187 (100), 186 (3), 174 (5), 161 (4), 159 (4), 146 (5).

5-Isopropenyl-3-isopropyl-2-[2-(6-methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone (5-51)

Yield : 18%. IR (CCl_4 sol.) cm^{-1}: 2939, 2836, 1704, 1606, 1550, 1496, 1256; ^1H NMR (C_6D_6) ι: 0.76 (d, J = 5.5, 3H), 0.79 (d, J = 5.5, 3H), 1.00 (s, 3H), 1.50 (s, 3H), 1.35-1.85 (m, 7H), 2.23-2.48 (m, 5H), 2.56 (t, J = 6.3, 2H), 2.84 (dd, J_1 = 5.8 & J_2 = 15.1, 1H), 3.32 (s, 3H), 4.90 (s, 2H), 5.99 (m, 1H), 6.59 (d, J = 2.7, 1H), 6.70 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.61 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 19.1 (q), 20.8 (q), 21.3 (q), 23.5 (t), 23.8 (t), 23.9 (q), 26.5 (d), 26.9 (t), 30.9 (t), 35.0 (t), 40.7 (d), 42.3 (t), 42.7 (d), 53.7 (s), 54.5 (q), 111.8 (t), 112.6 (d), 113.4 (d), 118.6 (d), 125.3 (d), 129.5 (s), 134.8 (s), 138.3 (s), 147.1 (s), 158.8 (s), 213.2(s). HRMS: M^+, found 380.2709. $C_{26}H_{36}O_2$ requires 380.2715. MS *m/e* (%) 380 (M^+, 8), 187 (100), 186 (4), 174 (6), 172 (2), 161 (3), 159 (2), 146 (4).

5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohex-3-enone (5-52) and **5-Isopropenyl-4-[2-(6-methoxy-3,4-dihydro-2H-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohex-2-enone (5-53)**

Compound **5-52**. Yield: 28% (mixture of 2 isomers 5:1). IR (CCl_4 sol.) cm^{-1}: 2974, 2950, 2836, 1713, 1606, 1496, 1233; ^1H NMR (C_6D_6) ι: 1.18 (s, 3H), 1.47 (s, 3H), 1.64 (quint., J = 6.2, 2H), 2.14 (dd, J_1 = 6.9 & J_2 = 14.2, 1H), 2.21-2.63 (m, 6H), 2.71 (dd, J = 8.9 & J = 14.2, 1H), 2.79-2.95 (m 1H), 3.34 (s, 3H), 4.68 (*M*, bs, 2H) & 4.71 (*m*, s, 1H) + 4.77 (*m*, s, 1H), 5.44 (*m*) & 5.49 (*M*) (m, 1H), 5.59 (dt, J_1 = 3.7 & J_2 = 9.9, 1H), 5.95 (dd, J_1 = 7.0 & J_2 = 8.6, 1H), 6.57 (d, J = 2.7, 1H), 6.72 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.53 (*m*) & 7.55 (*M*) (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 19.8

(*m*) & 20.0 (*M*) (q), 23.4 (t), 24.6 (*m*) & 25.0 (*M*) (q), 26.8 (t), 30.8 (t), 38.3 (t), 42.1 (*m*) & 42.6 (*M*) (t), 44.6 (*M*) & 44.9 (*m*) (d), 48.9 (s), 54.5 (q), 111.2 (*M*) & 111.4 (*m*) (t), 112.8 (d), 113.3 (d), 117.0 (*M*) & 117.2 (*m*) (d), 125.3 (d), 128.5 (d), 129.2 (s), 135.4 (d), 136.2 (*m*) & 136.4 (*M*) (s), 138.7 (s), 146.4 (s), 159.0 (s), 211.4 (*m*) & 211.6 (*M*) (s). HRMS: M^+, found 336.2084. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 3.3), 187 (100), 159 (2.6), 146 (4.1), 145 (2.1), 128 (2.2), 115 (1.7). *Compound* **5-53**. Yield: 26%. IR (CCl_4 sol.) cm^{-1}: 2970, 2937, 2836, 1678, 1606, 1550, 1496, 1233; ^1H NMR (C_6D_6) ι: 1.26 (s, 3H), 1.26-1.60 (m, 1H), 1.68 (quint, *J* = 6.2, 2H), 1.91 (s, 3H), 1.95-2.65 (m, 9H), 3.41 (s, 3H), 4.73 (s, 1H), 4.78 (s, 1H), 5.78-5.88 (m, 1H), 6.40 (bs, 1H), 6.67 (d, *J* = 2.8, 1H), 6.85 (dd, J_1 = 2.8 & J_2 = 8.7, 1H), 7.62 (d, *J* = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: 15.9 (q), 18.6 (q), 23.3 (t), 26.9 (t), 30.8 (2t), 39.6 (d), 43.0 (t), 48.9 (d), 54.5 (q), 112.8 (d), 112.9 (t), 113.3 (d), 118.5 (d), 125.2 (d), 128.9 (s), 134.9 (s), 136.1 (s), 138.6 (s), 145.3 (s), 147.3 (d), 159.0 (s), 197.5 (s). HRMS: M^+, found 336.2085. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 10), 187 (100), 174 (7), 161 (3), 159 (3), 146 (5), 128 (2), 115 (2).

General procedure for ring closure

3-Methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (5-35)

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (**5-27**, 100 mg, 0.35 mmol)) was dissolved in benzene (5 ml) and a crystal of *para*-toluene sulfonic acid (*p*-TsOH) was added. The reaction mixture was stirred at 40 °C for 4 hrs, then diluted with Et_2O (15 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 9:1) yielding **5-35** as white crystals in 87% (81 mg). Recrystallisation from MeOH gave white needles (mp 89-92 °C). IR ($CHCl_3$ sol.) cm^{-1}: 3000, 2929, 2840, 1603, 1562, 1497, 1465, 1431, 1304, 1286, 1261, 1243, 1041; ^1H NMR (C_6D_6) ι: 1.01 (s, 3H), 1.50-1.93 (m, 4H), 2.11-2.82 (m, 8H), 3.38 (s, 3H), 5.54 (bs, 1H), 6.78-6.81 (m, 2H), 1.79-7.24 (m, 1H); ^{13}C NMR (C_6D_6) ι: 21.5 (q), 23.9 (t), 24.2 (t), 28.8 (t), 30.2 (t), 36.1 (t), 40.8 (t), 43.0 (s), 54.0 (q), 111.2 (d), 113.5 (d), 120.5 (d), 124.2 (d), 126.0 (s), 129.0 (s), 129.7 (s), 138.0 (s), 148.8 (s), 158.9 (s). HRMS: M^+, found 266.1673. $C_{19}H_{22}O$ requires 266.1671. MS *m/e* (%) 266 (M^+, 100), 251 (11), 238 (7), 223 (6), 187 (7), 171 (5).

3-Methoxy-13-methyl-17-vinyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (5-36)

Yield: 82% (isomeric ratio 2:1). IR (CCl_4 sol.) cm^{-1}: 3077, 2929, 2839, 1730, 165, 1562, 1497, 1465, 1285, 1250, 1040; ^1H NMR (C_6D_6) ι: 0.87 (*M*) & 1.02 (*m*) (s, 3H), 0.78-2.98 (m, 11H), 3.39 (s, 3H), 4.86-5.17 (m, 2H), 5.46 (*m*) & 5.51 (*M*) (bs, 1H), 5.65-6.10 (m, 1H), 6.65-6.79 (m, 2H), 7.11-7.23 (m, 1H); ^{13}C NMR (C_6D_6) ι: 16.9 (*M*) & 23.3 (*m*) (q), 23.8 (t), 24.0 (*M*) & 24.2 (*m*) (t), 28.8 (t), 30.6 (*m*) & 34.6 (*M*) (t), 35.8 (*M*) & 37.3 (*m*) (t), 46.2 (*M*) & 46.5 (*m*) (s), 54.5 (q), 54.5 (*M*) & 56.4 (*m*) (d), 111.3 (d), 113.3 (*m*) & 115.3 (*M*) (t), 113.6 (d), 118.6 (*m*) & 119.3 (*M*) (d), 124.3 (d), 125.8 (*M*) & 126.1 (*m*) (s), 129.2 (s), 129.5 (s), 138.0 (s), 138.8 (*M*) & 141.0 (*m*) (d), 147.2 (*m*) & 149.2 (*M*) (s), 158.8 (s). MS *m/e* (%) 292 (M^+, 100), 277 (7), 264 (7), 263 (7), 187 (6).

17-Isopropyl-3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (5-37)

Yield: 79%, as white crystals (recryst. from MeOH, mp. 123-125 °C). IR ($CHCl_3$ sol.) cm^{-1}: 2958, 2937, 2837, 1730, 1604, 1563, 1498, 1466, 1246, 1040; ^1H NMR (C_6D_6) ι: 0.91 (d, *J* = 6.4, 3H), 0.94 (s, 3H), 0.98 (d, *J* = 6.4, 3H), 1.43-1.87 (m, 3H), 2.03-2.80 (m, 9H), 3.39 (s, 3H), 5.55 (bs, 1H), 6.70-6.79 (m, 2H), 7.21 (d, *J* = 8.1, 1H); ^{13}C NMR (C_6D_6) ι: 16.7 (q), 23.6 (t), 23.9 (t), 24.8 (t), 25.0 (t), 29.8 (t), 30.5 (d), 37.4 (2t), 46.2 (s), 55.5 (q), 60.1 (d), 112.2 (d), 114.5 (d), 120.6 (d), 125.1 (d), 126.9 (s), 129.5 (s), 130.5 (s), 138.9 (s), 150.9 (s), 159.7 (s). HRMS: M^+, found 308.2143. $C_{22}H_{28}O$ requires 308.2140. MS *m/e* (%) 308 (M^+, 100), 293 (4), 265 (11), 237 (4), 187 (7).

2-(3-Methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-propionic acid methyl ester (5-38)

Yield: 91% (isomeric ratio 7:5).

Main isomer: IR (CCl_4 sol.) cm^{-1}: 2941, 2838, 1729, 1605, 1498, 1435, 1254, 1167, 1040; ^1H NMR (C_6D_6) ι: 0.83 (s, 3H), 0.96-1.14 (m, 1H), 1.20 (d, *J* = 6.8, 3H), 1.46-1.69 (m, 1H), 1.82-2.02 (m, 1H), 2.02-2.83 (m, 9H), 3.38 (s, 3H), 3.39 (s, 3H), 5.47 (bs, 1H), 6.68-6.81 (m, 2H), 7.11-7.27 (m, 1H); ^{13}C NMR (C_6D_6) ι: 15.5 (q), 17.2 (q), 23.7 (t), 23.9 (t), 28.7 (t), 35.7 (t), 36.4 (t), 41.5 (d), 45.3 (s), 50.7 (q), 54.2 (d), 54.5 (q), 111.3 (d), 113.6 (d), 119.4 (d), 124.2 (d), 125.7 (s), 128.7 (s), 129.3 (s), 138.0 (s), 149.4 (s), 158.8 (s), 176.1 (s). MS *m/e* (%) 352 (M^+, 100), 265 (14), 264 (19), 263 (14), 249 (10), 187 (13), 171 (7), 110 (7).

Minor isomer: white crystals (recryst. from MeOH, mp. 152-155 °C). IR (CCl_4 sol.) cm^{-1}: 2939, 2892, 2836, 1728, 1604, 1498, 1458, 1434, 1250, 1164, 1040; ^1H NMR (C_6D_6) ι: 1.03 (s, 3H), 1.09

(d, *J* = 6.8, 3H), 1.55-1.76 (m, 1H), 1.83-2.78 (m, 11H), 3.37 (s, 3H), 3.40 (s, 3H), 5.43-5.52 (m, 1H), 6.64-6.78 (m, 2H), 7.12-7.23 (m, 1H); ^{13}C NMR (C_6D_6) ι: 16.0 (q), 17.3 (q), 23.7 (t), 23.9 (t), 28.7 (t), 34.9 (2t), 40.2 (d), 45.0 (s), 50.6 (q), 54.5 (d), 54.5 (q), 111.2 (d), 113.6 (d), 118.6 (d), 124.2 (d), 125.5 (s), 129.0 (s), 129.4 (s), 138.0 (s), 149.9 (s), 158.8 (s), 176.3 (s). MS *m/e* (%) 352 (M^+, 100), 264 (11), 187 (13), 184 (15), 171 (8), 161 (17).

13-Ethyl-3-methoxy-17-vinyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (5-39)

Yield: 87% (2 isomers in ratio 2:1). IR (CCl_4 sol.) cm^{-1}: 2975, 2938, 2839, 1734, 1605, 1498, 1244; ^{1}H NMR (C_6D_6) ι: 0.86 (*M*) & 0.89 (*m*) (t, *J* = 7.4, 3H), 1.13-1.86 (m, 5H), 1.98-2.90 (m, 8H), 3.38 (s, 3H), 4.88-5.18 (m, 2H), 5.47 (*M*) & 5.60 (*m*) (bs, 1H), 5.80 (*M*, dt, J_1 = 9.7 & J_2 = 17.0) & 6.06 (*m*, ddd, J_1 = 7.3, J_2 = 10.3 & J_3 = 17.2) (1H), 6.68-6.80 (m, 2H), 7.12-7.22 (m, 1H); ^{13}C NMR (C_6D_6) ι: 8.8 (*M*) & 9.5 (*m*) (q), 23.8 (t), 24.0 (t), 26.8 (t), 26.9 (t), 28.7 (*M*) & 33.8 (*m*) (t), 37.2 (*m*) & 37.7 (*M*) (t), 49.5 (*M*) & 56.7 (*m*) (d), 50.0 (s), 54.5 (q), 111.2 (d), 112.9 (*M*) & 114.9 (*m*) (t), 113.5 (d), 118.7 (*M*) & 119.6 (*m*) (d), 124.2 (d), 125.9 (s), 129.3 (s), 129.4 (s), 137.9 (s), 138.9 (*m*) & 141.2 (*M*) (d), 147.3 (s), 158.7 (s). MS *m/e* (%) 306 (M^+, 100), 278 (17), 277 (29), 249 (6), 169 (6), 165 (5).

8-Methoxy-12a-methyl-1-vinyl-1,2,3,5,6,11,12,12a-octahydro-chrysene (5-42)

Yield: 75% (2 isomers in ratio 2:1). IR (CCl_4 sol.) cm^{-1}: 2937, 2838, 1606, 1499, 1250, 1040; ^{1}H NMR (C_6D_6) ι: 1.00 (*M*) & 1.14 (*m*) (s, 3H), 1.30-2.75 (m, 13H), 3.44 (s, 3H), 5.00-5.21 (m, 2H), 5.72-6.49 (m, 2H), 6.77-6.86 (m, 2H), 7.25-7.30 (m, 1H); ^{13}C NMR (C_6D_6) ι: 18.3 (*M*) & 25.1 (*m*) (q), 22.9 (t), 23.3 (*m*)& 23.9 (*M*) (t), 23.5 (*m*) & 24.2 (*M*) (t), 24.8 (*m*) & 26.0 (*M*) (t), 29.1 (t), 33.5 (*m*) & 34.4 (*M*) (t), 34.1 (*m*) & 34.8 (*M*) (s), 49.8 (*m*) & 50.2 (*M*) (d), 54.5 (q), 111.2 (d), 113.2 (d), 114.6 (*m*) & 115.2 (*M*) (t), 119.5 (*m*) & 119.9 (*M*) (d), 124.1 (d), 124.1 (s), 129.8 (s), 137.9 (s), 139.4 (s), 140.3 (*M*) & 140.6 (*m*) (d), 141.8 (s), 158.6 (s). HRMS: M^+, found 306.1989. $C_{22}H_{26}O$ requires 306.1984. MS *m/e* (%) 306 (M^+, 100), 291 (5), 252 (8), 237 (6), 223 (5), 171 (4).

1-Isopropenyl-8-methoxy-4-methyl-1,4,4a,5,6,11,12,12a-octahydro-2H-chrysen-3-one (5-54)

Yield: 54% (2 isomers in ratio 3:1). IR (CCl_4 sol.) cm^{-1}: 2936, 2835, 1712, 1608, 1500, 1252, 1045; ^{1}H NMR (C_6D_6) ι: 1.10 (*m*) & 1.14 (*M*) (d, *J* = 6.9, 3H), 1.54 (*m*) & 1.56 (*M*) (s, 3H),1.25-2.75 (m, 13H), 3.46 (*M*) & 3.47 (*m*) (s, 3H), 3.30-3.55 (m, 1H), 4.80-4.85 (m, 2H), 6.75-6.87 (m, 2H), 7.15-7.20 (m, 1H); ^{13}C NMR (C_6D_6) ι: 15.2 (*M*) & 16.1 (*m*) (q), 19.1 (*m*) & 19.9 (*M*) (q), 24.4 (*M*) & 25.7 (*m*) (t), 24.6 (*M*) & 26.5 (*m*) (t), 27.2 (*m*) & 28.7 (*M*) (t), 28.9 (*M*) & 29.0 (*m*) (t), 33.7 (*M*) &

35.2 (*m*) (d), 39.8 (*m*) & 46.0 (*M*) (d), 40.9 (*M*) & 41.6 (*m*) (t), 44.3 (*m*) & 46.0 (*M*) (d), 46.1 (*M*) & 46.8 (*m*) (d), 54.6 (q), 111.1 (*M*) & 111.2 (*m*) (d), 112.3 (*m*) & 112.6 (*M*) (t), 113.3 (*M*) & 113.5 (*m*) (d), 123.3 (*m*) & 123.4 (*M*) (d), 129.4 (s), 130.3 (s), 132.3 (s), 137.5 (s), 146.0 (*m*) & 146.5 (*M*) (s), 158.6 (s), 211.1 (*M*) & 213.0 (*m*) (s). HRMS: M^+, found 336.2088. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 12), 265 (100), 212 (32), 211 (34), 210 (28), 171 (8), 84 (11).

8-Methoxy-1,2,3,5,6,11,12,12a-octahydro-chrysene (5-40)

6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (**5-3**, 204 mg, 1 mmol) and *tert*-Butyl-(cyclohex-1-enyloxy)-dimethylsilane (**5-24**, 678 mg, 3 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to –20 ^oC. $ZnBr_2$ (a few crystals, appr. 60 mg) was added as the catalyst and the reaction mixture was stirred for 3 hrs at –15 to –10 ^oC, then slowly warmed to room temperature and stirred overnight. P_2O_5 (appr. 10 mg) is then added and stirring is continued for 30 min at room temperature until all of compound **5-32** had disappeared (TLC). The reaction mixture was diluted with EtOAc (50 ml) and washed with saturated $NaHCO_3$ solution (25 ml) and brine (25 ml). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 98:1:1) yielding **5-40** as a slightly yellow oil in 33% yield (89 mg) over 2 steps. IR (CCl_4 sol.) cm^{-1}:2934, 2835, 1606, 1563, 1466, 1430, 1249, 1041; ^1H NMR ($CDCl_3$) ι: 1.00-2.75 (m, 15H), 3.40 (s, 3H), 5.79 (bs, 1H), 6.73 (s, 1H), 6.78 (s, 1H), 7.15-7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) ι: 22.3 (t), 23.1 (t), 23.5 (t), 24.2 (t), 25.2 (t), 30.7 (t), 31.3 (t), 36.0 (d), 54.5 (q), 111.2 (d), 113.2 (d), 119.8 (d), 123.9 (d), 125.8 (s), 128.6 (s), 129.3 (2s), 137.8 (s), 158.6 (s). HRMS: M^+, found 266.1667. $C_{19}H_{22}O$ requires 266.1671. MS *m/e* (%) 266 (M^+, 100), 238 (11), 223 (7), 165 (5), 133 (3).

8-Methoxy-12a-methyl-1,2,3,5,6,11,12,12a-octahydro-chrysene (5-41)

2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone (**5-33**, 110 mg, 0.37 mmol)) was dissolved in CH_2Cl_2 (5 ml) and a catalytic amount of P_2O_5 (approximately 10 mg) was added. The reaction mixture was refluxed for 3 hrs, diluted with EtOAc (25 ml) and washed with water (10 ml), a saturated $NaHCO_3$ solution (10 ml) and brine (10 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 4:1) yielding **5-41** as a slightly yellow oil in 88% yield (91 mg). IR (CCl_4 sol.) cm^{-1}: 2936, 2837, 1606, 1498, 1250, 1078, 1043; ^1H NMR ($CDCl_3$) ι: 1.01 (s, 3H), 1.26-1.92 (m, 6H), 2.04-2.37 (m, 3H), 2.45-2.85 (m, 5H), 3.80 (s, 3H), 5.81 (t, J = 3.9, 1H), 6.70-6.77 (m, 2H), 7.24 (d, J = 8.1, 1H). ^{13}C NMR ($CDCl_3$) ι: 18.1 (t), 22.9 (t),

23.4 (q), 23.7 (t), 26.6 (t), 29.0 (t), 32.0 (s), 37.2 (t), 38.3 (t), 55.3 (q), 110.9 (d), 113.1 (d), 120.5 (d), 123.7 (d), 127.0 (s), 128.7 (s), 129.8 (s), 138.0 (s), 141.6 (s), 158.0 (s). HRMS: M^+, found 280.1830. $C_{20}H_{24}O$ requires 280.1827. MS *m/e* (%) 280 (M^+, 100), 265 (9), 223 (5), 171 (4), 140 (4).

17-Isopropyl-3-methoxy-13-methyl-7,11,12,13,14,15,16,17-octahydro-6H-cyclopenta[a]phenanthrene (5-55)

A suspension of $Pd/CaCO_3$ (5 wt%, 50 mg) in benzene (2 ml) was stirred for 1 hr at room temperature under an atmosphere of H_2. Compound **5-37** (154 mg, 0.5 mmol) in benzene (4 ml) was then added and stirring was continued for 3 hrs more. The reaction mixture was filtered over a short plug of Hyflo, which was carefully washed with Et_2O (25 ml). Evaporation of the solvent then yielded the pure product as white crystals (145 mg, 93%), which were recrystallised from MeOH (mp. 114-116 ^oC). IR ($CHCl_3$ sol.) cm^{-1}: 2952, 2837, 1607, 1570, 1498, 1467, 1430, 1302, 1250, 1038; ^1H NMR (C_6D_6) ι: 0.69 (s, 3H), 0.89 (d, J = 6.4, 3H), 1.00 (d, J = 6.4, 3H), 0.84-2.85 (m, 15H), 3.41 (s, 3H), 6.71-6.83 (m, 2H), 7.02-7.15 (m, 1H). ^{13}C NMR (C_6D_6) ι: 11.4 (q), 22.5 (q), 23.1 (q), 23.3 (t), 24.6 (t), 25.4 (t), 28.9 (2t), 31.5 (d), 36.7 (t), 42.3 (s), 52.6 (d), 54.5 (q), 56.7 (d), 110.9 (d), 113.7 (d), 123.0 (d), 125.4 (s), 129.4 (s), 132.5 (s), 137.0 (s), 158.3 (s). HRMS: M^+, found 310.2297. $C_{22}H_{30}O$ requires 310.2297. MS *m/e* (%) 310 (M^+, 100), 308 (28), 267 (7), 225 (15), 174 (51), 173 (11), 171 (21), 93 (15).

17-Isopropyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (5-56)

Compound **5-55** (65 mg, 0.21 mmol) was dissolved in dry benzene (5 ml) and Et_3SiH (0.35 ml) and CF_3COOH (0.35 ml) were added. The reaction mixture was stirred for 12 hrs at room temperature, diluted with Et_2O (25 ml), washed with a saturated solution of NH_4Cl (10 ml) and brine (10 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 9:1) yielding **5-56** as white crystals (56 mg, 86%) which could be recrystallised from MeOH (mp. 112-114 ^oC). IR ($CHCl_3$ sol.) cm^{-1}: 2954, 2872, 1608, 1498, 1466, 1238, 1039; ^1H NMR (C_6D_6) ι: 0.60 (s, 3H), 0.90 (d, J = 6.6, 3H), 0.97 (d, J = 6.6, 3H), 0.98-2.27 (m, 15H), 2.68-2.84 (m, 2H), 3.41 (s, 3H), 6.69 (d, J = 2.7, 1H), 6.79 (dd, J_1 = 2.7 & J_2= 8.6, 1H), 7.21 (d, J = 8.6, 1H); ^{13}C NMR (C_6D_6) ι: 11.9 (q), 22.4 (q), 23.2 (q), 23.9 (t), 26.9 (t), 27.9 (t), 28.5 (t), 29.9 (t), 31.0 (d), 38.9 (d), 39.9 (t), 42.7 (s), 43.8 (d),

54.4 (q), 55.2 (d), 58.3 (d), 111.6 (d), 113.8 (d), 126.3 (d), 132.7 (s), 137.7 (s), 157.9 (s). HRMS: M^+, found 312.2458. $C_{22}H_{32}O$ requires 312.2453. MS *m/e* (%) 312 (M^+, 100), 227 (12), 199 (10), 186 (7), 174 (10), 173 (13), 160 (7), 147 (9).

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Synthesis of a chiral ring D precursor for the generation of enantiomerically pure steroid skeletons

Chapter 6

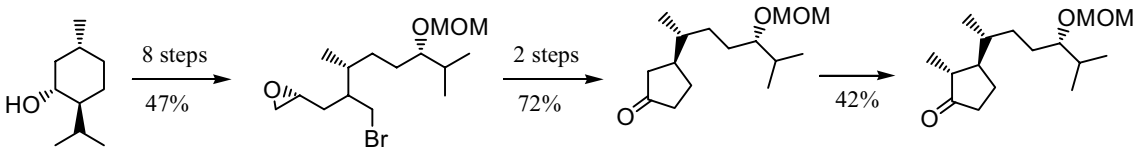
6.1. Introduction

An ultimate goal in steroid synthesis is the development of short and efficient routes to enantiomerically pure compounds. Evaluating the good results obtained in the coupling reactions of the Torgov reagent **5-1** (i.e. **6-53**) with silyl enol ether derivatives of five-membered ring D precursors (see chapter 5), we considered this chemistry promising for a chiral approach. Suitably functionalised optically active five-membered rings possessing the right configuration around the ring system are, however, not overabundant and syntheses for such compounds are usually long or low yielding, or both.

Most of the existing routes were developed to obtain ring D precursors for the synthesis of vitamin D analogs[1-9] or steroids[8-12]. Three routes starting from a chiral natural product have been published[2,7-9,13,14], next to several routes using a chiral auxiliary during synthesis[1,3,4,10,15-18], and one route using a chiral starting material obtained through biotransformation[5,6].

Daniewski and Warchol published a route starting from (-)-menthol **6-1**, giving compound **6-4** in 11 steps through ring opening, using a Bayer-Villiger reaction, to compound **6-2** followed by ring closure, through treatment with active copper, to cyclopentanone **6-3**. Methylation was necessary to obtain the desired product and could only be performed with modest regioselectively in 42% yield. This led to compound **6-4** in 14% overall yield[2].

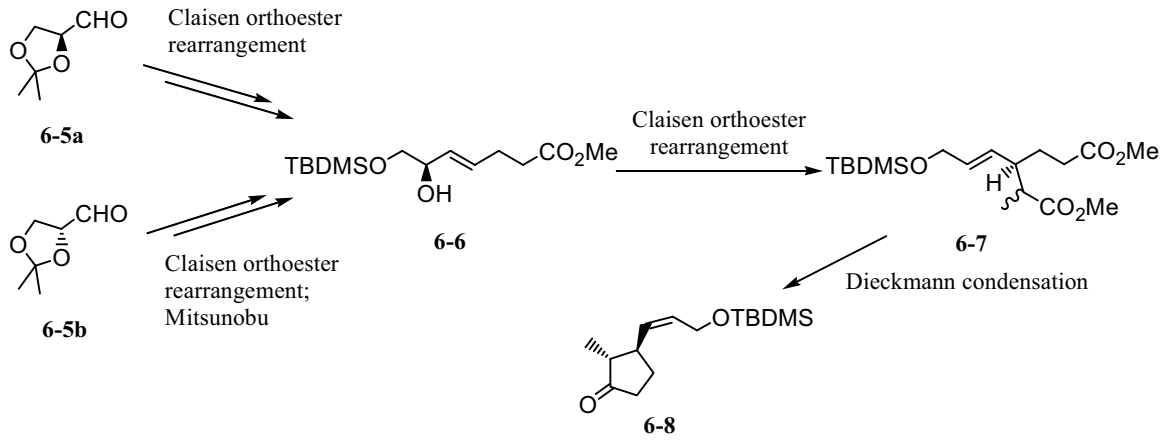
Scheme 1



6-1 **6-2** **6-3** **6-4**

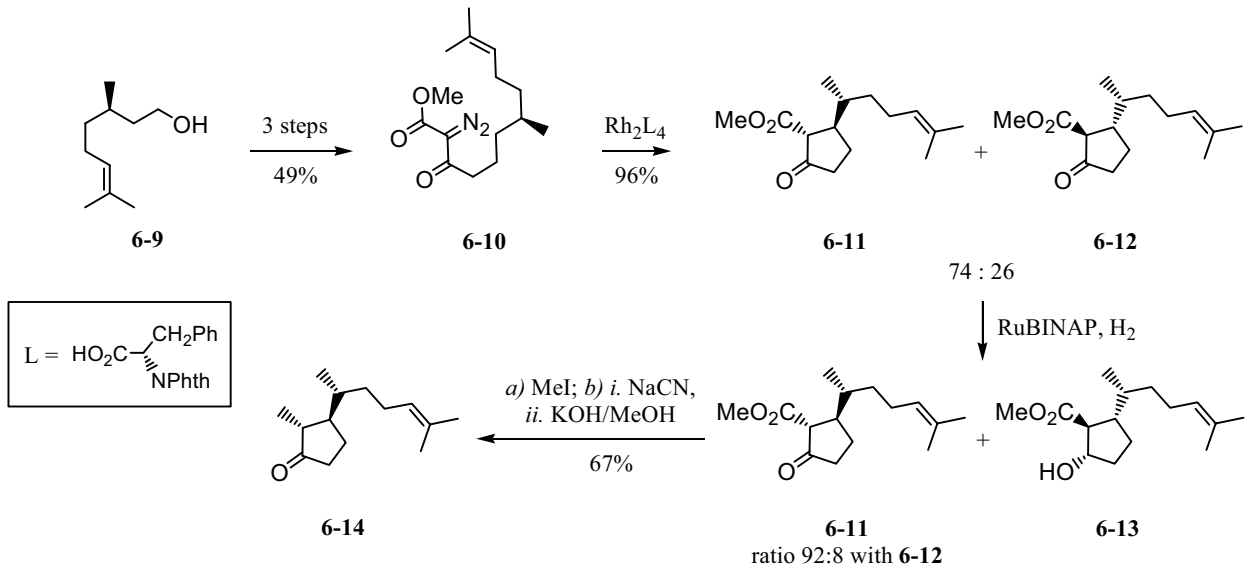
Suzuki and co-workers published two routes, both leading to optically pure compound **6-8**, starting either from (*S*)- or (*R*)-2,3-*O*-isopropylidene glyceraldehyde (resp. **6-5a** and **6-5b**), which can be obtained respectively from D-mannitol or L-ascorbic acid[8,9,14]. After Grignard addition with vinyl magnesium bromide, the routes involved a Claisen orthoester rearrangement with trimethyl orthoacetate, followed for compound **6-5b** by a Mitsunobu reaction to obtain inversion of the C6 position. A second orthoester Claisen rearrangement, this time using trimethyl orthopropionate, and a consecutive Dieckmann condensation then gave compound **6-8** in 39% overall yield in 8 steps from compound **6-5a**. The yields for the route starting from **6-5b** were much lower, being 3% overall from D-mannitol, also in 8 steps.

Scheme 2



Taber recently published an enantioselective route starting from citronellol **6-9**[7,13]. After transformation of this compound to ζ-diazo-η-ketoester **6-10**, cyclisation using a chiral rhodium catalyst led to cyclopentanone rings **6-11** and **6-12**, in the best case with a yield of 96% and a 74:26 ratio. The ratio could however be improved to 92:8 using kinetic resolution by Ru-BINAP hydrogenation, out of which pure **6-11** could be obtained *via* recrystallisation from the diastereomeric mixture. The ester function in compound **6-11** was then converted in a methyl group through methylation followed by cyanation and consecutive decarbomethoxylation leading to compound **6-14** in 23% overall yield from citronellol.

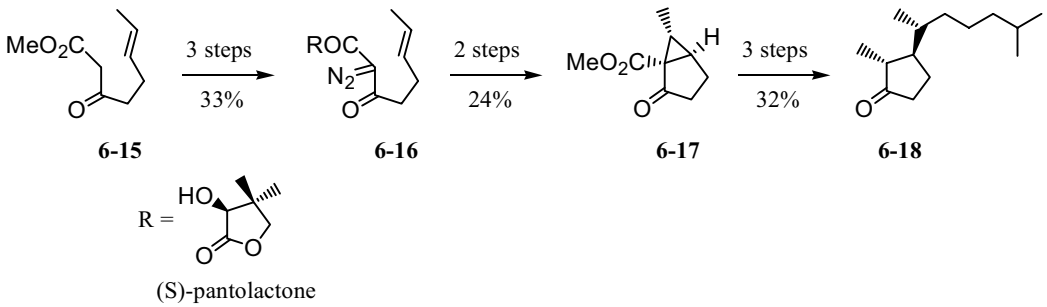
Scheme 3



The group of Tanimori published a similar synthesis using cyclisation of an ζ-diazo-η-ketoester, starting from unsaturated ketoester **6-15** and using (S)-pantolactone as a chiral auxiliary instead of a chiral catalyst[4]. Cyclisation of chiral unsaturated ζ-diazo-η-ketoester **6-16** gave a cyclopropane ring

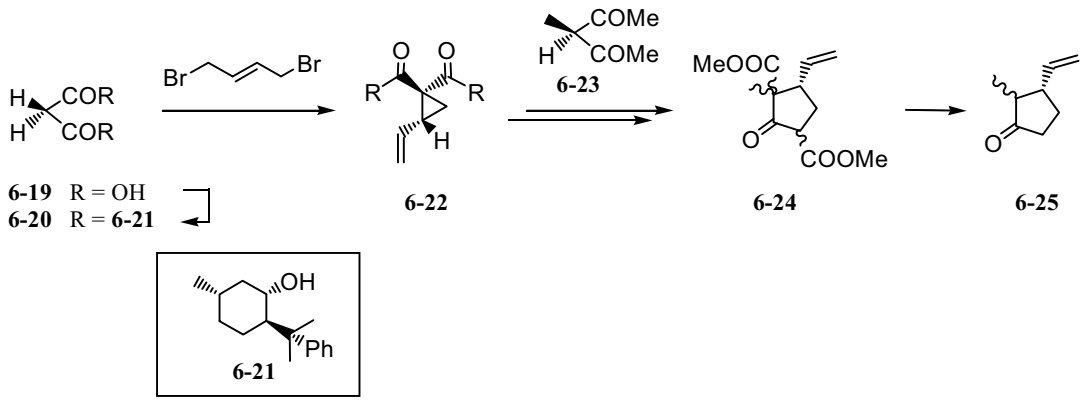
and led in two steps to bicyclic compound **6-17**. Three more steps gave compound **6-18** in 3% overall yield from **6-15**. After opening of the cyclopropane ring, the obtained intermediate bears a methylester on C2. This ester function can quite easily be converted into a methyl group in a similar fashion to the chemistry mentioned in scheme 3. Both Covey and Deslongchamps also published routes to chiral cyclopentanones using this cyclopropanation chemistry[11,12].

Scheme 4



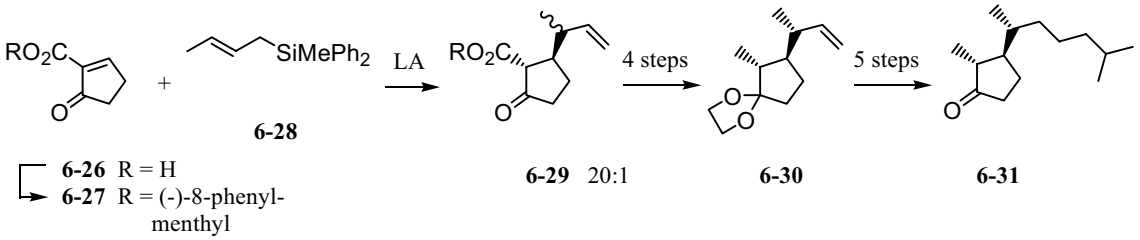
Quinkert published a route starting from malonic acid **6-19** in which (-)-8-phenyl menthol **6-21** was used as a chiral auxiliary[10]. This route involved a selective cyclopropanation reaction followed by ring opening of the cyclopropane ring. This was done *via* transesterification of the ester functions in **6-22** with methanol and consecutive, methanolate induced, condensation of the cyclopropane intermediate with the enolate of methyl malonic methyl ester **6-23,** followed by elimination of dimethylcarbonate. This gave the five-membered ring compound **6-24**, which led through decarboxylation to 2-methyl-3-vinyl-cycplopentanone **6-25** as a mixture of isomers on C2, in 25% overall yield from malonic acid. Under optimised conditions the cyclopropane compound **6-22** could be obtained as one single isomer in 65%. Compound **6-25** is the wrong stereoisomer on C3 but with the use of (+)-8-phenyl menthol as chiral auxiliary, inversion of stereochemistry can be obtained.

Scheme 5



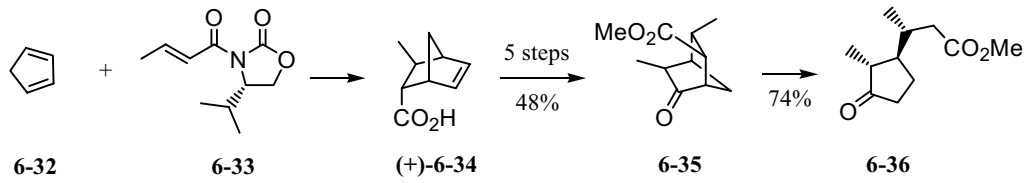
Also Pan and Tokoroyama published a route using 8-phenylmenthol as a chiral auxiliary[1,15]. They coupled (+)-8-phenylmenthol to 2-carboxy-2-cyclopentenone and could in this way perform a stereoselective addition of the product **6-27** with *E*-crotylsilane **6-28**, obtaining **6-29** with complete stereoselectivity on C2 and C3 and good stereoselectivity in the side chain. The ester function on C2 was then converted into a methyl group and further transformation led to ring D precursor **6-31**. Unfortunately, no yields were reported for this synthesis route.

Scheme 6



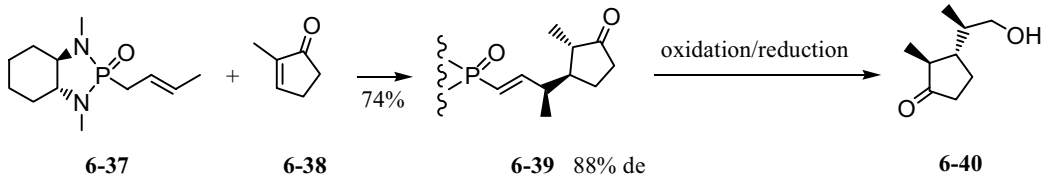
Shimizu and co-workers used norbornane skeleton **(+)-6-34** as starting material[3,16]. This compound can be obtained pure from a stereoselective Diels-Alder addition of chiral crotonyl amide **6-33** and cyclopentadiene in 82% yield[19] and was converted in 5 steps into compound **6-35**. Ring opening then led to 2-methylcyclopentanone **6-36** in 35% overall yield from **6-34**.

Scheme 7



Hanessian and co-workers published a route involving an addition of *ζ,β*-unsaturated ketones with chiral, non-racemic bicylcic phosphonamides, coupled with a crotyl or allyl group[17]. This addition gave *trans* coupled products and reported yields varied from 74% to 80%. One of the synthesised compounds was **6-39**, which has the wrong absolute configuration for our purpose but an easy

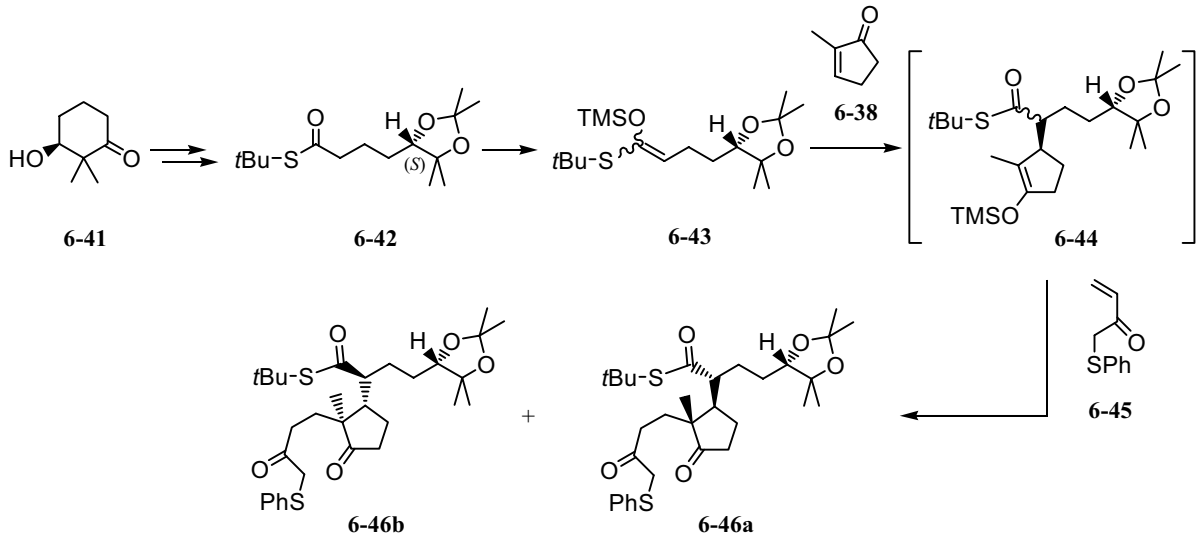
Scheme 8



switch to its enantiomer should be possible by using the opposite phosphonamide. Consecutive oxidation and reduction yielded compound **6-40**. Later on Fuji's group published a similar route using a different chiral phosphonamide but they obtained mainly *cis* coupled products[18].

Finally, Wicha and co-workers published a route that led in 7 steps to silyl enol ether **6-44**, which was not isolated but immediately reacted further with ζ3η-unsaturated ketone **6-45**[5,6]. This gave compounds **6-46a** and **6-46b** as a 75:25 diastereomeric mixture in 23% overall yield from compound **6-41**. The latter compound was first obtained in optically pure form using Baker's yeast reduction of 2,2-dimethyl-cyclohexane-1,3-dione, following the method of Mori[20]. Later publication showed that the stereoselectivity of the first Mukaiyama coupling reaction was dependent of the chain length between the silyl enol ether and the remote chiral centre used for asymmetric induction. Indeed, inversion of facial selectivity was observed when was switched between 1,3- and 1,4- asymmetric induction[6].

Scheme 9

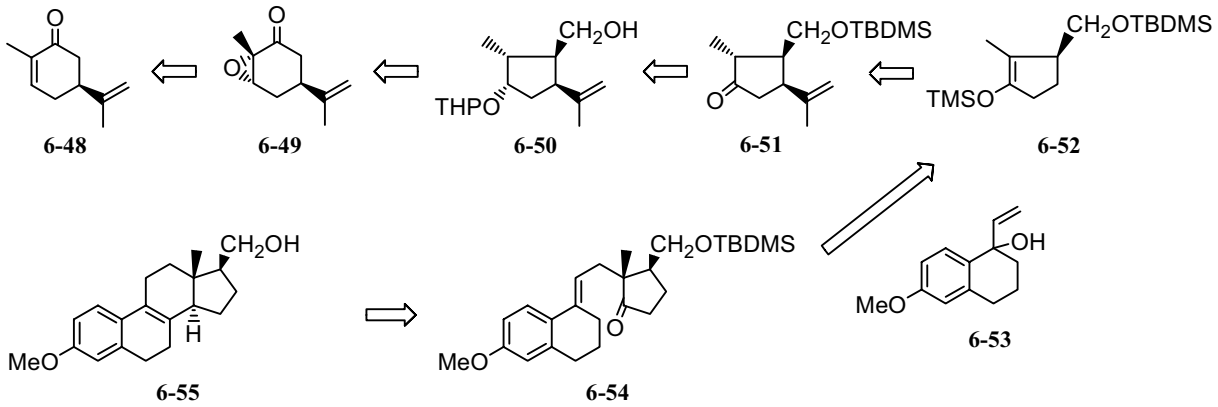


6.2. Synthesis of a chiral ring D precursor

Compounds from the chiral pool seemed to offer good opportunities to access a chiral ring D precursor and we decided to explore a synthesis starting from carvone. A sequence involving a ring contraction of the carvone molecule using a Favorskii rearrangement has been reported in the literature and leads in five steps to compound **6-50** in 36% overall yield[21]. Further transformation then could lead in a few more steps to compound **6-52**, suitable as a chiral ring D precursor for our synthesis of steroid skeletons with a functionalised substituent at C17 (see scheme 10).

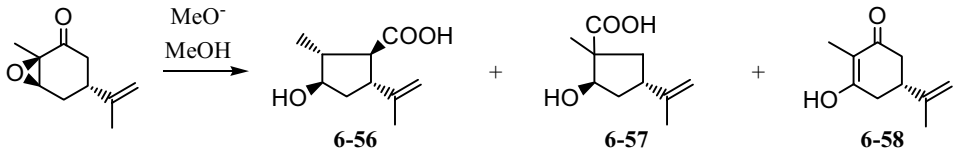
To obtain the correct stereochemistry on C3 in compound **6-52** (C17 in the final steroid compound) the reaction sequence must be started from (*S*)-(+)-carvone. Epoxidation of the double bond then leads directly to compound **6-49** and opens up the possibility for a Favorskii rearrangement.

Scheme 10



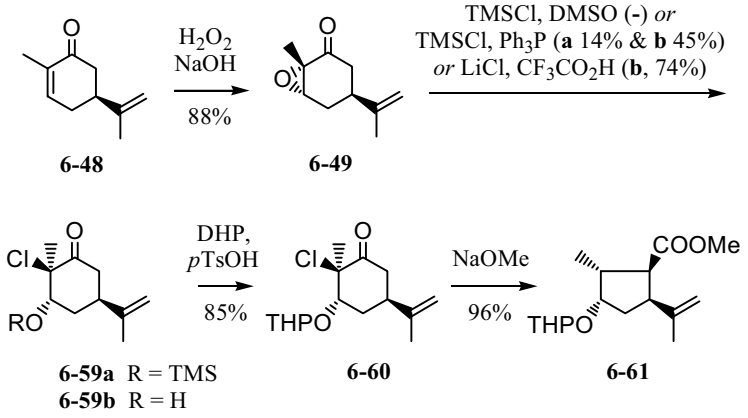
Unfortunately, when the Favorskii rearrangement is performed starting directly from the epoxide, this does not give only the desired product **6-56**, but also regioisomer **6-57** and compound **6-58** in which ring contraction has not taken place, but only opening of the epoxide ring has occurred (scheme 11)[21-24].

Scheme 11



For a better result, the epoxide ring has first to be opened stereoselectively to compound **6-59**. Although in the literature a good epoxide-ring opening in compound **6-49** was reported using TMSCl[21], in our hands this did not give a reasonable yield and we obtained better results using LiCl in combination with trifluoroacetic acid[25], giving directly the free alcohol. In this way the consecutive protection of the alcohol as a diastereomeric mixture of the THP (tetrahydropyranyl)

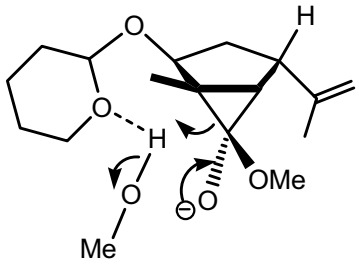
Scheme 12



ethers to compound **6-50** also became more straightforward, not requiring an intermediate deprotection step. Protection using a THP-group was found to be necessary for complete stereo- and regioselectivity in the Favorskii rearrangement[21,25].

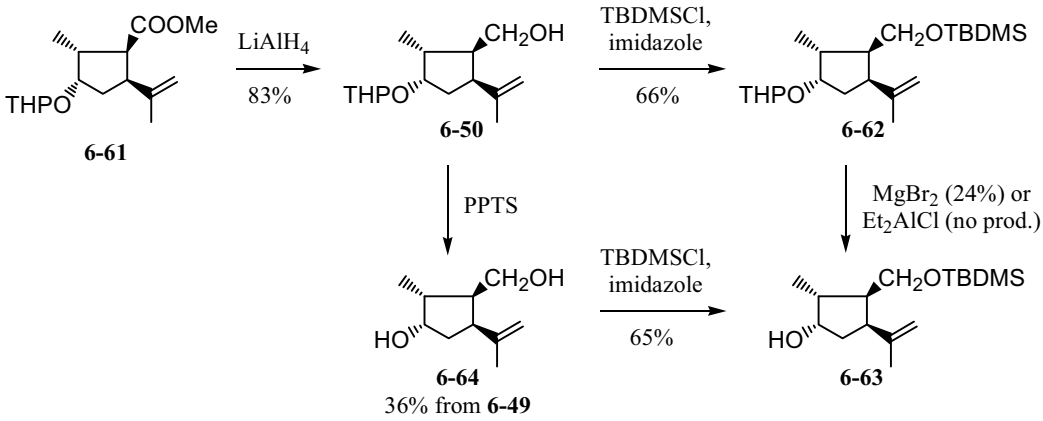
The use of other protecting groups on the alcohol moiety, such as silyl groups, did not give as good results as with the THP ethers[26]. The exact reason for the enhancement in selectivity using this protecting group is not known but coordination of the oxygen in the THP ring with the alcohol molecule that will donate its proton during the rearrangement could be a possible explanation, making the desired regioselective opening of the cyclopropane ring more easy and opening on the other side, giving rearrangement to regioisomer **6-57** less probable (see figure 1 and scheme 11).

Figure 1



Compound **6-50**, obtained after reduction of the rearrangement product **6-61**, could be easily converted into compound **6-63** *via* compound **6-64** (scheme 13). Our attempts to first protect the primary alcohol and then selectively remove the THP group using $MgBr_2$[27] or Et_2AlCl[28] failed to give reasonable yields, giving respectively 24% of product **6-63** or no desired product at all. Deprotection followed by selective reprotection of the primary alcohol gave better results. Although a yield of 65% for the selective reprotection of the primary alcohol in the diol **6-64** is still not extremely high, the remaining products consist of unreacted diol (21%) and the double protected compound (12.5%), which can be separated easily from the desired compound **6-63** and from each

Scheme 13

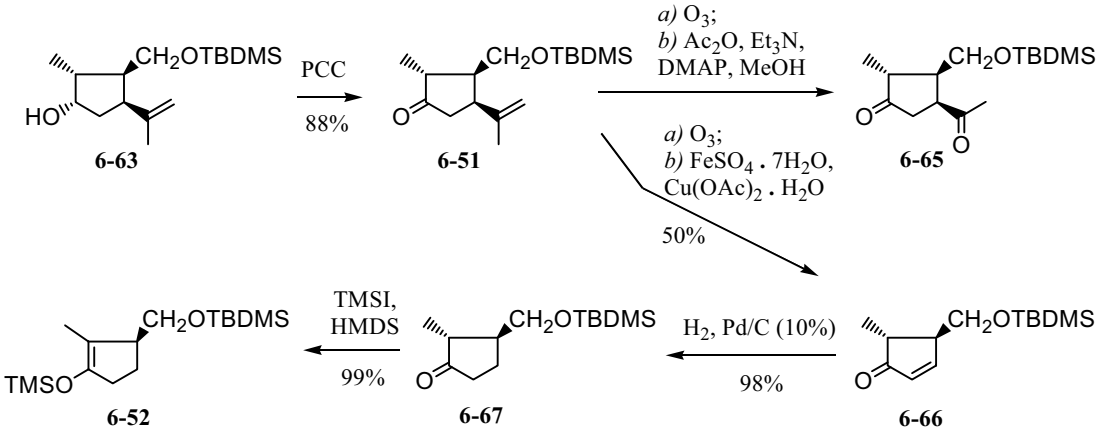


other. The latter can be deprotected (e.g. using 1.1 eq. of TBAF in THF for 1 hr at room temperature) and can be put into reaction again together with the non-reacted diol.

Oxidation of the secondary alcohol group in **6-63** opens up the possibility for regioselective elimination of the isopropenyl tail to compound **6-51** (scheme 14). Ozonolysis followed by Criegee rearrangement under standard conditions[29,30] was troublesome in our hands and usually gave product **6-65**, in which normal ozonolysis of the double bond to the ketone had taken place. Only with the use of $FeSO_4$ and $CuSO_4$ salts for decomposition of the intermediate a fair yield (50%) of the desired product **6-66** was obtained.

Catalytic reduction of the double bond and regioselective formation of the silyl enol ether, both in near quantitative yields, finally led to the desired chiral ring D precursor **(+)-6-52** in 10% overall yield starting from (*S*)-(+)-carvone.

Scheme 14



6.3. Synthesis of an optically pure steroid skeleton

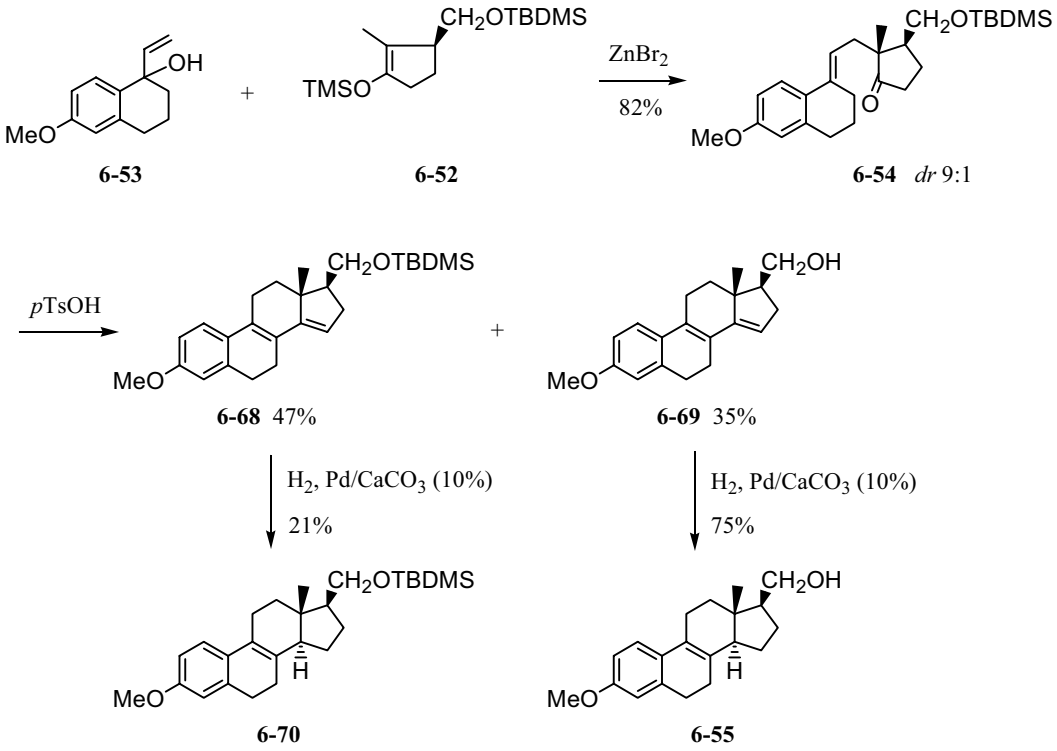
Compound **(+)-6-52** was put into reaction with Torgov reagent **6-53**, which yielded secosteroid **(-)-6-54** in 82% yield as two diastereomers on C13, with a diastereomeric ratio of 9:1 (scheme 14). Although no crystals could be obtained to prove the configuration of the main product using X-ray crystallography, the results from chapter 5 suggest that this main product is most probably the compound with the desired η-configuration on C13.

Subsequent cyclisation gave the steroidal diene **(-)-6-68** in 47% yield, next to compound **(-)-6-69**, in 35% yield, in which deprotection of the alcohol function in the side chain had also taken place. Selective reduction was tried on both these compounds. Reduction of the protected diene **(-)-6-68** only yielded 21% of reduced **6-70**, together with some starting material and a large amount of decomposition products. Better results were obtained with **(-)-6-69**, giving a yield of 75% of **6-55**, the remaining being unreduced starting material. Moreover, compound **(-)-6-68** appeared unstable upon storage, quickly decomposing to a complex mixture of products, even when kept at –18 ^{o}C.

Product **(-)-6-69** however remained stable upon storage and complete deprotection of the alcohol moiety in the side chain (e.g. using TBAF in THF) directly following the cyclisation, and previous to further transformation of the compound, is therefore the best procedure.

Complete conversion of the dienes to reduced products appeared troublesome in both cases. As the product and the starting material are not easily separable, conversion to completeness was attempted, but mainly decomposition occurred for an unknown reason and almost no desired product could be isolated. Milder conditions should therefore be tried for this reaction step.

Scheme 15



Although the overall yield of optically active steroid compounds **6-70** and **6-55** from (*S*)-(+)-carvone are low, the applicability of this reaction sequence for the generation of enantiomerically pure steroid skeletons has clearly been shown. The development of straightforward, easy and high yielding syntheses for *chiral* ring D precursors would make this route a very good method for accessing optically active steroid skeletons, and is therefore essential to achieve easy generation of this important class of pharmaceuticals.

Experimental

3-Hydroxymethyl-4-isopropenyl-2-methyl-cyclopentanol (6-64)

To a cooled solution (at –15 ^{o}C) of (*S*)-(+)-carvone (**6-48**) (10 g, 0,066 mol) in methanol (66 ml) and 22 ml of H_2O_2 (30%, 0,198 mol), 5 ml of 6.6M NaOH solution in H_2O was added dropwise over a period of 5 min. During the addition the temperature was carefully kept below 0 ^{o}C. The mixture was stirred for 2 hr at 0^{o}C and then the solution was allowed to warm to room temperature over a period of 1 hr. The reaction mixture was poured in water (400ml) and the water solution was extracted 4 times with diethyl ether (100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 9.8 g of crude product **6-49**, which was used without any further purification in the next step. ^{1}H NMR (C_6D_6) ι: 1.31 (s, 3H), 1.62 (s, 3H), 1.75-2.05 (m, 2H), 2.28 (bd, *J* = 14.6, 1H), 2.38-2.75 (m, 2H), 3.37 (d, *J* = 2.8, 1H), 4.63 (bs, 1H), 4.70 (bs, 1H); ^{13}C NMR (C_6D_6) ι: 15.2 (q), 20.5 (q), 28.6 (t), 34.9 (d), 41.7 (t), 58.6 (s), 61.2 (d), 110.4 (d), 146.3 (s), 205.3 (s).

To an ice-cooled solution of **6-49** (4.3 g, 26 mmol) in dry THF (100 ml), LiCl (1.8 g, 43 mmol) and CF_3COOH (4.9 g, 43 mmol) were added. The mixture was stirred for 20 min at 0^{o}C and during 2 hrs at room temperature. Water (500 ml) was added and the reaction mixture was extracted with diethyl ether (3x100 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (100ml), water (100 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product (5.2 g) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) ι: 1.63 (s, 3H), 1.73 (s, 3H), 1.87 (ddt, J_1 = 2.1, J_2 = 3.6, J_3 = 14.2, 1H), 2.28-3.10 (m, 5H), 4.23 (dd, J_1 = 3.7, J_2 = 6.3, 1H), 4.75 (bs, 1H), 4.78 (bs, 1H); ^{13}C NMR (C_6D_6) ι: 20.3 (q), 22.1 (q), 32.8 (t), 38.9 (d), 41.1 (t), 67.9 (s), 76.8 (d), 110.6 (t), 146.4 (s), 205.3 (s).

A solution of the product from the former reaction (5.2 g) in dry CH_2Cl_2 (100 ml) was cooled on ice and DHP (dihydropyran, 6.4 g, 76 mmol) was added, followed by a catalytic amount of *p*-TsOH (50 mg). The mixture was stirred for 2 hrs during which the temperature was allowed to rise to room temperature (the reaction mixture became green). After evaporation of CH_2Cl_2 under reduced pressure, the residue was dissolved in PE and purified over a short plug of silica (5 g), yielding 4.7 g of crude product **6-60** as a mixture of diastereomers, which were used without any further purification in the next step.

To 20 ml of an ice-cooled solution of NaOMe (1.2M) in methanol, 4.7 g of **6-60**, from the former experiment, in 10 ml of dry methanol was added dropwise over a period of 10 min. During the addition, a precipitate started to form and it appeared necessary to keep the temperature of the reaction below 15 ^{o}C. The reaction mixture was stirred for a further 15 min, before water (300 ml)

was added and the mixture was extracted with diethyl ether (3x100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 4.43 g of crude product **6-61** as a slightly yellow oil (mixture of two diastereomers). The crude product was used without any further purification in the next step.

To an ice-cooled mixture of $LiAlH_4$ (1g, 26 mmol) in dry diethyl ether (20 ml) was added dropwise a solution of **6-61** (4.43 g) in dry diethyl ether (10 ml), over a period of 10 min. The reaction mixture was stirred for a 2 hrs at room temperature. Then 1 ml of water was carefully added (ice-cooling), followed by 4 ml of a 4M NaOH solution and again 4 ml of water. After stirring for 30 min the reaction mixture was filtered to remove the inorganic precipitate, which was carefully washed with ether (20 ml), and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product **6-50** (3.31 g, slightly yellow oil) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) ι: 0.98 & 1.09 (2d, *J* = 6.6, 3H), 1.30-2.15 (m, 10H), 2.78-3.10 (m, 1H), 3.47 (q, *J* = 5.5, 2H),3.80-3.93 (m, 1H), 4.00-4.15 (m, 1H)m 4.52-4.67 (m, 1H), 4.76 (bs, 1H), 4.85 (bs, 1H).

The crude product **6-50** from the former experiment (3.1 g) in 35 ml of methanol and a catalytic amount of pyridinium *para*-toluenesulfonic acid (PPTS, 10 mol%) were stirred at 50 ^{o}C during 2 hrss. After evaporation of methanol under reduced pressure, the residue (2.35 g) was purified by rapid column chromatography (PE:EtOAc 10:1), yielding 1.5 g of pure **6-64** (32% overall yield from (*S*)-(+)-carvone). $[\zeta]_D^{20}$ +13.6 (c 12.0 in CH_3Cl); IR (film) cm^{-1}: 3356 (br), 3081, 2957, 2932, 1646, 1453, 1375, 1080, 1041, 891; ^{1}H NMR ($CDCl_3$) ι: 1,01 (d, *J*=6,7 Hz, 3H), 1,65-2,23 (m, 9H), 2,94-3,04(m, 1H), 3,44 (d, *J*=5 Hz, 2H), 4,11 (m, 1H), 4,72 (s, 1H), 4,82 (s, 1H). ^{13}C NMR ($CDCl_3$) ι: 14.01 (q), 23,83(q), 38,75(t), 41,6(d), 44,76(d), 47,96(d), 63,61(t), 74,47(d), 110,55(t), 147,0 (s). HRMS: M^+, found 170.1308. $C_{10}H_{18}O_2$ requires 170.1307. MS *m/e* (%) 170 (M^+, <1), 155 (3), 152 (4), 121 (81), 99 (55), 81 (100), 72 (64), 71 (66), 55 (69), 43 (56).

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanol (6-63)

A solution of **6-64** (3.8 g, 22 mmol) in dimethylformamide (DMF, 70 ml) was cooled to 5 ^{o}C and TBDMSCl (3.7 g, 24 mmol) in DMF (20 ml) was added by rapid dropping (5 min), followed by a solution of imidazole (3.8 g, 56 mmol) in DMF (10 ml). The reaction mixture was stirred for 20 min at 5 ^{o}C and then for 3 hrs at 30 ^{o}C. Water was added (500 ml) and the water layer was extracted with Et_2O (4 x 100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EA 15:1), yielding 4.15 g of **6-63** (65%), 1.1 g of the diprotected compound (12.5%) and 0.46 g of unreacted material **6-64** (12%). $[\zeta]_D^{20}$ –3.1 (c 5.0 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 3631, 3491 (br),

3083, 2951, 2894, 2858, 1647, 1471, 1459, 1255, 1093, 1003, 889; ^{1}H NMR (C_6D_6) ι: 0.16 (s, 6H), 0.86 (s, 9H), 1.08 (d, J = 6.9, 3H), 1.75 (s, 3H), 1.64-2.04 (m, 5H), 2.89-2.98 (m, 1H), 3.28 (dd, J_1 = 7.6 & J_2 = 10.1, 1H), 3.47 (dd, J_1 = 5.3 & J_2 = 10.1, 1H), 4.17 (dd, J_1 = 3.6 & J_2 = 4.4, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) ι: -5.5 (2q), 14.7 (q), 18.2 (s), 23.8 (q), 25.9 (3q), 38.8 (t), 42.5 (d), 44.8 (d), 47.5 (d), 64.1 (t), 74.6 (d), 110.1 (t), 145.2 (s). HRMS: $[M\text{-}t\text{Bu}]^+$, found 227.1470. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 251 ($[M\text{-}CH_3\text{-}H_2O]^+$, 2), 227 (32), 209 (76), 185 (20), 95 (18), 93 (14), 75 (100), 73 (29).

Diprotected compound. ^{1}H NMR (C_6D_6) ι: 0.07 (s, 6H), 0.09 (s, 6H), 0.89 (s, 18H), 1.02 (d, J = 6.6, 3H), 1.60 (dd, J_1 = 6.4 & J_2 = 12.4, 1H), 1.77 (s, 3H), 1.70-1.97 (m, 3H), 2.89-3.02 (m, 1H), 3.28 (dd, J_1 = 7.1 & J_2 = 10.0, 1H), 3.47 (dd, J_1 = 5.1 & J_2 = 10.0, 1H), 4.09-4.13 (m, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) ι: -5.4 (2q), -4.7 (q), -4.6 (q), 15.5 (q), 18.2 (s), 23.9 (q), 25.9 (6q), 39.5 (t), 43.2 (d), 43.7 (d), 47.5 (d), 64.2 (t), 74.8 (d), 109.7 (t), 145.7 (s).

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanone (6-51)

To a solution of **6-63** (4.1 g, 14.4 mmol) in dry CH_2Cl_2 (120 ml), to which 4 g of molecular sieves (3Å) were added, 4.5 g of pyridinium chlorochromate (PCC, 21.6 mmol) was added in three portions over a period of 3 hrs. The reaction mixture was stirred for 2 hrs more, filtered over a short plug of silica and evaporated under reduced pressure. The residue was dissolved in Et_2O (200 ml) washed with water and brine, dried ($MgSO_4$) and evaporated again under reduced pressure. The crude product was purified by flash chromatography (PE:EtOAc 15:1), yielding 3.6 g of **6-51** (88%), next to some minor unidentified products. $[\zeta]_D^{20}$ +21.2 (c 1.25 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 2958, 2931, 2859, 1743, 1471, 1254, 1091; ^{1}H NMR ($CDCl_3$) ι: 0.01 (s, 6H), 0.83 (s, 9H), 1.13 (d, J = 7.5, 3H), 1.77 (s, 3H), 2.05-2.60 (m, 5H), 2.97 (bq, J = 8.0, 1H), 3.57 (d, J = 7.9, 2H), 4.69 (s, 1H), 4.88 (s, 1H). ^{13}C NMR ($CDCl_3$) ι: -5.7 (2q), 15.9 (q), 18.1 (s), 22.6 (q), 25.7 (3q), 41.7 (t), 42.6 (d), 45.6 (d), 47.9 (d), 62.8 (t), 111.5 (t), 143.9 (s), 221.2 (s). HRMS: $[M\text{-}CH_3]^+$, found 267.1782. $C_{15}H_{27}O_2Si$ requires 267.1780. MS *m/e* (%) 282 (M^+, 0.03), 267 (2.7), 225 (100), 195 (8), 133 (20), 131 (15), 75 (59), 73 (22).

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-cyclopent-2-enone (6-66)

A stirred solution of **6-51** (1 g, 3.54 mmol) in CH_2Cl_2 (24 ml) and MeOH (20 ml) was cooled to –78 ^{o}C and purged with ozone until a pale blue colour appeared (~15 min). Nitrogen was then bubbled through for 30 min to remove the excess of ozone and $FeSO_4.7H_2O$ (0.98 g, 3.54 mmol) and $Cu(OAc)_2.H_2O$ (1.4 g, 7.1 mmol) were added. The reaction mixture was allowed to warm to room temperature overnight, after which the solvents were evaporated under reduced pressure. The

residue was dissolved in water and extracted with Et_2O (4 x 100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 15:1), yielding 0.43 g of **6-66** (50%), next to some unidentified products and **6-65**. $[\zeta]_D^{20}$ +122.4 (c 6.6 in CH_3Cl); ^1H NMR ($CDCl_3$) ι: 0.02 (s, 6H), 0.75 (s, 9H), 1.17 (d, J = 7.4, 3H), 2.09 (dq, J_1 = 2.5 & J_2 = 7.5, 1H), 2.65 (m, 1H), 3.68 (m, 2H), 6.15 (dd, J_1 = 2.0 & J_2 = 5.8, 1H) 7.56 (dd, J_1=2.3 & J_2=5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) ι: -5.5 (2q), 14.9 (q), 18.9 (s), 25.8 (3q), 43.2 (d), 52.9 (d), 64.3 (t), 133.7 (d), 163.9 (d), 212.1 (s).

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-cyclopentanone (6-67)

To a solution of **6-66** (200 mg, 0.83 mmol) in *t*BuOMe (10 ml) was added Pd on C (10%, 20 mg) and the suspension was shaken under hydrogen atmosphere pressure (50 psi [3.45 bar]) during 1 hr. The reaction mixture was filtered over a short plug of Hyflo, which was then carefully washed with ether. The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure yielding pure **6-67** (198 mg, 98%), which needed no further purification. $[\zeta]_D^{20}$ –46.3 (c 1.7 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 2957, 2925, 2876, 2858,1743, 1470, 1255, 1107; ^1H NMR ($CDCl_3$) ι: 0.03 (s, 6H), 0.88 (s, 9H), 1.16 (d, J = 7, 3H), 1.61-2.44 (m, 6H), 3.7 (m, 2H); ^{13}C NMR ($CDCl_3$) ι: -5.1 (2q), 12.8 (q), 23.6 (t), 25.8 (3q), 37.2 (t), 46.2 (d), 46.8 (d), 64.3 (t). HRMS: $[M\text{-}CH_3]^+$, found 227.1471. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 227 ($[M\text{-}CH_3]^+$, 2.6), 185 (100), 141 (13), 129 (18), 75 (58), 73 (11).

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-1-trimethylsilanyloxy-cyclopentene (6-52)

Compound **6-67** (174 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (5 ml) and hexamethyl disilazane (HMDS, 0.550 ml, 2.6 mmol) was added, followed by TMSI (0.312 ml, 2.2 mmol). The reaction mixture was stirred overnight at room temperature, diluted with Et_2O (15 ml) and washed with a saturated solution of $NaHCO_3$ and brine. After drying (Na_2SO_4) the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:Et_2O:Et_3N 98:1:1) giving 225 mg of pure product **6-52** (99%). $[\zeta]_D^{20}$ +15.4 (c 5.5 in *n*-C_6H_{12}); IR (CCl_4 sol.) cm^{-1}: 2958, 2924, 2898, 2857, 1685, 1329, 1253, 1205, 1107, 1065, 1006, 920; ^1H NMR (C_6D_6) ι: 0.03 (s, 6H), 0.14 (s, 9H), 0.97 (s, 9H), 1.67 (s, 3H), 1.64-1.93 (m, 2H), 2.15-2.34 (m, 2H), 2.50-2.67 (m, 1H), 3.44 (dd, J_1 = 6.3 & J_2 = 9.7, 1H), 3.59 (dd, , J_1 = 4.8 & J_2 = 9.7, 1H); ^{13}C NMR (C_6D_6) ι: -5.4 (2q), 0.6 (3q), 10.8 (q), 18.4 (s), 24.0 (t), 26.0 (3q), 32.8 (t), 47.9 (d), 66.1 (t), 113.4 (s), 148.3 (s). HRMS: M^+, found 314.2095. $C_{16}H_{34}O_2Si_2$ requires 314.2097. MS *m/e* (%) 314 (M^+, 2), 299 (2), 257 (2), 169 (100), 147 (2), 73 (20).

3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (6-54)

6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (**6-53**, 68 mg, 0.33 mmol) and compound **6-52** (314 mg, 1 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to –20 ^oC. $ZnBr_2$ (a few crystals, appr. 20 mg) was added as the catalyst and the reaction mixture was stirred for 4 hrs at -5 ^oC. When all of compound **6-53** had disappeared (TLC), EtOAc (25 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc 9:1) yielding compound **6-54** as mainly one diastereomer (ratio 9:1) and a colourless oil in 82% yield (116 mg, ratio 9:1). *Main diastereomer.* $[\zeta]_D^{20}$ –16.5 (c 2.34 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 2953, 2932, 2896, 2859, 1740, 1606, 1496, 1464, 1255, 1100; ^1H NMR (C_6D_6) ι: 0.02 (s, 6H), 0.94 (s, 9H), 0.97 (s, 3H), 1.10-1.34 (m, 1H), 1.60-1.95 (m, 4H), 2.05-2.26 (m, 2H), 2.30-2.64 (m, 6H), 3.33 (s, 3H), 3.35-3.62 (m, 2H), 6.00 (bt, J = 7.8, 1H), 6.57 (d, J = 2.7, 1H), 7.72 (dd, J_1 = 2.7 & J_2 = 8.7, 1H), 7.60 (d, J = 8.7, 1H); ^{13}C NMR (C_6D_6) ι: -5.7 (2q), 17.2 (q), 18.1 (s), 22.8 (t), 23.5 (t), 25.8 (q), 26.9 (t), 30.8 (t), 35.9 (t), 36.8 (t), 44.6 (d), 51.1 (s), 54.5 (q), 64.4 (t), 112.7 (d), 113.3 (d), 117.3 (d), 125.3 (d), 129.3 (s), 136.6 (s), 138.6 (s), 159.0 (s), 220.1 (s). HRMS: M^+, found 428.2755. $C_{26}H_{40}O_3Si$ requires 428.2747. MS *m/e* (%) 428 (M^+, 8.1), 187 (100), 174 (3.2), 161 (3.1), 159 (3.5), 75 (2.6), 73 (3.4).

***tert*-Butyl-(3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]-phenanthren-17-ylmethoxy)-dimethyl-silane (6-68) and (3-Methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-methanol (6-69)**

Compound **6-54** (108 mg, 0.25 mmol)) was dissolved in benzene (5 ml) and a crystal of *para*-toluenesulfonic acid (*p*-TsOH) was added. The reaction mixture was stirred at 40 ^oC for 6 hrs, then the reaction mixture was diluted with Et_2O (15 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE: EtOAc 9:1) yielding 47% of **6-68** (48 mg) and 35% of **6-69** (26 mg).

6-68. $[\zeta]_D^{20}$ –9.3 (c 2.89 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2858, 1607, 1464, 1255; ^1H NMR (C_6D_6) ι: 0.10 (s, 6H), 1.00 (s, 3H), 1.02 (s, 9H), 1.20-1.38 (m, 1H), 1.55-1.78 (m, 2H), 2.10-2.80 (m, 8H), 3.38 (s, 3H), 3.65-3.88 (m, 2H), 5.53 (bs, 1H), 6.68-6.79 (m, 2H), 7.19 (d, J = 9.3, 1H); ^{13}C NMR (C_6D_6) ι: -5.5 (2q), 16.1 (q), 18.2 (s), 23.8 (t), 24.0 (t), 25.9 (3q), 28.8 (t), 33.8 (t), 36.1 (t), 44.9 (s), 53.6 (q), 54.5 (d), 63.7 (t), 111.2 (d), 113.6 (d), 119.3 (d), 124.2 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.0 (s), 149.8 (s), 158.8 (s). HRMS: M^+, found 410.2639. $C_{26}H_{38}O_2Si$ requires

410.2641. MS *m/e* (%) 410 (M^+, 100), 395 (4), 353 (8), 278 (43), 263 (33), 89 (9), 75 (17), 73 (23). **6-69**. $[\zeta]_D^{20}$ –34.0 (c 1.08 in CH_3Cl); IR (CCl_4 sol.) cm^{-1}: 2933, 2835, 1606, 1561, 1498, 1248, 1216, 1044; ^1H NMR (C_6D_6) ι: 0.91 (s, 3H), 1.01 (b, 1H), 1.50-1.70 (m, 1H), 1.95-2.73 (m, 10H), 3.37 (s, 3H), 3.45-3.70 (m, 2H), 5.50 (bs, 1H), 6.68-6.75 (m, 2H), 7.17 (d, J = 9.8, 1H); ^{13}C NMR (C_6D_6) ι: 16.1 (q), 23.8 (t), 24.0 (t), 28.8 (t), 34.1 (t), 35.9 (t), 44.8 (s), 53.7 (d), 54.5 (q), 63.2 (t), 111.3 (d), 113.6 (d), 119.3 (d), 124.3 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.1 (s), 149.7 (s), 158.8 (s). HRMS: M^+, found 296.1774. $C_{20}H_{24}O_2$ requires 296.1776. MS *m/e* (%) 296 (M^+, 100), 265 (7), 263 (9), 249 (3), 225 (3), 165 (4), 139 (3).

tert-Butyl-(3-methoxy-13-methyl-7,11,12,13,14,15,16,17-octahydro-6*H*-cyclopenta[*a*]phenanthren-17-ylmethoxy)-dimethyl-silane (6-70)

A suspension of $Pd/CaCO_3$ (5 wt%, 10 mg) in benzene (1 ml) was stirred for one hour at room temperature under an atmosphere of H_2. 17-Isopropyl-3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (**5-68**, 37 mg, 0.09 mmol) in benzene (4 ml) was then added and stirring was continued for 3 hrs more. The reaction mixture was filtered over a short plug of Hyflo, which was carefully washed with ether (25 ml). Evaporation of the solvent, followed by column chromatography (PE:EtOAc 2:1) then yielded 10 mg of a 2:1 mixture of the product **6-70** with remaining starting material **6-68**. ^1H NMR (C_6D_6) ι: 0.00 (s, 6H), 0.90 (s, 3H), 0.94 (s, 9H), 1.05-2.60 (m, 14H), 3.30 (s, 3H), 3.38-3.64 (m, 2H), 6.62-6.68 (m, 2H), 7.01-7.04 (m, 1H); ^{13}C NMR (C_6D_6) ι: -5.5 (2q), 11.6 (q), 18.2 (s), 23.6 (t), 24.5 (t), 25.5 (t), 25.6 (t), 25.9 (3q), 28.9 (t), 35.9 (t), 41.7 (s), 51.2 (d), 52.1 (d), 54.5 (q), 64.6 (t), 110.9 (d), 113.7 (d), 123.1 (d), 125.6 (s), 129.5 (s), 132.2 (s), 137.0 (s), 158.2 (s).

(3-Methoxy-13-methyl-7,11,12,13,14,15,16,17-octahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-methanol (6-55)

Yield: 75%, in a 3:1 mixture with starting material **6-69**. ^1H NMR (C_6D_6) ι: 0.67 (s, 3H), 1.15-2.80 (m, 13H), 3.45 (s, 3H), 3.30-3.70 (m, 2H), 6.75-6.83 (m, 2H), 7.15-7.20 (m, 1H); ^{13}C NMR (C_6D_6) ι: 11.7 (q), 23.6 (t), 24.5 (t), 25.5 (t), 25.8 (t), 28.9 (t), 35.8 (t), 41.6 (s), 51.3 (d), 52.0 (d), 54.5 (q), 64.2 (t), 110.9 (d), 113.7 (d), 123.1 (d), 124.3 (s), 125.5 (s), 132.2 (s), 137.0 (s), 158.7 (s).

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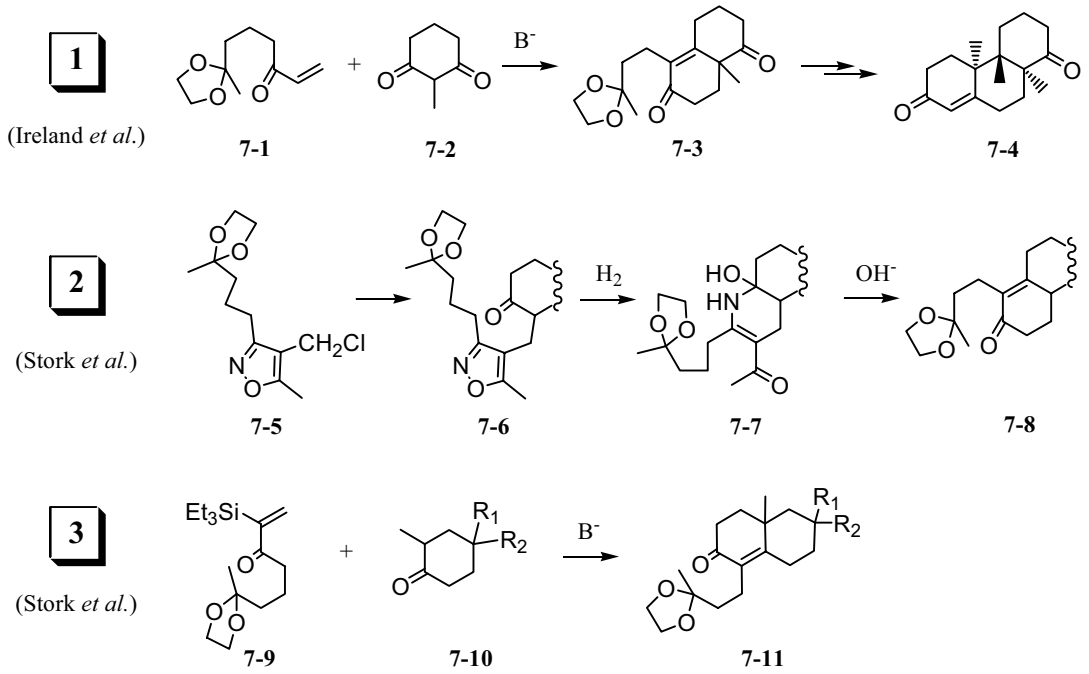
1-Phenylthio-3-vinyl-3-cyclohexenol, a new reagent for bis-annelation of silyl enol ethers

Chapter 7

7.1 Introduction

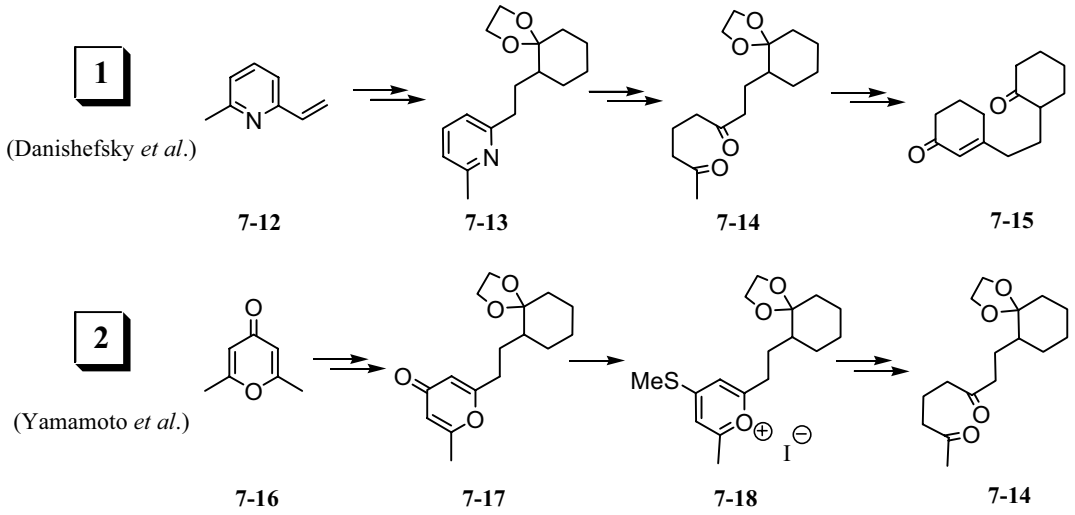
Bis-annelation usually refers to the attachment of two new, fused six-membered rings in a consecutive reaction sequence and it is a valuable method for the synthesis of polycyclic natural products. In principle, bis-annelation can be achieved using two consecutive, but nonetheless separate annelation reactions with methyl vinyl ketone (MVK) or an equivalent thereof[1-16]. To achieve a more efficient annelation of two six-membered rings, several equivalents of oct-7-ene-2,6-dione have been mentioned in literature (see scheme 1, entries 1-3)[6,10,17].

Scheme 1



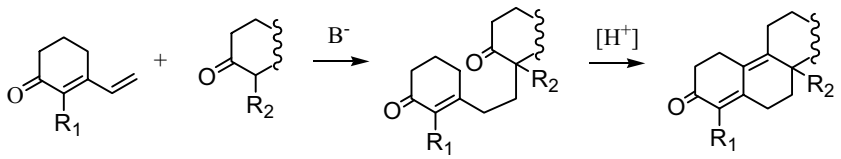
Another possibility is offered by 6-methyl-2-vinylpyridine, which can be connected to enolates by Michael addition (scheme 2, entry 1)[18-21]. Birch reduction of the pyridine followed by hydrolysis of the resulting double enamine and cyclisation results in a cyclohexenone, which can undergo a vinylogous aldol condensation to complete the bis-annelation. An annelation starting from 2,6-dimethyl-4*H*-pyran-4-one can also lead to polycyclic compounds. After transformation of the pyran-4-one ring into a 1,5-diketone *via* formation of the pyrylium salt, hydrolysis of the oxonium function and consecutive desulfurisation, the same consecutive cyclisation steps as for entry 4 lead to the tricyclic compound (scheme 2, entry 2)[22]. A few more bis-annelating reagentia are known, such as for example compound **8-12** used in chapter 8[23,24], but their discussion is not of interest here.

Scheme 2



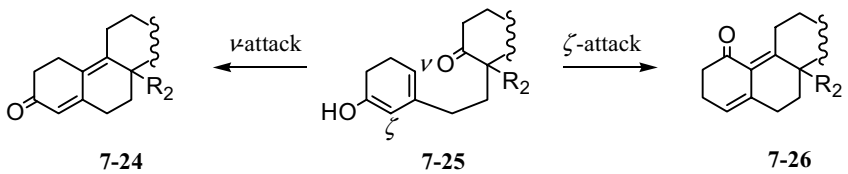
Examples of already partly cyclised bis-annelation agents are 3-vinylcyclohexenones. An extended (1,6)-Michael addition leads to intermediate **7-22**, identical to an intermediate present in the sequences of the two entries of scheme 2 (**7-15**). Also here a vinylogous aldol condensation results in the annelation of the two rings (scheme 3)[25-27].

Scheme 3



The aldol cyclisation of compounds like **7-22** (R_1 = H) can, in theory, take place *via* either the ζ- or the ν-position in the dienol intermediate (**7-25**, see scheme 4). It appears however that the cyclisation occurs preferentially on the ν-carbon, leading to dienones like **7-24**[21,22,27].#

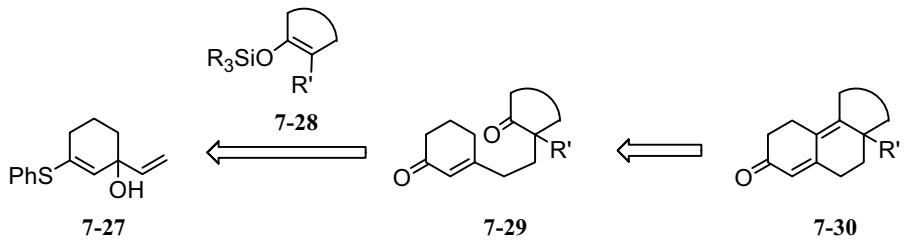
Scheme 4



In the previous chapters we have focussed on additions of carbocations to silyl enol ethers as the key step in the synthesis of steroids. A prerequisite for this type of chemistry is that the carbocation should be generated under relatively mild Lewis acid conditions, which are compatible with the silyl enol ether function. After addition, the resulting intermediates were cyclised in different ways to (D-homo) steroid skeletons.

A similar strategy may be possible for bis-annelations, when a precursor for 3-vinylcyclohexenone can be found from which a carbocationic intermediate can be generated under mild Lewis acid conditions, that can react with suitable silyl enol ethers. We found that 1-phenylthio-3-vinyl-cyclohex-1-en-3-ol **7-27** can meet these requirements (see scheme 5). Grieco *et al*. found a similar reaction for phenylthio enol stabilised carbocations[28]. Cyclisation of compounds like **7-29** to polycyclic **7-30** has been described in literature (see above).

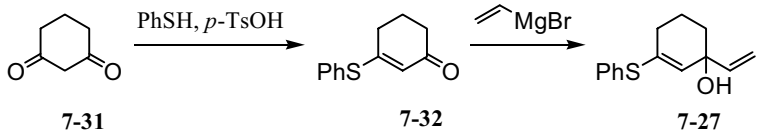
Scheme 5



7.2 Synthesis of reagent 7-27

Ketone **7-32** was obtained from 1,3-cyclohexanedione **7-31** and thiophenol using a standard procedure[29]. Addition of vinyl magnesium bromide to **7-32** gave allylic alcohol **7-27** (scheme 6), but purification of **7-27** on silica gel led to decomposition. That is why, after a standard work up procedure, the compound was directly used in the annelation reactions with silyl enol ethers. However, storage for some time is also possible when kept in (a slightly basic) solution.

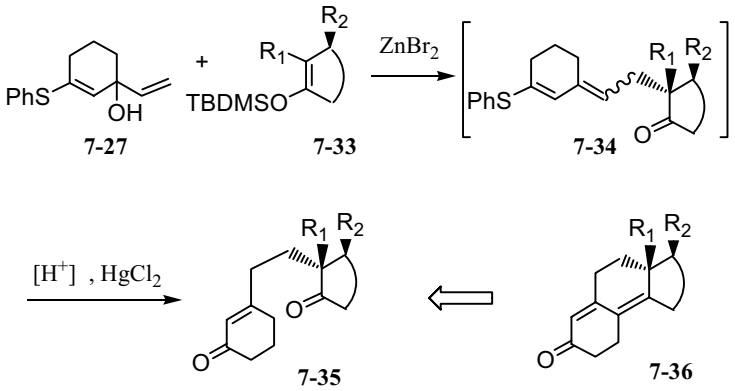
Scheme 6



7.3 Reaction of compound 7-27 with different silyl enol ethers

To get information about the stability and reactivity of reagent **7-27**, its Lewis acid catalysed reaction with several silyl enol ethers was investigated (see table 1). The silyl enol ethers shown in table 1 were selected to get an impression about the influence of steric hindrance and electronic factors on the reaction and about its stereoselectivity. A moderate excess (1.5-2 eq.) of silyl enol ether over reagent **7-27** was found to be favourable for the reaction yield. Although compound **7-27** is not very stable and shows a tendency to dehydrate, taking an excess of this compound or even a 1:1 ratio with the silyl enol ether caused quick lowering of the addition yields.

Scheme 7

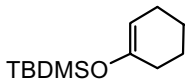
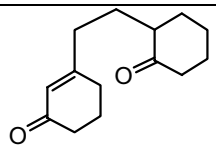
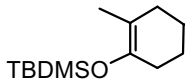
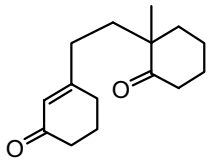
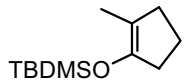
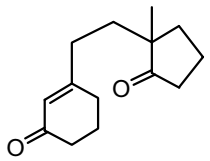
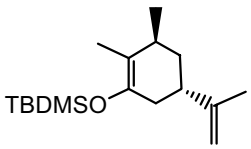
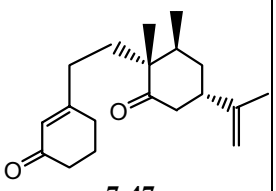
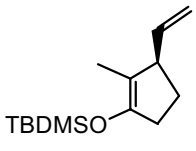
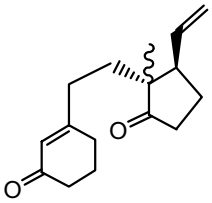
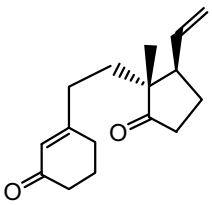
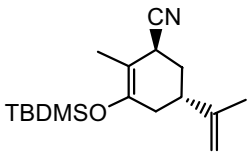


The Lewis acid used had to be powerful enough to generate a carbocation from **7-27**, but it should leave the silyl enol ether intact as long as possible. In the previous chapters we obtained good results with the use of $ZnBr_2$ and therefore this Lewis acid was also here our first catalyst of choice. Usually a stoichiometric amount of $ZnBr_2$ was used, as applying a large excess of Lewis acid appeared to cause hydrolysis of the silyl enol ethers. A catalytic amount of $ZnBr_2$ was not tried but according to the results mentioned in chapter 5, the reaction should then also be possible.

The solvent and reaction temperature also proved to be important for proper results. The nature of the solvent influenced the rate and as a consequence also the yield of the reactions. Dichloromethane had given good results in the carbocation reactions performed until then (see chapters 3, 4, 5 and 6) and was therefore also tried first here. The yields of coupled product were however very low due to instability of reagent **7-27** in this slightly acidic medium. For the most reactive silyl enol ethers good results were obtained in tetrahydrofuran as solvent (table 1, entries 1 and 2). As soon as the reactivity of the silyl enol ether was somewhat lowered (see below), a mixture of tetrahydrofuran with dichloromethane gave the best results. This indicates that the slightly basic character of tetrahydrofuran has a stabilising effect, most probably on the

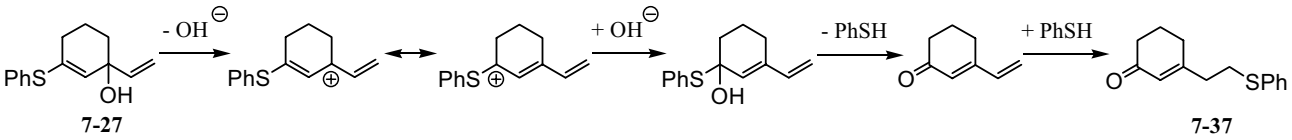
intermediate carbocation generated from **7-27**, and that dichloromethane possesses an accelerating effect in this type of addition reactions.

Tabel 1

	Silyl enol ethers	equiv. of silyl enol ether	equiv.of $ZnBr_2$	Solvent	Coupling products	Yields
1	 **7-38**	1.5	1	THF	 **7-44**	54%
2	 **7-39**	1.5	1	THF	 **7-45**	55%
3	 **7-40**	2.0	1	$THF:CH_2Cl_2$	 **7-46**	65%
4	 **7-41**	1.5	1	$THF:CH_2Cl_2$	 **7-47**	44%
5	 **7-42**	1.7	2.2	THF	 (dr 3:1)	16%
		1.7	1	$THF:CH_2Cl_2$	 **7-48**	28%
6	 **7-43**	1.4	1	$THF:CH_2Cl_2$	no product	-

A side product that was isolated in most of the reactions, typically in a yield of about 30%, is compound **7-37**. Formation of this product can be explained by carbocation formation and hydrolysis of the phenylthioenol ether, followed by renewed addition of the thiophenol to the dienone.

Scheme 8



7-27 **7-37**

The intermediate phenylthio dienes **7-34** are stable enough to allow isolation, but this was carried out only in the reaction with silyl enol ether **7-38**. In general, mixtures of stereoisomers were obtained, which were hydrolysed immediately to the corresponding enones without prior purification. Acidic conditions and $HgCl_2$ catalysis can be applied for unmasking the phenylthio dienes **7-34** to enones **7-35** (see scheme 7). These enones can be cyclised in a vinylogous aldol condensation to dienones **7-36** (see below and references[19-22,25-27,30]).

The reactions with silyl enol ethers **7-38**, **7-39** and **7-40** proceeded without problems and the corresponding enones were obtained in 54, 55 and 65% overall yields respectively. The introduction of a methyl group on C2 in the silyl enol ether seemed to have a rate accelerating effect (determined by following the reactions on TLC), although in both cases reactions were left to stir overnight for complete conversion.

The stereoselectivity of the reaction was tested with silyl enol ether **7-41**, which can be obtained from carvone[31]. The overall yield of enone **7-47** was 44% which is high for a two step reaction and also the stereoselectivity was nearly complete (10:1, on C6). The reactions with the silyl enol ether **7-42** gave a lower yield but here the stereoselectivity was complete when a mixture of dichloromethane and tetrahydrofuran was used as solvent. NOE measurements proved this compound to be the *trans*-coupled product. When only tetrahydrofuran was used as solvent, a 3:1 ratio of respectively the *trans*- and *cis*-coupled products was obtained, which clearly shows the influence of dichloromethane on the stereoselectivity of the reaction. This is probably due to the rate accelerating effect of the dichloromethane on the reaction, favouring the addition from the less hindered side leading to the *trans*-fused product.

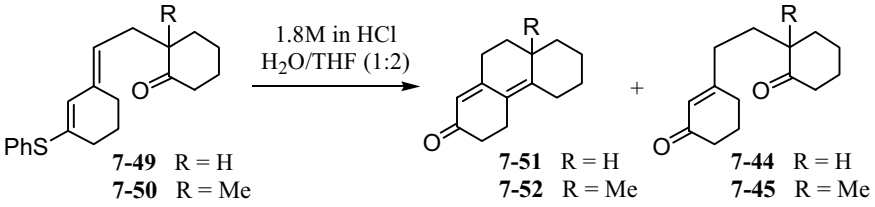
No reaction could be observed with silyl enol ether **7-43**, which probably has to be attributed to the lower nucleophilicity of the silyl enol ether due to the negative inductive effect of the cyano group (see chapter 8)[32].

The reactions of reagent **7-27** with these silyl enol ethers show that enones can be obtained in good yields in two steps. Steric factors decrease the yield but improve the stereoselectivity of the reaction, which is in agreement with the reactions of silyl enol ethers with other carbocation precursors (see chapter 5)[33].

7.4 Ring closure reactions to tricyclic systems

Cyclisation was first attempted on the coupled thiophenol intermediates **7-49** and **7-50**, adding a solution of HCl in water to the reaction mixture in THF and omitting in this way the $HgCl_2$ deprotection step. For the cyclohexanone derivative **7-49**, this gave a reasonable overall yield of 29% of compound **7-51** (4 steps), which means an average yield of 73% per step, together with 14% of non-cyclised compound **7-44**. For compound **7-50** the yield dropped to 16% of **7-51** (average of 63% per step), together with 18% of compound **7-45**.

Scheme 9



In literature, good yields, typically around 80-90%, were mentioned for the cyclisation of intermediates resembling **7-35**, but usually bearing a ketone on C7, using *para*-toluenesulfonic acid (*p*-TsOH) in acetic acid under reflux conditions[19-22,25-27,30]. We therefore investigated the cyclisation of compound **7-45** using these conditions (scheme 9) and compared the yields of **7-52** using varying amounts of *p*-TsOH (catalytic, equimolar and large excess, see table 2).

Scheme 10

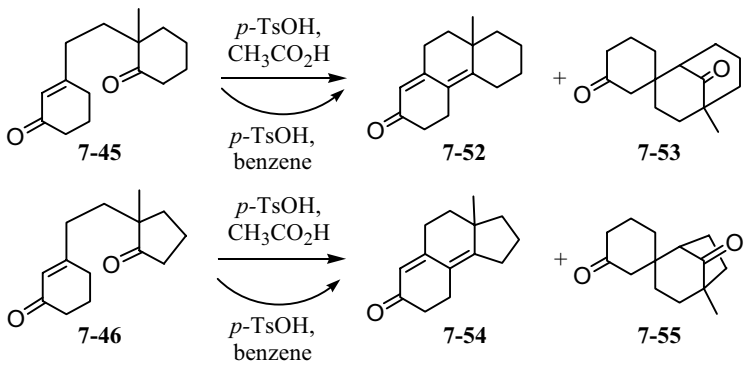


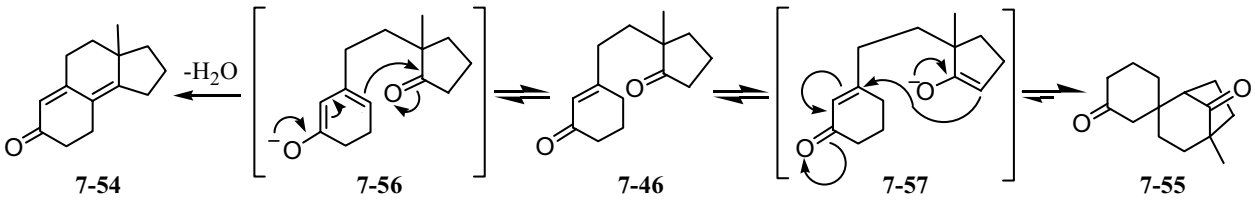
Table 2.

Entry	Conditions	*p*-TsOH (eq.)	Yield of **7-52** (%)
1	Refluxing AcOH	0.2	40
2	Refluxing AcOH	1	48
3	Refluxing AcOH	3	44

The use of equimolar amounts gave slightly higher yields but, in our hands, the yields were not as good as in literature and never exceeded those obtained with the HCl catalysed cyclisation (see table 2). Moreover, when applying these conditions to the cyclisation of compound **7-46**, the yields dropped dramatically, giving only 16% of the cyclised product **7-54**, next to starting material (22%) and a large amount (61%) of a product to which was assigned the depicted spiro-structure **7-55**[34]. Having obtained good yields for cyclisation in the chemistry discussed in chapters 5 and 6 using a solution of *p*-TsOH in benzene, we switched to this system here, but no improvement of yield was obtained. Similar disappointing results were obtained when these conditions were tried on **7-45,** giving only 44% of cyclised **7-52**.

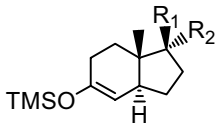
The formation of the spiro-compound, although seemingly exotic and, to our knowledge, only mentioned twice in literature for similar compounds[27,35], can easily be explained by the enolisation of the unconjugated carbonyl leading to a Michael reaction instead of the extended aldol cyclisation that was expected (scheme 10, respectively intermediates **7-57** and **7-56**).

Scheme 11



Apparently with the five-membered ring the Michael reaction is the predominant one, leading to spiro-compound **7-55**. A closer look to the cyclisation reactions of compound **7-45** revealed that also here formation of a similar compound **7-53** had taken place, although in a lower yield (19 to 33%). In the six-membered ring compound steric hindrance in the Michael adduct is probably increased and the equilibrium of the cyclisation reaction is shifted more towards the side of the starting material, ultimately leading to a higher yield of product **7-52**, resulting from the extended aldol cyclisation.

7.5 Synthesis of a D-homo steroid skeleton



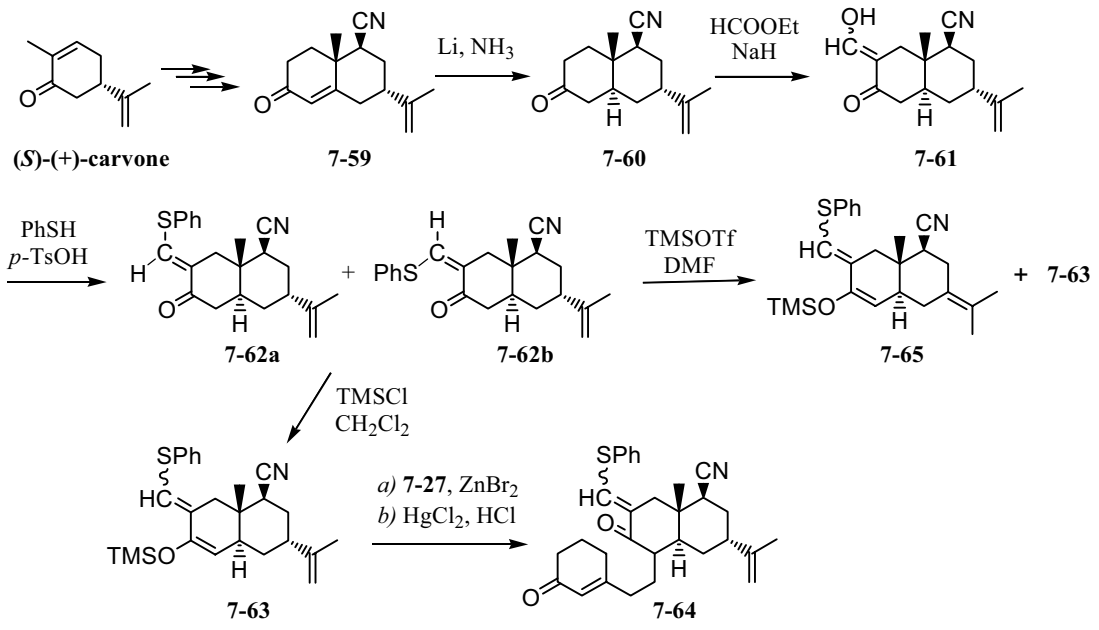
7-58
R_1R_2 = =O *or*
R_1 = O*t*Bu, R_2 = H

To apply reagent **7-27** in steroid total synthesis, a suitable CD ring system must be obtained first on which the annelation reaction can be carried out. To reach steroid skeletons with a natural five-membered D-ring compound **7-58**, which is a known intermediate in steroid synthesis[36,37], could for example be used. On the other hand, to obtain new D-homo steroid derivatives that might possess interesting new pharmaceutical properties, a chiral decaline system should be used. A sequence starting from carvone has been published previously, leading in three steps to enantiomerically pure bicyclic system **7-59**, which seemed suited for this purpose (see scheme 8, and chapter 8)[31].

Reduction of **7-59** with Li in liquid ammonia gave ketone **7-60**. The *trans*-fusion between the two rings was proven by NOE measurements. Formylation and reaction with thiophenol led to a mixture of isomers **7-62a** and **7-62b** in a ratio 4:1. The structures of the isomers were determined on the base of their ^{1}H NMR data. For compound **7-62a** the signal of the vinyl proton next to thiophenyl moiety shifts to lower field in comparison with the corresponding signal of its isomer **7-62b**, due to shielding by the carbonyl group. The isomers were separated for analysis purposes, but used as a mixture in the consecutive reaction.

Attempts to prepare the TBDMS ether of compound **7-62** failed. For this reason the TMS ether **7-63** was prepared and used in the coupling reaction with reagent **7-27**. The acid catalysed hydrolysis gave product **7-64** as a mixture of two isomers, which were partly separated by

Scheme 12



column chromatography. The yield of the coupling and consecutive hydrolysis reactions is, with 20%, not high but the reaction sequence has only been carried out once and consequently has not been optimised. Taking into account the yields obtained after optimisation in the coupling reactions with monocyclic enol ethers, a higher yield should also be attainable here. Since the reaction of **7-62** with TMS chloride in dichloromethane proceeded very slowly, also a reaction with TMS-triflate in DMF was tried for the preparation of the silyl enol ethers. However these conditions led to a mixture of compound **7-63** with compound **7-65**, in which migration of the double bond in the isopropenyl moiety had taken place.

Cyclisation of the D-homo seco steroid skeleton has not yet been attempted and the coupling reaction has to be improved but, considering the results mentioned in paragraph 7.4, a reasonable yield of the desired product should be accessible. It is expected that formation of the spiro compound would in this case not form a major side reaction, as steric hindrance is much increased compared to the simple tricyclic systems, shifting the equilibrium of the reaction more to the side of the extended aldol cyclisation and hence permitting the isolation of a higher yield of the desired multifunctionalised D-homo steroid skeleton.

Experimental

3-Phenylthio-cyclohex-2-enone (7-32)

1,3-Cyclohexandione (5.0 g, 44 mmol) and thiophenol (5.5 ml, 53 mmol) were dissolved in benzene (100 ml) and stirred at reflux temperature for 6 hrs in a Dean-Stark apparatus. After cooling, the solution was diluted with saturated $NaHCO_3$ solution (50 ml), the layers were separated and the water layer was extracted with EtOAc (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc grad. 20:1 – 1:1) giving compound **7-32** in 71% yield (6.5 g)[29]. M.p. 43-44 ºC (hexane-EtOAc); IR (CCl_4 sol.) cm^{-1}: 2950, 1672, 1579, 1290; ^1H NMR ($CDCl_3$) ι: 1.94-2.07 (m, 2H), 2.34 (t, J = 6.2, 2H), 2.49 (t, J = 6.1, 2H), 5.44 (s, 1H), 7.36-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) ι: 22.89 (t), 30.18 (t), 37.20 (t), 120.71 (d), 127.47 (s), 129.51 (2d), 130.15 (d), 135.46 (2d), 166.95 (s), 196.12 (s); HRMS: M^+, found 204.0607. $C_{12}H_{12}OS$ requires 204.0609. MS *m/e* (%) 204 (M^+, 100), 187 (12), 176 (74), 171 (23), 148 (45), 147 (39), 127 (35), 110 (20), 67 (81).

3-Phenylthio-1-vinyl-cyclohex-2-enol (7-27) *(general procedure A)*.

To a solution of ketone **7-32** (1.0 mmol) in tetrahydrofuran (4 ml) was added vinyl magnesium bromide (1.5 mmol, 1M solution in tetrahydrofuran) at 0 ºC. After 10 min the cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. Then it was poured into a cold saturated solution of ammonium chloride and extracted with *tert*-butyl methyl ether. The combined organic fractions were dried over sodium sulfate and evaporated in vacuum to give alcohol **7-27**, which was used for reactions with the silyl enol ethers **7-33** without further purification. An analytical sample of alcohol **7-27** was prepared by flash column chromatography on silica gel. ^{1}H NMR (C_6D_6) ι: 1.34-1.68 (m, 4H), 2.01-2.11 (m, 2H), 4.97 (dd, J_1 = 1.5 & J_2 = 10.6, 1H), 5.23 (dd, J_1 = 1.5 & J_2 = 17.4, 1H), 5.76 (s, 1H), 5.83 (dd, J_1 = 10.5 & J_2 = 17.3, 1H), 6.95-7.10 (m, 3H), 7.41-7.47 (m, 2H); ^{13}C NMR (C_6D_6) ι: 19.87 (t), 29.80 (t), 35.81 (t), 71.64 (s), 112.61 (t), 127.45 (d), 129.14 (2d), 131.24 (d), 132.50 (2d), 133.42 (s), 137.01 (s), 144.15 (d).

*Coupling reaction of allylic alcohol **7-27** and silyl enol ether **7-33** (general procedure **B**)*.

A solution of silyl enol ether **7-33** (1.5 – 2 mmol) in tetrahydrofuran or dichloromethane (1 ml, use of choice mentioned in procedure) was added to a suspension of $ZnBr_2$ (1 mmol) in tetrahydrofuran or dichloromethane (1 ml, as above, use of choice mentioned in procedure) at -40 ºC. Then to this mixture a solution of allylic alcohol **7-27** (obtained from 1 mmol of ketone **7-32**) in tetrahydrofuran (1.5 ml) was added dropwise. During the next 3-4 hours the reaction mixture was warmed gradually to room temperature and left stirring overnight. Then the reaction mixture was mixed with cold brine and extracted with *tert*-butyl methyl ether. The combined organic fractions were dried over sodium sulfate and evaporated under vacuum to give phenylthiodiene **7-34** as a crude oil.

*Hydrolysis of phenylthiodiene **7-34** to diketone **7-35** (general procedure **C**)*.

To a solution of unpurified product **7-34** in ethanol (2 ml) was added dropwise a solution of mercury (II) chloride (2 mmol, calculated on the amount of used ketone **7-32**) in water (0.5 ml) and 37% hydrochloric acid (0.5 ml). The obtained mixture was stirred for 3 hours at room temperature. The precipitate was filtered and washed with ethanol. The filtrate was mixed with pyridine (0.5 ml) and concentrated in vacuum. The residue was mixed with brine and extracted with dichloromethane. The combined organic fractions were washed with a saturated $NaHCO_3$ solution and a saturated NH_4Cl solution, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The obtained oil was purified by column chromatography (PE:EtOAc grad. 15:1 ♥ 1:1) to give compound **7-35**, and usually some amount of compound **7-37**.

7-37. ^{1}H NMR ($CDCl_3$) ι: 1.84-2.05 (m, 2H), 2.17-2.40 (m, 4H), 2.49 (t, *J* = 7.4, 2H), 3.03 (t, *J* = 7.5, 2H), 5.86 (s, 1H), 7.12-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) ι: 22.5 (t), 29.4 (t), 31.1 (t), 37.2 (t), 37.4 (t), 126.5 (d), 126.7 (d), 129.0 (2d), 129.8 (2d), 135.4 (s), 163.4 (s), 199.5 (s).

3-[2-(2-Oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (7-44)

Obtained according to the general procedures **A**-**C** in 54% yield (245 mg) from ketone **7-32** (420 mg). Procedure **B** included the use of 1.5 equiv. of silyl enol ether **7-38**, 1 equiv. of $ZnBr_2$ and tetrahydrofuran as solvent. IR (CCl_4 sol.) cm^{-1}: 2938, 2866, 1713, 1674, 1627; ^{1}H NMR (C_6D_6) ι: 1.02-2.28 (m, 19H), 6.02 (s, 1H); ^{13}C NMR (C_6D_6) ι: 22.7 (t), 24.9 (t), 26.9 (t), 27.8 (t), 29.2 (t), 33.9 (t), 35.4 (t), 37.4 (t), 41.8 (t), 49.7 (d), 125.7 (d), 164.4 (s), 197.5 (s), 210.1 (s). HRMS: M^+, found 220.1463. $C_{14}H_{20}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 15), 123 (100), 110 (30), 98 (21), 55 (11).

3-[2-(1-Methyl-2-oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (7-45)

Obtained according to the general procedures **A**-**C** in 55% yield (253 mg) from ketone **7-32** (400 mg). Procedure **B** included the use of 1.5 equiv. of silyl ether **7-39**, 1 equiv. of $ZnBr_2$ and tetrahydrofuran as solvent. IR ($CHCl_3$ sol.) cm^{-1}: 2939, 2869, 2356, 2252, 1702, 1664, 1623, 1455; ^{1}H NMR (C_6D_6) ι: 0.93 (s, 3H), 1.25-2.21 (m, 18H), 5.99 (s, 1H); ^{13}C NMR (C_6D_6) ι: 20.8 (t), 22.4 (q), 22.7 (t), 27.2 (t), 29.4 (t), 32.1 (t), 34.8 (t), 37.4 (t), 38.4 (t), 38.8 (t), 47.7 (s), 125.6 (d), 164.1 (s), 197.3 (s), 212.5 (s). HRMS: M^+, found 234.1615. $C_{15}H_{22}O_2$ requires 234.1620. MS *m/e* (%) 234 (M^+, 5), 123 (81), 112 (100), 110 (13), 97 (21), 55 (13).

3-[2-(1-Methyl-2-oxo-cyclopentyl)-ethyl]-cyclohex-2-enone (7-46)

Obtained according to the general procedures **A**-**C** in 65% yield (211 mg) from ketone **7-32** (300 mg). Procedure **B** included the use of 2 equiv. of silyl enol ether **7-40**, 1 equiv. of $ZnBr_2$ and dichloromethane as solvent. IR (CCl_4 sol.) cm^{-1}: 2960, 1738, 1674, 1628; ^{1}H NMR (C_6D_6) ι: 0.81 (s, 3H), 1.21-1.62 (m, 8H), 1.62-2.11 (m, 6H), 2.11-2.24 (m, 2H), 5.94 (s, 1H); ^{13}C NMR (C_6D_6) ι: 18.5 (t), 21.5 (q), 22.6 (t), 29.2 (t), 32.5 (t), 33.7 (t), 35.2 (t), 37.1 (t), 37.3 (t), 47.3 (s), 125.7 (d), 164.1 (s), 197.4 (s), 220.1 (s). HRMS: M^+, found 220.1463. $C_{14}H_{20}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 7), 123 (100), 110 (7), 98 (48), 83 (6), 67 (4), 55 (14).

3-[2-(4-Isopropenyl-1,2-dimethyl-6-oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (7-47)

Obtained according to the general procedures **A**-**C** in 44% yield (91 mg) from ketone **7-32** (146 mg). Procedure **B** included the use of 1.5 equiv. of silyl enol ether **7-41**, 1 equiv. of $ZnBr_2$ and

dichloromethane as solvent. IR ($CHCl_3$ sol.) cm^{-1}: 3088, 2938, 2889, 2252, 1699, 1666, 1626, 1456, 1428, 1257; ^1H NMR (C_6D_6) ι: 0.69 (d, *J* = 7.0, 3H), 0.88 (s, 3H), 1.55 (s, 3H), 2.16 (t, *J* = 6.3, 2H), 2.37 (s, 2H), 4.77 (s, 1H), 4.82 (s, 1H), 6.00 (s, 1H). ^{13}C NMR (C_6D_6) ι: 15.5 (q), 18.8 (q), 20.9 (q), 22.7 (t), 29.3 (t), 32.2 (t), 32.3 (t), 33.9 (t), 35.0 (d), 37.3 (t), 40.3 (d), 42.4 (t), 51.1 (s), 110.8 (t), 125.7 (d), 147.3 (s), 163.9 (s), 197.3 (s), 212.6 (s). HRMS: M^+, found 288.2086. $C_{19}H_{28}O_2$ requires 288.2089. MS *m/e* (%) 288 (M^+, 4), 166 (18), 151 (8), 123 (100), 110(15), 97 (9), 69 (11), 67 (9), 41 (17).

3-[2-(1-Methyl-2-oxo-5-vinyl-cyclopentyl)-ethyl]-cyclohex-2-enone (7-48)

Mixture of *cis*:*trans* (1:3), obtained according to the general procedures **A**-**C** in 16% yield (24 mg) from ketone **7-32** (126 mg). Procedure **B** included the use of 1.7 equiv. of silyl enol ether **7-42**, 2.2 equiv. of $ZnBr_2$ and tetrahydrofuran as solvent. ^1H NMR (C_6D_6) ι: 0.66 and 0.93 (s, s, 3H), 0.85-2.37 (m, 15H), 4.85-5.10 (m, 2H), 5.41-5.65 (m, 1H), 5.96 and 6.01 (s, s, 1H); ^{13}C NMR – *cis* isomer (C_6D_6) ι: 19.8 (q), 22.6 (t), 23.7 (t), 28.5 (t), 29.5 (t), 31.6 (t), 35.4 (t), 37.3 (t), 50.4 (s), 52.0 (d), 116.3 (t), 125.4 (d), 136.8 (d), 164.0 (s), 197.5 (s), 218.7 (s).

Trans–isomer, obtained according to the general procedures **A**-**C** in 28% yield (62 mg) from ketone **7-32** (182 mg). Procedure **B** included the use of 1.7 equiv. of silyl enol ether **7-42**, 1 equiv. of $ZnBr_2$ and dichloromethane as solvent. IR (CCl_4 sol.) cm^{-1}: 2964, 1740, 1674, 1628; ^1H NMR (C_6D_6) ι: 0.65 (s, 3H), 0.81-2.31 (m, 15H), 4.92 (d, *J* = 17.1, 1H), 5.00 (d, *J* = 10.3, 1H), 5.46 (ddd, J_1 = 7.8 & J_2 = 10.3 Hz, J_2 = 17.1 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (C_6D_6) ι: 17.5 (q), 22.6 (t), 24.2 (t), 29.1 (t), 32.5 (t), 32.7 (t), 36.5 (t), 37.3 (t), 47.4 (d), 50.7 (s), 116.3 (t), 125.9 (d), 137.2 (d), 163.8 (s), 197.3 (s), 219.3 (s). HRMS: M^+, found 246.1618. $C_{16}H_{22}O_2$ requires 246.1620. MS *m/e* (%) 246 (M^+, 3.5), 124 (80), 123 (100), 110 (7), 109 (12, 95 (6), 81 (7).

4,5,6,7,8,8a,9,10-Octahydro-3H-phenanthren-2-one (7-51)

After having performed procedures **A** and **B** starting from 0.86 mmol **7-32**, the crude reaction mixture was cooled on ice to 5 °C and 1 ml of concentrated HCl (37%) was added dropwise. The colour of the reaction mixture immediately turned red. The temperature was kept at 5 °C for 30 min, after which the mixture was allowed to warm to room temperature and 5 ml of water, followed again by 1 ml of conc. HCl (37%), was added. The mixture was left to stir overnight, diluted with a saturated Na_2CO_3 solution and extracted with *tert*butyl methyl ether (3 x 15 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE:EtOAc grad. 20:1 Ÿ 1:1) yielding 29% of

compound **7-51** (50 mg), next to 14% of compound **7-44** (26 mg, for data see above). ^{1}H NMR ($CDCl_3$) ι: 1.10-2.85 (m, 17H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$) ι: 25.4 (t), 26.1 (t), 27.6 (t), 29.3 (t), 30.3 (2t), 35.4 (t), 37.2 (t), 39.5 (d), 122.1 (d), 124.3 (s), 147.2 (s), 158.1 (s), 200.1 (s). Data are in accordance with literature data[18].

Cyclisation of 7-45.

p-*TsOH in AcOH*.

Compound **7-45** (200 mg, 0.86 mmol) was dissolved in acetic acid (AcOH, 6 ml) and *p*-TsOH was added (different amounts, see table 2). The reaction mixture was stirred during 1 hr at reflux, then cooled and neutralised with a saturated $NaHCO_3$ solution (50 ml). The mixture was extracted with CH_2Cl_2 (3 x 50 ml) and the organic fractions were combined and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the resulting crude oil was purified by column chromatography (PE: EtOAc grad. 20:1 – 2:1), yielding compound **7-52** (for yields see table 2) as a thick slightly yellow oil, next to some amount of compound **7-53** (~25%) as a mixture of 2 isomers (1:1).

p-*TsOH in benzene*.

Compound **7-45** (115 mg, 0.49 mmol) was dissolved in benzene (15 ml) and *p*-TsOH (190 mg, 0.49 mmol) was added. The reaction mixture was stirred under N_2 during 5 hrs at 60 ^{o}C, then cooled and neutralised with a saturated $NaHCO_3$ solution (50 ml). The mixture was extracted with CH_2Cl_2 (3 x 50 ml) and the organic fractions were combined and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the resulting crude oil was purified by column chromatography (PE: EtOAc grad. 20:1 – 2:1), yielding compound **7-52** (47 mg, 44%) as a thick slightly yellow oil, next to some amount of compound **7-53** (33%) as a mixture of 2 isomers (2:1), and a small amount of **7-26(R_2 = Me)** (9%).

8a-Methyl-4,5,6,7,8,8a,9,10-octahydro-3H-phenanthren-2-one (7-52). IR (CCl_4 sol.) cm^{-1}: 2932, 1669, 1606, 1448, 1381, 1340, 1271, 1219; ^{1}H NMR (C_6D_6) ι: 0.89 (s, 3H), 0.92-2.45 (m, 16H), 5.86 (s, 1H); ^{13}C NMR (C_6D_6) ι: 22.2 (t), 23.4 (d), 25.7 (t), 26.3 (t), 27.7 (t), 28.1 (t), 36.6 (s), 37.6 (t), 38.6 (t), 42.3 (t), 123.0 (d), 124.5 (s), 148.8 (s), 155.5 (s), 197.5 (s). HRMS: M^+, found 216.1516. $C_{15}H_{20}O$ requires 216.1514. MS *m/e* (%) 216 (M^+, 67), 201 (100), 187 (7), 173 (9), 160 (11), 159 (15), 148 (10), 131 (11), 117 (10), 91 (11). Data are in accordance with literature data[38].

7-53. IR (CCl_4 sol) cm^{-1}: 2937, 1716, 1455, 1381, 1313, 1231; ^{1}H NMR ($CDCl_3$) ι: 0.92 (s, 3H), 1.43-2.34 (m, 21H); ^{13}C NMR ($CDCl_3$) ι: 21.2 (*M*) & 21.3 (*m*) (t), 21.8 (*M*) & 21.9 (*m*) (t), 24.6 (q), 29.8 (*m*) & 30.2 (*M*) (t), 31.2 (*M*) & 31.5 (*m*) (t), 34.0 (*m*) & 35.3 (*M*) (t), 37.4 (*M*) & 37.7 (*m*) (t), 41.2 (*M*) & 41.3 (*m*) (t), 43.1 (*M*) & 43.2 (*m*) (t), 46.3 (s), 47.9 (s), 51.5 (*M*) & 52.3 (*m*) (t), 56.5 (*m*)

& 57.6 (*M*) (d), 210.6 (*M*) & 211.0 (*m*) (s), 219.4 (*M*) & 219.8 (*m*) (s). HRMS: M^+, found 234.1622. $C_{15}H_{22}O_2$ requires 234.1620. MS *m/e* (%) 234 (M^+, 33), 123 (100), 112 (30), 111 (53), 95 (7), 93 (7), 79 (7), 67 (9), 55 (15), 41 (11).

7-26(R_2 = Me). IR (CCl_4 sol) cm^{-1}: 2931, 1869, 1676, 1456, 1385, 1322, 1290; ^1H NMR ($CDCl_3$) ι: 0.96 (s, 3H), 1.20-2.55 (m, 16H), 6.46 (dd, J_1= 4.0 Hz & J_2= 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) ι: 18.6 (t), 22.7 (t), 23.5 (q), 27.2 (t), 30.2 (t), 32.6 (t), 37.2 (t), 37.9 (s), 39.4 (t), 40.7 (t), 126.9 (d), 130.5 (s), 134.5 (s), 155.1 (s), 200.0 (s). HRMS: M^+, found 216.1513. $C_{15}H_{20}O$ requires 216.1514. MS *m/e* (%) 216 (M^+, 100), 201 (84), 160 (18), 149 (17), 148 (17), 145 (13), 135 (18), 91 (15), 55 (10).

Cyclisation of 7-46.

p-*TsOH in AcOH*.

3a-Methyl-1,2,3,3a,4,5,8,9-octahydro-cyclopenta[a]naphthalen-7-one (7-54). Yield: 16%, as a slightly yellow oil. IR (CCl_4 sol) cm^{-1}: 2931, 1742, 1667, 1634, 1582, 1440, 1261, 1233, 1024; ^1H NMR ($CDCl_3$) ι: 0.97 (s, 3H), 0.92-2.77 (m, 14H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$) ι: 21.7 (t), 23.1 (q), 25.5 (t), 29.4 (t), 30.1 (t), 35.9 (t), 37.1 (t), 42.0 (t), 43.3 (s), 121.9 (d), 123.2 (s), 156.5 (s), 158.0 (s), 200.1 (s). HRMS: M^+, found 202.1358. $C_{14}H_{18}O$ requires 202.1358. MS *m/e* (%) 202 (M^+, 45), 187 (100), 174 (10), 160 (12), 159 (10), 145 (11), 131 (11), 117 (12), 91 (15).

7-55. Yield: 61%, as a slightly yellow oil (mixture of 2 isomers, ratio 2:1). IR (CCl_4 sol) cm^{-1}: 2939, 2875, 1747, 1716, 1452, 1319, 1230; ^1H NMR ($CDCl_3$) ι: 0.91 (s, 3H), 0.90-2.27 (m, 19H); ^{13}C NMR ($CDCl_3$) ι: 18.2 (*m*) & 18.6 (*M*) (t), 19.1 (q), 21.8 (*M*) & 21.9 (*m*) (t), 27.7 (*M*) & 29.5 (*m*) (t), 29.9 (*M*) & 30.0 (*m*) (t), 32.2 (*m*) & 35.8 (*M*) (t), 38.7 (*m*) & 38.9 (*M*) (t), 41.3 (*M*) & 41.4 (*m*) (t), 45.7 (s), 49.2 (*M*) & 52.2 (*m*) (t), 49.7 (s), 53.2 (*m*) & 55.8 (*M*) (d), 210.8 (*M*) & 210.9 (*m*) (s), 219.2 (*M*) & 219.4 (*m*) (s). HRMS: M^+, found 220.1467. $C_{14}H_{20}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 60), 192 (7), 123 (100), 110 (10), 97 (65), 55 (12).

p-*TsOH in benzene*.

Yields: 16% **7-54** and 63% **7-55**.

Compound (7-60)

At –78 ∀C a solution of of compound **7-59**[31] (7.0 g, 30.5 mmol) in tetrahydrofuran (40 ml) was added to an intensively stirred mixture of liquid ammonia (150 ml, distilled over sodium) and lithium (0.7 g, 100.8 mmol) in tetrahydrofuran (100 ml). After 30 min the excess of lithium was quenched with NH_4Cl (7 g), the reaction mixture was warmed to room temperature and the ammonia was carefully removed at reduced pressure. The residue was mixed with a saturated

NH_4Cl solution (200 ml) and extracted with dichloromethane (3 x 200 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated in vacuum. The obtained oil was purified by column chromatography (PE:EtOAc grad. 25:1 ♥ 5:1) to give 3.38 g of compound **7-60** (48%). M.p. 87-88 ∀C (from EtOAc); IR (KBr) cm^{-1}: 3087, 2953, 2864, 2232, 1706, 1645, 1446, 1425, 1226; ^1H NMR (C_6D_6) ι: 0.68 (s, 3H), 0.80 (dt, J_1 = 5.4 & J_2 = 12.4, 2H), 1.05 (dq, J_1 = 2.4 & J_2 = 14.2, 1H), 1.19 (dt, J_1 = 3.6 & J_2 = 13.0, 1H), 1.44-2.20 (m, 10H), 4.41 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (C_6D_6) ι: 10.7 (q), 22.1 (q), 27.1 (t), 29.2 (t), 35.4 (s), 36.6 (d), 37.2 (d), 37.3 (t), 37.9 (t), 37.9 (d), 43.7 (t), 111.7 (t), 120.1 (s), 144.1 (s), 206.5 (s). HRMS: M^+, found 231.1619. $C_{15}H_{21}NO$ requires 231.1623. MS *m/e* (%) 231 (M^+, 40), 189 (72), 188 (96), 174 (10), 160 (13), 146 (16), 124 (100), 107 (26), 82 (26), 55 (40).

Compound (7-61)

A solution of compound **7-60** (0.3 g, 1.3 mmol) and ethyl formate (0.2 ml, 2.6 mmol) in Et_2O (3 ml) was added dropwise to a suspension of NaH (0.05 g, 2.0 mmol) in Et_2O (2 ml). The reaction mixture was stirred for 2 hrs at room temperature and then acidified with a 1M solution of hydrochloric acid until pH = 2. The layers were separated and the water layer was extracted with EtOAc (3 x 5 ml). The combined organic fractions were washed with brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The obtained oil was used in next step without purification. An analytical sample of compound **7-61** was prepared by flash chromatography on silica gel (PE:EtOAc grad. 15:1 ♥ 5:1). IR ($CHCl_3$ sol.) cm^{-1}: 3090 (br), 2948, 2257, 1713, 1643, 1451; ^1H NMR (C_6D_6) ι: 0.63 (s, 3H), 1.39 (s, 3H), 4.48 (s, 1H), 4.81 (s, 1H), 8.10 (s, 1H). ^{13}C NMR (C_6D_6) ι: 11.2 (q), 22.1 (q), 27.1 (t), 28.4 (t), 32.9 (d), 34.8 (t), 34.9 (s), 36.2 (d), 37.1 (t), 37.2 (d), 106.7 (s), 111.7 (t), 120.1 (s), 144.1 (s), 182.8 (s), 187.3 (d). HRMS: M^+, found 259.1571. $C_{16}H_{21}NO_2$ requires 259.1572. MS *m/e* (%) 259 (M^+, 100), 244 (10), 231 (7), 216 (15), 152 (25), 137 (16), 98 (37).

Compound (7-62)

The mixture of crude compound **7-61**, obtained in the previous synthesis, *p*-toluenesulfonic acid (6 mg, 0.03 mmol) and thiophenol (0.13 ml, 1.3 mmol) in benzene (30 ml) was refluxed in a Dean-Stark apparatus for 3 hrs. After cooling, the reaction mixture was diluted with a saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 x 15 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent evaporated in vacuum. The residue was purified by column chromatography (PE:EtOAc grad. 15:1 ♥ 4:1) to give 200 mg of isomer **7-62a** (49%) and 50 mg of isomer **7-62b** (12%).

Main isomer. M.p. 160 ∀C (from EtOAc); IR (CCl_4 sol.) cm^{-1}: 2954, 1727, 1673, 1547; ^1H NMR ($CDCl_3$) ι: 1.09 (s, 3H), 1.32-1.53 (m, 1H), 1.72 (s, 3H), 1.64-2.49 (m, 8H), 2.64 (dd, J_1 = 3.3 & J_2 = 13.1, 1H), 2.85 (d, J = 16.6, 1H), 4.79 (s, 1H), 4.98 (s, 1H), 7.28-7.51 (m, 5H), 7.80 (dd, J_1 = 0.9 & J_2 = 2.7, 1H); ^{13}C NMR ($CDCl_3$) ι: 12.7 (q), 22.5 (q), 27.5 (t), 29.5 (t), 34.9 (d), 35.4 (s), 36.5 (d), 37.3 (d), 41.4 (t), 41.6 (t), 112.2 (t), 120.6 (s), 128.4 (d), 128.6 (s), 129.5 (d), 130.9 (d), 133.2 (s), 144.1 (d), 144.3 (s), 194.3 (s); HRMS: M^+, found 351.1653. $C_{22}H_{25}NOS$ requires 351.1657. MS *m/e* (%) 351 (M^+, 100), 274 (10), 149 (32), 147 (19), 110 (10), 91 (7).

Minor isomer. ^1H NMR ($CDCl_3$) ι: 1.02 (s, 3H), 1.31-1.58 (m, 1H), 1.68 (s, 3H), 1.55-2.94 (m, 10H), 4.73 (s, 1H), 4.94 (s, 1H), 6.96 (d, J = 2.0, 1H), 7.14-7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) ι: 12.1 (q), 22.5 (q), 27.4 (t), 29.3 (t), 35.4 (d), 36.1 (d), 36.2 (s), 37.3 (d), 41.7 (t), 45.5 (t), 112.2 (t), 120.6 (s), 126.2 (s), 128.2 (d), 129.4 (d), 130.8 (d), 137.4 (s), 144.4 (s), 146.4 (d), 197.1 (s).

Compound (7-63).

To a solution of the mixture of the two isomers **7-62** (0.8 g, 2.3 mmol) in dichloromethane (6 ml) and triethylamine (3.2 ml, 22.8 mmol) cooled at 0∀C, was added of TMS chloride (3 ml, 22.8 mmol). After 10 min the cooling bath was removed and the reaction mixture was stirred at room temperature for 48 hrs. After this time the reaction mixture was poured into a cold saturated $NaHCO_3$ solution and extracted with *tert*-butyl methyl ether (3 x 10 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc 80:1), to give 0.65 g of compound **7-63** (68%). IR (CCl_4 sol.) cm^{-1}: 3086, 2975, 2239, 1673, 1548, 1253; ^1H NMR ($CDCl_3$) ι: 0.20 (s, 9H), 1.027 (s, 3H), 1.75 (s, 3H), 1.44-2.56 (m, 7H), 2.65 (dd, J_1 = 3.4 & J_2 = 12.7, 1H), 2.93 (d, J = 15.1, 1H), 4.56 (d, J = 2.2, 1H), 4.82 (s, 1H), 4.99 (s, 1H), 6.67 (d, J = 2.0, 1H), 7.14-7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) ι: 0.3 (3q), 12.7 (q), 22.6 (q), 27.6 (t), 28.6 (t), 36.0 (d), 36.8 (s), 37.6 (d), 37.8 (d), 41.2 (t), 109.3 (d), 111.9 (t), 120.8 (s), 121.7 (d), 126.6 (d), 129.1 (d), 130.5 (s), 136.0 (s), 144.9 (s), 147.8 (s). HRMS: M^+, found 423.2050. $C_{25}H_{33}NOSSi$ requires 423.2052. MS *m/e* (%) 423 (M^+, 94), 408 (13), 351 (10), 330 (7), 314 (100), 301 (35), 193 (9), 110 (9), 73 (51).

Compound (7-64) was obtained according to the general procedures **A**-**C** in 20% yield (30 mg) from ketone **7-32** (63 mg). Procedure **B** included the use of 1.2 equiv. of silyl enol ether **7-63**, 2 equiv. of $ZnBr_2$ and tetrahydrofuran as solvent. ^1H NMR (C_6D_6) 0.50-2.45 (m, 19H), 0.85 (s, 3H), 1.49 (s, 3H), 3.02 (d, J = 15.0, 1H), 4.60 (s, 1H), 4.83 (s, 1H), 6.03 (s, 1H), 6.83-7.45 (m, 5H), 8.12-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$) ι: 13.4 (q), 20.3 (q), 22.6 (t), 25.6 (t), 29.0 (t), 30.2 (t), 30.4 (t), 34.1 (t), 34.5 (s), 37.3 (t), 41.0 (t), 42.5 (d), 42.8 (d), 43.4 (d), 48.1 (d), 110.1 (t), 119.9 (s), 125.4

(s), 126.2 (d), 127.9 (d), 129.4 (2d), 130.5 (2d), 133.4 (s), 142.7 (d), 147.4 (s), 163.9 (s), 194.9 (s), 197.4 (s).

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Chapter 8

The use of β-cyanoketones for the synthesis of functionalized polycyclic compounds

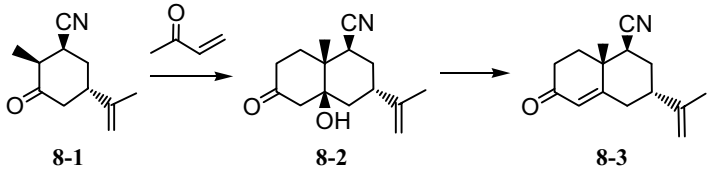
8.1 Introduction

Robinson annelation to cycloalkanone enolates is an established procedure for the synthesis of functionalized polycyclic compounds[1-6]. The yields in these annelations with simple alkyl vinyl ketones vary from 30% to 85%, depending on the stability against polymerisation of the enone, the steric requirements of the cycloalkanone and the use of protic or aprotic reaction conditions.

Usually better results were obtained in annelations with cycloalkanones bearing an electron withdrawing ζ-substituent, like a formyl, ester or cyano group, or with cyclic η-diketones[2,7-13]. Annelations of cyclic η-diketones procede in good yields and are broadly applied when a functional group in ring B is necessary or convenient in a total synthesis. When a (natural) product with a functionalised angular substituent was the synthetic goal, annelations to ζ-cyano ketones usually gave good results[14]. The ζ-cyano group enhanced the acidity of the ζ proton considerably with a minimum of extra steric hindrance. Furthermore, possible side reactions, which may occur by condensation reactions with the ζ-formyl or ester groups, were not observed with the cyano group. The cyano group is a flexible substituent that can be converted easily in many other substituents with an equal or lower level of oxidation.

In chapters 2 to 7 it was shown that several types of annelations can be achieved by additions of carbocations, generated by Lewis acid catalysis, to silyl enol ethers, followed by some ring closure reaction. In chapters 5 and 7 could be seen that attempted carbocation additions to silyl enol ether derivatives of η4cyanocarvone lacked any result. This was attributed to the electron withdrawing effect of the cyano function, in this way stabilising the neighbouring enol ether moiety and lowering the nucleophilicity of the ζ-position. On the other hand, previous results had shown that a Robinson annelation reaction could be carried out with η4cyanocarvone in very good yields (see scheme 1)[15]. If this behaviour could be extended to other η-cyano ketones in annelations with other enones, it would be a useful extention of the methodologies available for the synthesis of polycyclic systems. For this reason was decided to further investigate the scope of this reaction.

Scheme 1



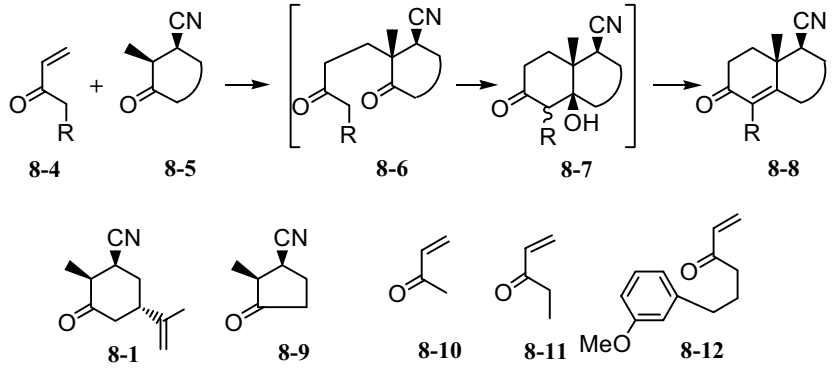
8-1 **8-2** **8-3**

Only a few examples of annelations using η-cyano ketones have been reported in the literature[16-19], but in these instances the beneficial effect of the η-cyano group has been noticed and appreciated. As mentioned above, very good results were obtained with the Robinson annelation to η-

cyanocarvone. The addition of methyl vinyl ketone afforded the corresponding cyano decalone **8-3** in 84% yield in two easy steps (scheme 1)[15].

To investigate the scope of this chemistry, first the Robinson annelations of methyl and ethyl vinyl ketone (MVK, **8-10** & EVK, **8-11**) with η-cyanocarvone **8-1** and 2-methyl-3-oxo-1-cyclopentanecarbonitrile **8-9**, respectively leading to cyano-substituted decalones and indanones (**8-8**), were explored. These compounds have potential as intermediates for the synthesis of isoprenoids, the ultimate objective of the research described in this thesis always being the synthesis of steroid and D-homo steroid skeletons. The use of 6-(3-methoxy-phenyl)-hex-1-en-3-one **8-12** was also investigated, as annelation using this compound could lead in only a few steps to the desired (D-homo) steroid skeletons. The starting η-cyano ketones should be easily accessible compounds by 1,4-addition of cyanide to the corresponding ζ3η-unsaturated ketones.

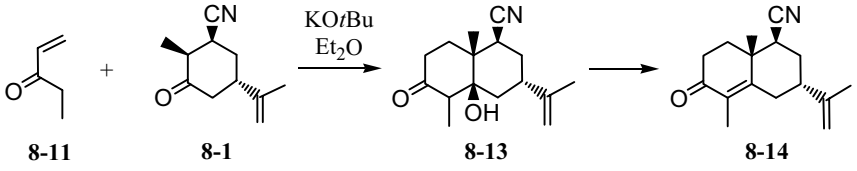
Scheme 2



8.2 Cyano-substituted decalones and indanones

The annelation of cyanocarvone **8-1** with MVK (**8-10**) under protic conditions using NaOMe in MeOH, proceeds in a high 90% yield to a pure crystalline ketol **8-2** (scheme 1). This ketol can be dehydrated in over 90% yield to the corresponding enone **8-3** (scheme 1)[15]. When a similar reaction of cyanocarvone was tried with EVK (**8-11**), the addition of methanol to the enone, forming methoxy-3-pentanone, was observed as the main reaction and only little ketol was obtained. A much better 74% yield of ketol **8-13** could be achieved under aprotic conditions with KO*t*Bu in diethylether (scheme 3). This is a high yield for a η-substituted ketone and comparable with yields

Scheme 3

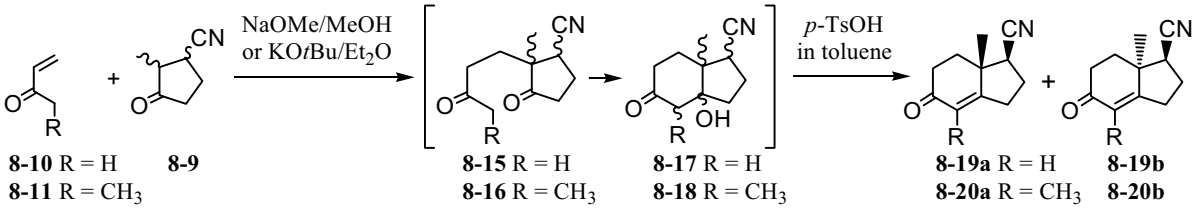


obtained in the annelation of η-unsubstituted ketones[20] and η-diketones[21], were yields around 70-80% were obtained. Dehydration of this intermediate ketol to enone **8-14** could be achieved easily with *p*-TsOH in toluene in 81% yield.

A good and convenient synthesis of **8-14** is important in total syntheses of natural products where a methyl group and a different ζ-substitutent are present at C4. Monomethylation of **8-3** is difficult to tune[22] and in a typical experiment a mixture of 10% of **8-14**, 40% of the dimethylated product and 40% of starting material **8-3** was obtained[23,24].

Addition of potassium cyanide to methylcyclopentenone gave a 2:1 mixture of two isomeric cyanopentanones **8-9** in 85% yield and a 2:1 ratio (*cis:trans*)[25]. The reaction of the isomeric mixture with methyl vinyl ketone was performed using NaOMe as base and gave a stereoisomeric mixture of diketone **8-15** and ketol **8-17** in high yield. This mixture was used without purification in the next dehydration reaction with *p*-TsOH in toluene, and after a reaction time of 2 hrs the known enone **8-19** was obtained in 75% overall yield as a single compound, which has probably the configuration depicted as **8-19a**.

Scheme 4



The mixture of cyanocyclopentenones **8-9** was reacted with ethyl vinyl ketone under aprotic conditions with KO*t*Bu in ether at 0 °C, giving a complex mixture of ketols **8-18** and enones **8-20**. This mixture was used in the next step without purification and the dehydration could be accomplished again by using *p*-TsOH in refluxing toluene. A mixture of the two isomers of **8-20** was obtained in 70% overall yield and 2:1 ratio (most probably **8-20a: 8-20b**), which could be separated by column chromatography on silica gel.

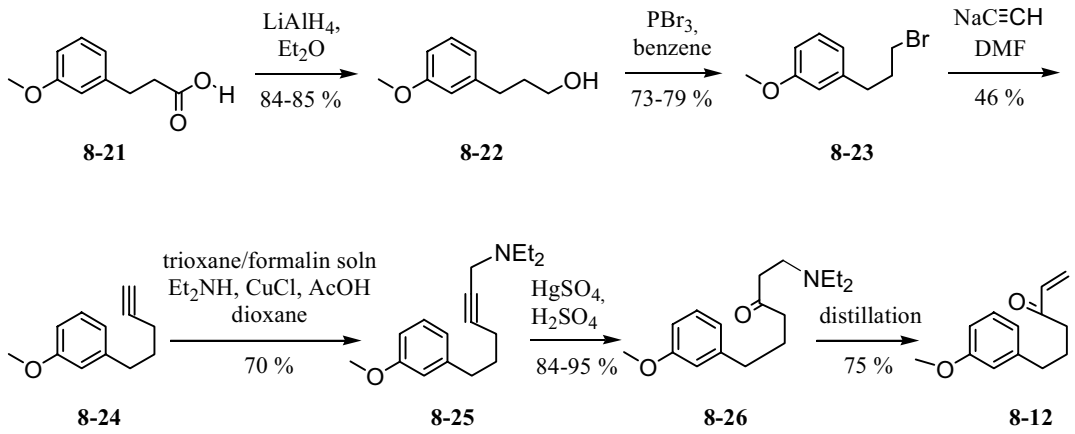
The relatively high yields in the annelation of the η-cyano ketones is related to the ease and selectivity of formation of the anions formed after deprotonation. Computational studies at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d,p) level of theory[26] show that the presence of a η-cyano moiety yields a relatively more stable anion. In comparison with a η-methyl or a η-hydrogen moiety this stabilisation is around 12-13 kcal/mol, and this difference is not significantly influenced by the nature of the ζ-substituent (hydrogen or methyl). This ease of formation of the anions also

improves the selectivity of the anion formation. In ketones with a η-methyl group both ζ4sites of the carbonyl group are about equally easy to deprotonate, which thus yields a mixture of anions and an overall decrease of selectivity. However, in the presence of a η-cyano group the ζ-site in between the carbonyl and the η-cyano moiety is so much easier to deprotonate than the other ζ-site, that effectively only one anion will be formed, with a concomitant increase of the selectivity and yield of the desired products. The extra stabilisation of the anion by the η-cyano group is not reflected in the charge distribution of the anions. The natural population charges of the formally negatively charged ζ-carbon atom, which could have been a measure of reactivity differences between the different anions, of the η-cyano and the η-methyl compounds, are identical within 0.01 electron. Thermodynamic rather than kinetic factors thus can explain the higher yields in annelations of the η-cyano ketones.

8.3 A cyano-substituted D-homo steroid skeleton

The enantioselective synthesis of D-homo steroid skeletons from cyanocarvone **8-1** may become possible when this compound could be annelated with 6-(3-methoxyphenyl)hex-1en-3-one (**8-12**). This enone was synthesized in 15% overall yield according to a known multi-step procedure published by Smith *et al.*, which starts from commercially available 3-(3-methoxyphenyl)-propionic acid (see scheme 5)[27,28].

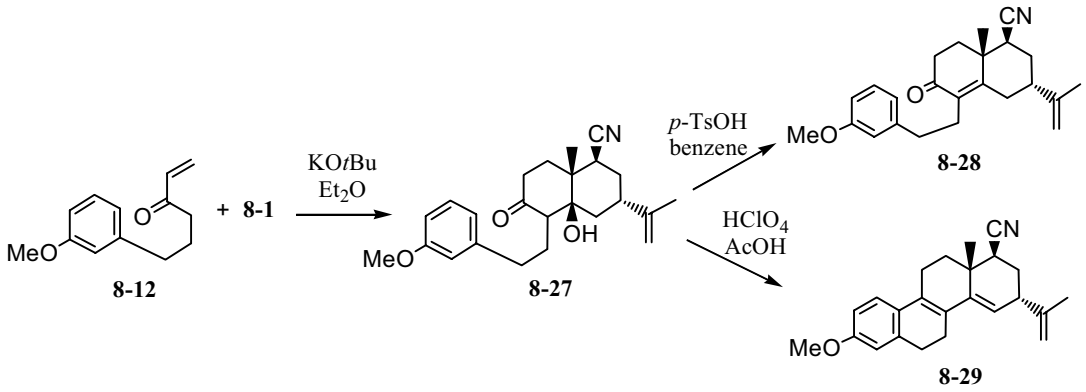
Scheme 5



A reaction of compound **8-12** with cyanocarvone could indeed be achieved, again under aprotic conditions with KO*t*Bu in diethylether, giving one ketol **8-27** in 76% yield (scheme 6). Dehydration of ketol **8-27** with *p*-TsOH in toluene did not give the expected result and enone **8-28** was isolated in only 9% yield. A slight improvement was obtained by the use of benzene as solvent, giving 21% of **8-28**, together with 19% of the starting ketol **8-27** and a small amount (2%) of product **8-29** in

which also ring B was closed. A fair yield of compound **8-29** could be obtained in a one pot reaction using $HClO_4$ in AcOH[29], which gave this D-homo steroid compound as the only product. This compound proved to be rather unstable and after purification only a 35 % yield of reasonably pure **8-29** was isolated. Migration of the double bond in the isopropenyl side chain and aromatisation of the ringsystem appear to be important side reactions, explaining this low yield. A better approach would probably consist in further conversion of the raw product material to a more stable compound, before isolation and purification.

Scheme 6



Experimental

Cis- and *trans*- 2-methyl-3-oxo-1-cyclopentanecarbonitrile (8-9)[25]

A solution of 3.76 g (57.7 mmol) of potassium cyanide in 9 ml of water was added dropwise to a stirred solution of 4.00 g (41.6 mmol) of 2-methyl-2-cyclopenten-1-one in 24 ml of ethanol at 0-5°C. Then 2.72 ml (41.6 mmol) of glacial AcOH was added in 2 h. The reaction mixture was stirred for 2 hrs at 0-5°C and then diluted with water. This mixture was extracted with ethyl acetate (3x), and the organic solution was washed with water (2x) and brine and dried over $MgSO_4$. Then the solvent was evaporated to give 4.34 g (85 %) of crude **8-9**, which was used for the next transformation without further purification. A small portion was purified by bulb-to bulb distillation for analytical purpose and gave a mixture of *cis*- and *trans*-**8-9** (2:1). IR (film) cm^{-1}: 2241, 1745; ^1H NMR ($CDCl_3$) ι 1.22 (*M*) & 1.25 (*m*) (d, *J*=6.7, 3H), 2.03-2.70 (m, 11H), 3.31-3.42 (m, 1H); ^{13}C NMR ($CDCl_3$) ι 11.7 (*M*) & 12.6 (*m*) (q), 25.0 (t), 32.7 (*m*) & 33.4 (*M*) (d), 35.3 (*m*) & 36.0 (*M*) (t), 45.3 (*m*) & 48.2 (*M*) (d), 119.3 (*m*) & 120.5 (*M*) (s), 214.0 (*M*) & 215.0 (*m*) (s). HRMS: M^+, found 123.0686. C_7H_9NO requires 123.0684. MS *m/e* (%): 123 (M^+, 61), 94 (25), 67 (58), 55 (100), 41 (32). Spectroscopic data were in accordance with the literature.

6-(3-Methoxy-phenyl)-hex-1-en-3-one (8-12)

6-(3-Methoxyphenyl)-hex-1-en-3-one (**8-12**) was prepared using the method of Douglas *et.al.*[27,28]. The oily product (bp 100-110 ^{o}C/0.01 mm) showed the following spectroscopic characteristics: IR (film) cm^{-1}: 1699, 1680; ^{1}H NMR ($CDCl_3$): ι 1.94 (q, *J*=7.1, 2H) 2.58 (t, *J*=7.1, 2H), 2.61 (t, *J*=7.1, 2H), 3.77 (s, 3H), 5.78 (dd, J_1 =10.0 & J_2 =1.7, 1H), 6.16 (dd, J_1 =17.6 & J_2 =1.6, 1H), 6.30 (dd, J_1 =17.6 & J_2 =10.0, 1H), 6.71-6.78 (m, 3H), 7.14-7.23 (m, 1H); ^{13}C NMR ($CDCl_3$): 25.2 (t), 35.1 (t), 38.7 (t), 55.1 (q), 111.3 (d), 114.2 (d), 120. 9 (d), 128.0 (t), 129.4 (d), 136.5 (d), 143.3 (s), 159.7 (s), 200.6 (s). HRMS: M^+, found 204.1156. $C_{13}H_{16}O_2$ requires 204.1150. MS *m/e* (%): 204 (M^+, 15), 134 (100), 121 (7), 104 (4), 91 (8), 78 (5), 77 (3) 55 (7).

4a-Hydroxy-3-isopropenyl-5,8a-dimethyl-6-oxo-decahydro-naphthalene-1-carbonitrile (8-13)

To a stirred solution of 1.77 g (10 mmol) of cyanocarvone **8-1**[15] and 1.50 ml (15.1 mmol) of ethyl vinyl ketone (EVK) in 50 ml of dry diethyl ether 1.12 g (10 mmol) of potassium *tert*-butoxide (KO*t*Bu) was added at 0 °C. After being stirred for 2.5 hrs at the same temperature, the reaction was quenched with 1 M HCl. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated. The remaining residue was flash chromatographed on silica gel with PE/EtOAc (75:25 Ÿ 50:50) to give 1.83 g (70 %) of **8-13** as a viscous oil. IR (film) cm^{-1}: 3477, 2239, 1709; ^{1}H NMR ($CDCl_3$): ι 1.03 (d, *J*=6.7, 3H), 1.4-2.7 (m, 10 H), 1.58 (s, 3H), 1.69 (s, 3H), 2.88 (q, *J*=6.7, 1H), 4.70 (s, 1H), 4.77 (s, 1H); ^{13}C NMR ($CDCl_3$): 6.0 (q), 19.9 (q_3), 20.9 (q), 28.7 (t), 31.5 (t), 33.1 (t), 35.7 (d), 37.1 (t), 37.3 (d), 39.6 (s), 51.7 (d), 77.3 (s), 110.3 (t), 121.8 (s), 147.1 (s), 209.0 (s). HRMS: M^+, found 261.1732. $C_{16}H_{23}NO_2$ requires 261.1729. MS *m/e* (%): 261 (M^+, 45), 243 (24), 177 (37), 158 (14), 134 (58), 84 (100).

3-Isopropenyl-5,8a-dimethyl-6-oxo-1,2,3,4,6,7,8,8a-octahydro-naphthalene-1-carbonitrile (8-14)

Alcohol **8-13** (0.783 g, 3 mmol) and *p*-TsOH (40 mg) in 50 ml of toluene were refluxed using a Dean-Stark adapter. After 5 hrs of refluxing the reaction mixture was cooled down, washed with sodium bicarbonate solution and water, dried over $MgSO_4$ and evaporated. The remaining residue was flash chromatographed on silica gel with PE/EtOAc (70:30) to give 0.59 g (81%) of **8-14** as yellow oil. Crystallisation from *t*-BuOMe gave white crystals, 84-86 mp °C. IR (CCl_4) cm^{-1}: 2240, 1674; ^{1}H NMR ($CDCl_3$): ι 1.40 (s, 3H), 1.6-2.7 (m, 9H), 1.73 (s, 3H), 1.82 (s, 3H), 2.95 (d, *J*=16.1, 1H), 4.60 (s, 1H), 4.89 (s, 1H); ^{13}C NMR ($CDCl_3$): ι 11.3 (q), 19.0 (q), 22.6 (q), 27.0 (t), 30.2 (t), 33.4 (t), 35.6 (t), 36.6 (d), 37.6 (s), 39.0 (d), 112.7 (t), 120.2 (s), 131.0 (s), 145.7 (s), 156.9 (s), 197.1 (s). HRMS: M^+, found 243.1618. $C_{16}H_{21}NO$ requires 243.1623. MS *m/e* (%): 243 (M^+, 54), 228 (21), 201 (13), 200 (14), 190 (54), 132 (100), 119 (22).

7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indene-1-carbonitrile (8-19)

To a stirred solution of 1.85 g (15 mmol) of cyanocyclopentanone **8-9** and 3.75 ml (45 mmol) of methyl vinyl ketone (MVK) in 30 ml of methanol was added dropwise 30 ml (30 mmol) of a 1 M sodium methoxide (NaOMe) solution in methanol at 0 °C. The reaction mixture was stirred for 2 hrs at 0 °C, stored in refrigerator overnight, then diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The remaining residue was flash chromatographed on silica gel with PE/EtOAc (1:1) to give a crude mixture of intermediates **8-15** and **8-17**, which was used for the next step without further purification.

To a solution of the crude mixture of **8-15** and **8-17** in 50 ml of toluene at reflux temperature, 150 mg of *p*-TsOH was added in two portions. The reaction mixture was refluxed for 2.5 hrs in a Dean-Stark apparatus. The reaction mixture was diluted with toluene, washed with a saturated aqueous sodium bicarbonate solution and water, dried over $MgSO_4$. The remaining residue (3.22 g) was flash chromatographed on silica gel with PE/EtOAc/pyridine (70:30:1) to give 1.98 g (75 %) of **8-19** as yellow oil. Crystallisation of **8-19** from ether gave white crystals with mp 70-71 °C. IR (film) cm^{-1}: 2240, 1670; ^1H NMR ($CDCl_3$): 1.34 (3H, s), 1.70-2.80 (9H, m), 5.80 (1H, s). ^{13}C NMR ($CDCl_3$): 18.7 (q), 26.0 (t), 28.6 (t), 32.9 (t), 34.0 (t), 40.7 (d), 45.4 (s), 118.9 (s), 123.2 (d), 171.5 (s), 197.6 (s). HRMS: M^+, found 175.0999. $C_{11}H_{13}NO$ requires 175.0997. MS *m/e* (%): 175 (M^+, 44), 147 (100), 132 (46), 118 (14), 94 (14), 43 (14);

4,7a-Dimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indene-1-carbonitrile (8-20)

To a stirred solution of 1.85 g (15 mmol) of cyanocyclopentanone **8-9** and 2.24 ml (22.5 mmol) of ethyl vinyl ketone (EVK) in 20 ml of dry diethyl ether, 1.85 g (16.5 mmol) of KO*t*Bu was added at 0 °C. The reaction mixture was stirred for 2.5 hrs at 0 °C, and then quenched with 1 M HCl. The mixture was diluted with ethyl acetate, and the organic solution was washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The residue (3.73 g) consisted of a crude mixture of several annelation products **8-18** and **8-20**, which was used in the next step without further purification.

To a stirred solution of the crude mixture of annelation products in 50 ml of toluene at reflux temperature, 200 mg of *p*-TsOH was added in two portions. The reaction mixture was refluxed for 4 hrs in a Dean-Stark apparatus. The reaction mixture was diluted with toluene, washed with a saturated aqueous sodium bicarbonate solution and water, dried over $MgSO_4$ and the solvent was evaporated to give 3.86 g of crude **8-20**. The further work up was performed in two ways:

A small portion of crude **8-20** was purified by bulb-to-bulb distillation to give 0.41 g (2.61 mmol) (14 %) of two isomers of **8-20**. This mixture of isomers was flash chromatographed on silica gel

with PE/EtOAc/pyridine (70:30:1) to give: 0.17 g (0.90 mmol) (6 %) of the first eluted isomer, 0.10 g (3.5%) of mixture of both isomers of **8-20** and 0.028 g of (0.14 mmol) (0.9 %) of the second eluted isomer.

The rest of the crude **8-20** was purified by flash chromatography as described above without bulb-to-bulb distillation to give: 1.093 g (5.8 mmol) (39 %) of pure first eluted isomer and 0.61 g (21 %) of pure second eluted isomer, next to some amount of unseparated isomers. The total yield of both isomers was 2.00 g (70 %).

Major isomer. IR (neat) cm^{-1}: 2236, 1662; ^{1}H NMR ($CDCl_3$): 1.12-2.80 (m, 9H), 1.26 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$) ι 11.2 (q), 19.1 (q), 26.4 (t), 28.1 (t), 32.9 (t), 34.2 (t), 41.2 (d), 45.3 (s), 119.2 (s), 129.0 (s), 164.7 (s), 197.2 (s). HRMS: M^+, found 189.1153.$C_{12}H_{15}NO$ requires 189.1154. MS *m/e* (%): 189 (M^+, 91), 174 (17), 161 (100), 147 (90) 146 (27), 136 (14), 132 (23), 118 (18), 93 (16).

Minor isomer. IR (neat) cm^{-1}: 2240, 1663; .^{1}H NMR ($CDCl_3$): 1.11-2.89 (m, 9H), 1.24 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$) ι 11.62 (q), 22.87 (q), 27.14 (t), 28.32 (t), 32.27 (t), 33.00 (t), 42.00 (d), 45.69 (s), 120.05 (s), 129.64 (s), 164.29 (s), 197.13 (s). HRMS: M^+, found 189.1157. $C_{12}H_{15}NO$ requires 189.1154. MS *m/e* (%): 189 (M^+, 95), 174 (19), 161 (65), 147 (100), 136 (13), 132 (23), 118 (15), 93 (16).

4a-Hydroxy-3-isopropenyl-5-[2-(3-methoxy-phenyl)-ethyl]-8a-methyl-6-oxo-decahydro-naphthalene-1-carbonitrile (**8-27**)

To a stirred solution of 0.584 g (3.3 mmol) of cyanocarvone **8-1** and 1.02 g (5.0 mmol) of 6(3-methoxyphenyl)hex-1-en-3-one (**8-12**) in 20 ml of dry diethyl ether, 0.403 g (3.6 mmol) of KO*t*Bu was added at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 hrs, and then quenched with 1 M HCl. The organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated. The remaining residue was flash chromatographed on silica gel with PE/EtOAc (1:3 Ÿ 1:1) to give 0.955 g (76 %) of hydroxyketone **8-27** as a viscous oil. IR (film) cm^{-1}: 3473, 2237, 1710; ^{1}H NMR ($CDCl_3$) ι 1.00-2.80 (m, 15H), 1.52 (s, 3H), 1.68 (s, 3H), 3.79 (s, 3H), 4.67 (s, 1H), 4.75 (s, 1H), 6.71-6.80 (m, 3H), 7.15-7.26 (m, 1H); ^{13}C ($CDCl_3$) ι 20.04 (q), 20.93 (q), 23.32 (t), 28.78 (t), 31.91 (t), 33.91 (t), 35.04 (t), 35.66 (d), 37.30 (d), 37.85 (t), 39.74 (s), 55.19 (q), 57.01 (d), 77.92 (s), 110.38 (t), 111.37 (d), 114.15 (d), 120.83 (d), 121.68 (s), 129.43 (d), 143.67 (s), 147.07 (s), 159.70 (s), 208.08 (s). HRMS: M^+, found 381.2305. $C_{24}H_{31}NO_3$ requires 381.2304. MS *m/e* (%): 381 (M^+, 24), 363 (26), 260 (13), 243 (10), 229 (14), 228 (10), 134 (100), 122 (19), 121 (17), 83 (13);

3-Isopropenyl-5-[2-(3-methoxy-phenyl)-ethyl]-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydro-naphthalene-1-carbonitrile (**8-28**)

To a stirred solution of 381 mg (1 mmol) of hydroxyketone **8-27** in 30 ml of benzene at reflux temperature, 55 mg of *p*-TsOH was added in five portions. The reaction mixture was refluxed for 12 hrs using a Dean-Stark apparatus. Then the reaction mixture was washed with a saturated aqueous sodium bicarbonate solution and water, dried over $MgSO_4$ and the solvent was evaporated. The remaining residue was flash chromatographed on silica gel with PE /EtOAc/pyridine (70:30:1) to give 72 mg (19 %) of unconverted **8-27**, 76 mg (21 %) of enone **8-28** and 6 mg (2 %) of **8-29** (vide infra) as pale yellow oils. The spectroscopic characteristics of **8-28** are: IR (film) cm^{-1}: 2238, 1666; ^1H NMR (C_6D_6) ι 1.00 (s, 3H), 1.20-1.61 (m, 4H), 1.34 (s, 3H), 1.78-1.87 (m, 2H), 2.10-2.80 (m, 7H), 3.00-3.15 (m, 1H), 3.40 (s, 3H), 4.48 (s, 1H), 4.68 (s, 1H), 6.69-6.81 (m, 3H), 7.06-7.15 (m, 1H); ^{13}C (C_6D_6) ι 18.78 (q), 22.20 (q), 26.74 (t), 27.85 (t), 29.28 (t), 33.53 (t), 34.82 (t), 35.34 (t), 36.37 (d), 37.27 (s), 38.58 (d), 54.50 (q), 111.34 (d), 112.43 (t), 114.77 (d), 119.85 (s), 121.22 (d), 129.32 (d), 134.25 (s), 143.37 (s), 145.83 (s), 156.80 (s), 160.03 (s), 195.08 (s). HRMS: M^+, found 363.2192. $C_{24}H_{29}NO_2$ requires 363.2198. MS *m/e* (%): 363 (M^+, 100), 242 (15), 228 (53), 134 (6), 122 (51), 121 (41), 91 (18);

3-Isopropenyl-8-methoxy-12a-methyl-1,2,3,4,4a,5,6,11,12,12a-decahydro-chrysene-1-carbonitrile (**8-29**)

To a stirred solution of 381 mg (1 mmol) of hydroxyketone **8-27** in acetic acid (8 ml) was added 0.077 ml (0.9 mmol) of 70 % $HClO_4$ at 15°C. The mixture was stirred for 2 hrs at 15°C, and then for 2.5 hrs at 30 °C. The now purple solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with a saturated sodium bicarbonate solution, brine, dried over $MgSO_4$ and the solvent was evaporated. The remaining residue was flash chromatographed on silica gel with PE/EtOAc/pyridine (15:84:1) to give 120 mg (35%) of **8-29** as a yellow oil. IR (neat) cm^{-1}: 2237; ^1H NMR (C_6D_6) ι 1.11-2.20 (m, 6H); 1.17 (s, 3H); 1.53 (s, 3H); 2.20-2.60 (m, 6H); 3.44 (s, 3H); 4.60 (s, 1H); 4.82 (s, 1H); 5.48 (d, *J*=4.8, 1H); 6.77-6.82 (m, 2H); 7.16-7.20 (m, 1H). ^{13}C (C_6D_6) ι 19.02 (q); 21.68 (q); 22.50 (t); 24.10 (t); 25.53 (t); 28.81 (t); 34.57 (s); 34.82 (t); 35.43 (d); 41.06 (d); 54.55 (q); 111.30 (d); 113.06 (t); 113.35 (d); 120.62 (d); 120.99 (s); 124.39 (d); 127.01 (s); 128.70 (s); 128.96 (s); 137.94 (s); 140.63 (s); 146.81 (s); 159.01 (s). HRMS: M^+, found 345.2090. $C_{24}H_{27}NO$ requires 345.2093. MS *m/e* (%): 345 (M^+, 100), 343 (10), 330 (9), 314 (5), 304 (20), 302 (5);

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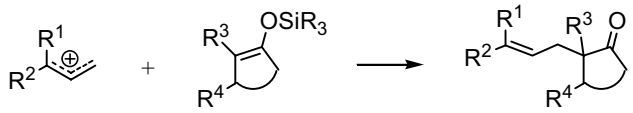
Chapter 9

Discussion

The research presented in this thesis concerns the development of new, short and versatile routes to steroid and D-homo steroid skeletons. As shown in the introduction, a multitude of reaction routes to steroids have already been published and developing more just for the sake of it would not make much sense. To be of interest, a new route should be short, enantioselective and lead to polyfunctionalised steroid skeletons. The research described has attempted to fulfil these conditions. Several new short syntheses of (D-homo) steroids have been developed focussing on additions of carbocations to silyl enol ethers as the key transformation (scheme 1). The demand for enantioselectivity was met by the use of carvone as a chiral element in practically all approaches.

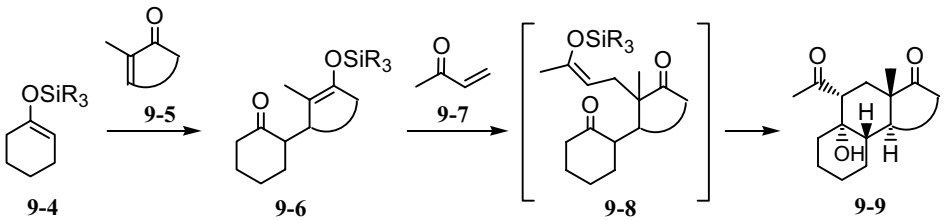
Scheme 1



9-1 **9-2** **9-3**

In chapter 2 an interesting domino reaction sequence, which could be carried out as a one-pot procedure, was shown to lead rapidly to tricyclic systems using Mukaiyama chemistry (scheme 2). Subsequently, further development of this sequence to the synthesis of tetracyclic steroid skeletons was attempted. Unfortunately the Mukaiyama reactions appeared sensitive to electronic and steric effects, quickly lowering the yields of the addition reactions. The electronic delocalisation of the ketone in ring B (steroid numbering) also prevented the final aldol cyclisation step and led to a retro-reaction in the coupling with MVK. As a consequence, the envisaged use of either (*S*)-(+)-carvone or 6-methoxytetralone as starting silyl enol ethers did not lead to the desired steroid precursors *via* this chemistry. The procedures published in literature using domino Mukaiyama reactions and leading to polysubstituted compounds did not encounter these problems because no aldol reactions on ζ,η-unsaturated ketones were used and steric hindrance directly next to the reaction centres was limited (see scheme 1, chapter 2)[1-3].

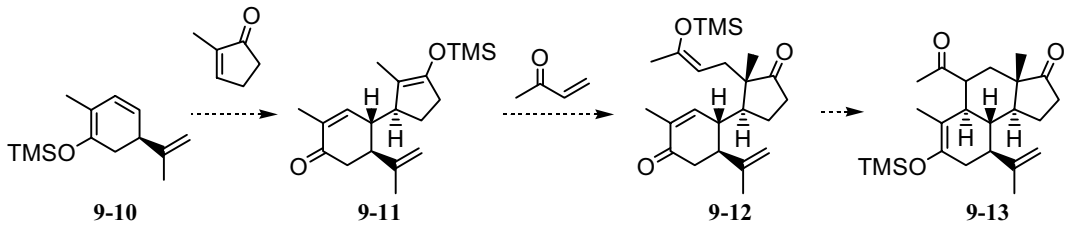
Scheme 2



9-4 **9-6** **9-8** **9-9**

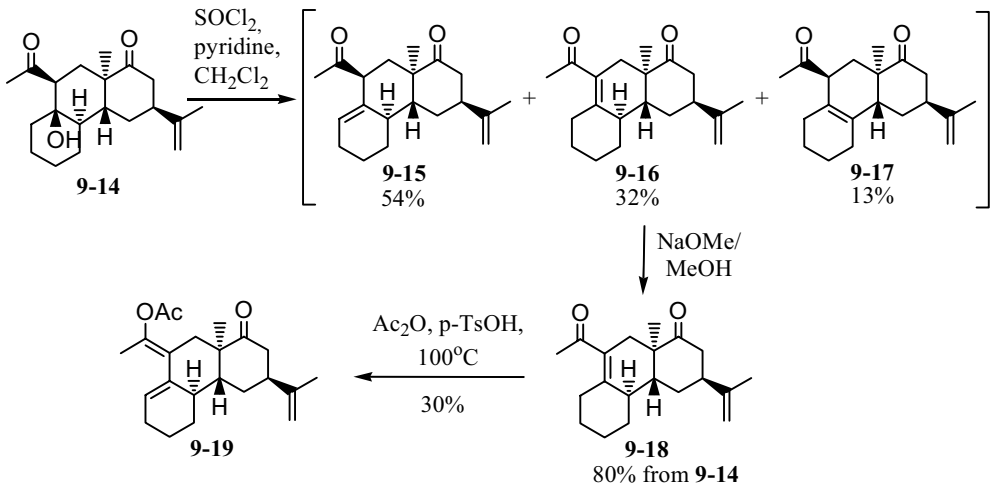
One route that has not yet been explored due to time restrictions, but which could maybe circumvent the mentioned problems encountered with the previous starting silyl enol ethers is the use of the dienol ether of (*R*)-(-)-carvone (**9-10**). Silyl dienol ethers have been reacted with methyl cyclopentenone, with transfer of the silyl group to form a new silyl enol ether of the accepting enone[4]. This new silyl enol ether was then used as a substrate for further alkylation to give ultimately steroid skeletons. The use of the dienol ether of (*R*)-(-)-carvone would lead to intermediate **9-12** in which the steric hindrance around the reaction site in the carvone moiety is reduced, due to the flat structure of the enone. Moreover, the electronic delocalisation of the enone is not counteracting the cyclisation reaction anymore as it is actually used in this step, now involving a Michael reaction instead of the aldol cyclisation (scheme 3). We even have speculated on the possibility of a reaction of **9-13** with a second molecule of MVK, leading to the generation of the complete steroid skeleton.

Scheme 3



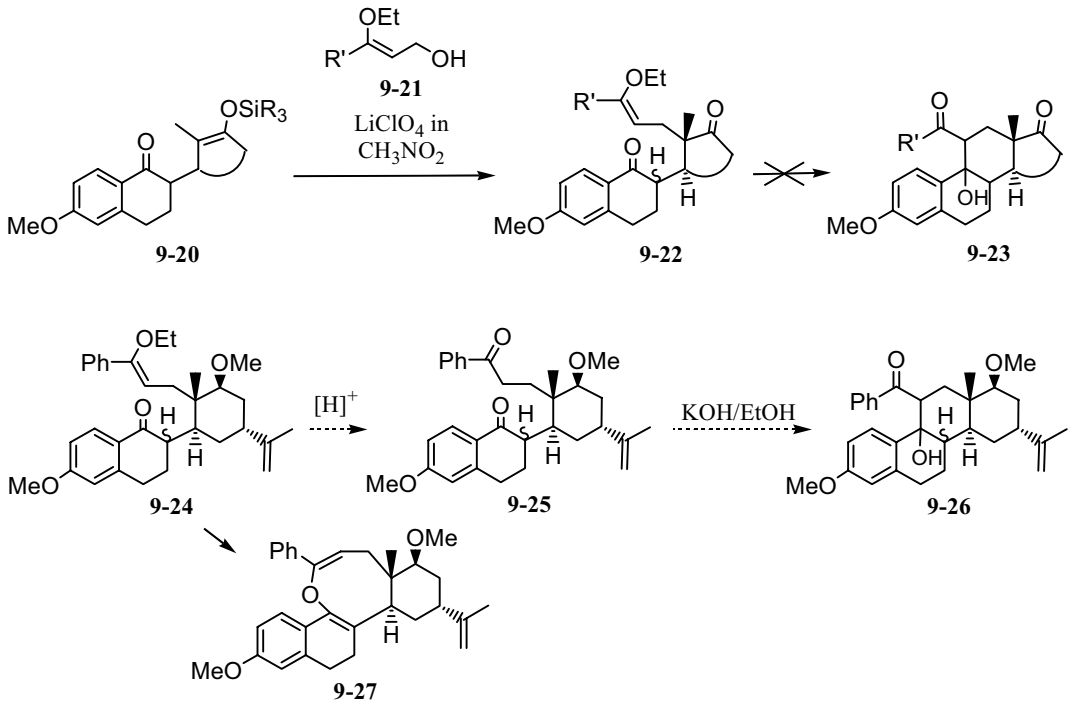
It would of course also be possible to further transform the tricyclic system obtained in the addition reactions with the silyl enol ether of cyclohexanone. A start was made for such a route (see scheme 4) but was quickly abandoned as this would lead to a rather long sequence of steps, which is countering the original concept of this research project, being the development of *short* synthesis routes.

Scheme 4



In chapter 3 an alternative for the Mukaiyama addition of MVK to the tetralone derivatives was found in the Lewis acid catalysed addition of reactive carbocation precursors **9-21**. This yielded an intermediate (**9-22**) in which theoretically an aldol cyclisation step would still be possible (scheme 5).

Scheme 5

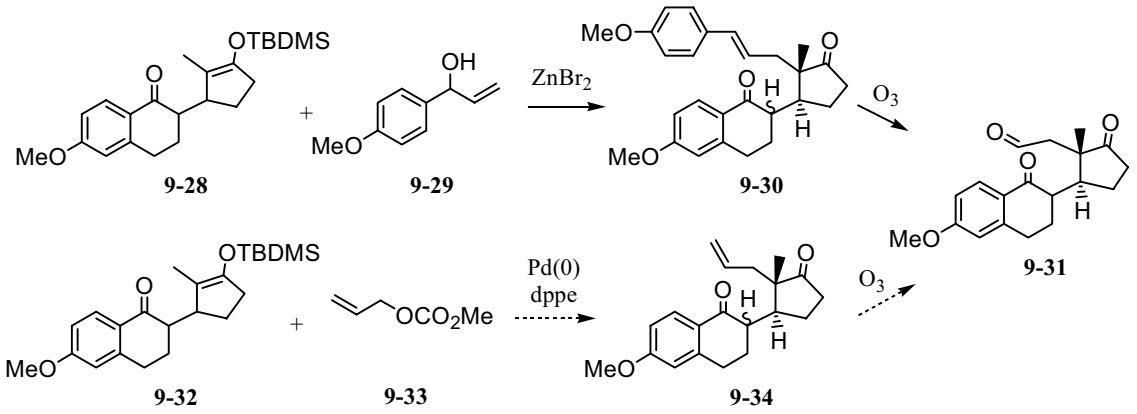


However, this cyclisation step appeared troublesome in practice. Indeed, all attempts to cyclise compound **9-22** in this manner, even when excluding potential side reactions, failed. Reactions were attempted on the intermediates having carvone as ring D or those having a five-membered D ring originating from 2-methyl cyclopentenone. The failure of the aldol cyclisation was attributed to the enolisation of the carbonyl group in the tetralone moiety, on which reaction should take place. Literature data showed that cyclisation is possible when enolisation is prevented[5] and that the reaction can also be forced under strong basic (KOH/EtOH) conditions when no side reactions can take place[6-9]. Forcing the reaction under strong basic conditions is something we did not try in our reaction scheme, although it could have been attempted on compound **9-24**, in which the ketone in ring D has been reduced and protected to avoid reactions taking place on this position. However, this should then be done on the crude material obtained immediately after the preceding reaction, as compound **9-24** is very unstable and almost immediately converts into compound **9-27** upon work-up. Moreover, the enol ether function present would have to be hydrolysed first to the ketone, but the acidic hydrolysis conditions would very probably lead again to formation of ether **9-27** (scheme 5). In addition, the yield of the reaction leading to compound **9-22** with carvone as ring D

is low (20%) and, in our opinion, the overall method, next to not being really short, would not have become more elegant.

A better route was found in the reaction of silyl enol ether **9-28** with a carbocation generated from 3-hydroxy-3-(4-methoxyphenyl)-propene **9-29**. Ozonolysis of the double bond in adduct **9-30** followed by a McMurry reaction, published previously for the five-membered ring D compound **9-31** (scheme 6)[10-13], then gives ring C closure.

Scheme 6

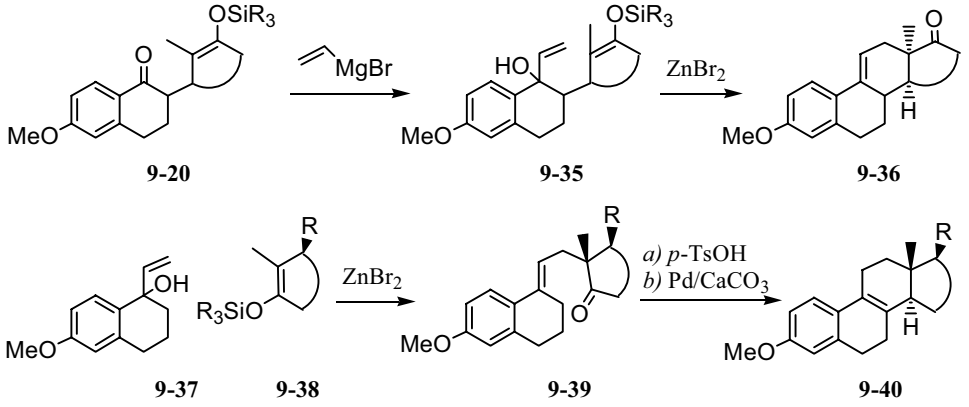


An alternative and more atom efficient method of obtaining this triketonic intermediate might have been the application of a Tsuji reaction. This reaction is known for the introduction of allylic substituents on the ζ-position next to ketones *via* a palladium catalysed addition of an allylic carbonate to an enol ether derivative of the ketone[14-17]. Ozonolysis of the double bond in the coupling product would lead to the same triketone **9-31** (scheme 6). This reaction scheme was not investigated as the research described in this thesis focussed on the addition of carbocations to silyl enol ethers. Besides, probably not much improvement in the yield of around 90% for the carbocation addition reaction would have been attained by switching to the Tsuji reaction. Moreover in the ozonolysis reaction of compound **9-30**, the original starting material for compound **9-29**, *para*-anysaldehyde, is regenerated. This compound can then be reused in a new reaction run, making the complete reaction sequence more economically and environmentally sound.

Next to a selective reaction on the newly formed silyl enol ether in the intermediates obtained after the first Mukaiyama addition **9-20**, selective reactions become possible on the freed carbonyl from the starting silyl enol ether (scheme 7, **9-20** Ÿ **9-36**). This insight opened up a route involving the addition of vinyl magnesium bromide to the free carbonyl group of methoxytetralone in compound **9-20**. In this way, a carbocation precursor was accessed which could then be cyclised under mild Lewis acidic conditions by an intramolecular reaction with the silyl enol ether in ring D (chapter 4).

The products obtained were *cis* fused between rings C and D and the five-membered D-ring compound was a racemate. With the use of (*R*)-(-)-carvone as ring D, an enantiomerically pure D-homo steroid could be attained. This compound was converted into its oxime for X-ray analysis purposes. Isomerisation of the C,D-ring junction from *cis* to *trans* should be possible[18] and also methods for ring contraction of ring D are known[19-23], but these routes are not very short and a better alternative to reach a short synthesis for enantiomerically pure C,D-*trans* fused steroids was found in an intermolecular variation of this method.

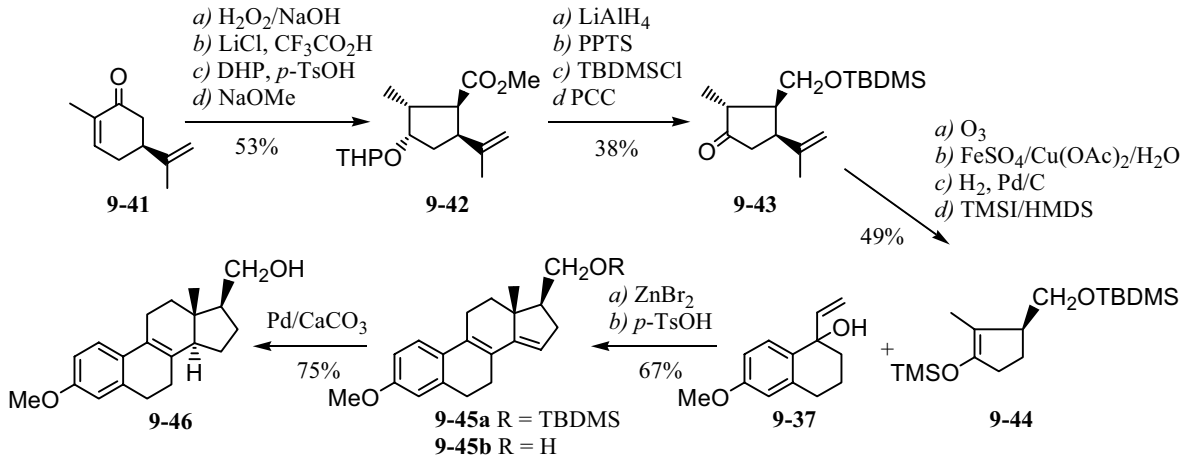
Scheme 7



This *intermolecular* variant leads to C,D-*trans* fused steroid skeletons by first transforming 6-methoxytetralone into a carbocation precursor **9-37** and then reacting this compound with a silyl enol ether ring D precursor (scheme 7, **9-37** Ÿ **9-40**). This route resembles the synthesis route published by Torgov and co-workers in the late fifties[24,25]. This new variation does however have some advantages, as it enables the introduction of a wide variety of substituents on both C13 and C17 in a short, efficient and enantioselective way. This leads in an easy way to a large group of compounds that could possess interesting new pharmaceutical properties. As discussed in chapter 5, only a few routes have been published that rely on the Torgov chemistry and lead to enantiopure compounds, but all of the products obtained in these routes need further transformation after synthesis of the steroid skeleton. A short and efficient way for the synthesis of enantiomerically pure chiral cyclopentanones with selective substitution on the ζ#and#η#positions would make of our reaction sequence an attractive way for accessing optically active steroids. The silyl enol ether ring D precursors used in chapter 5 are all racemic but we have attempted to devise a synthesis of an enantiomerically pure ring D precursor starting from carvone (scheme 8). This route, presented in chapter 6, is however still quite long, counting 11 steps, and, although there is probably still room for improvement, the overall yield of 10% is not high enough to be interesting for more extended applications. This optically pure ring D precursor was used to synthesise the corresponding dienic

steroid skeleton. This diene was obtained as a mixture of the protected and deprotected alcohols on C17 (respectively compounds **9-45a** and **9-45b**), but both were obtained as mainly one enantiomer, proving the concept of the method. Complete deprotection of the alcohol moiety in compound **9-45** prior to further transformation gives the best results in this reaction sequence as the free alcohol compound is more stable and gives a higher yield in the selective reduction (>75%),.

Scheme 8

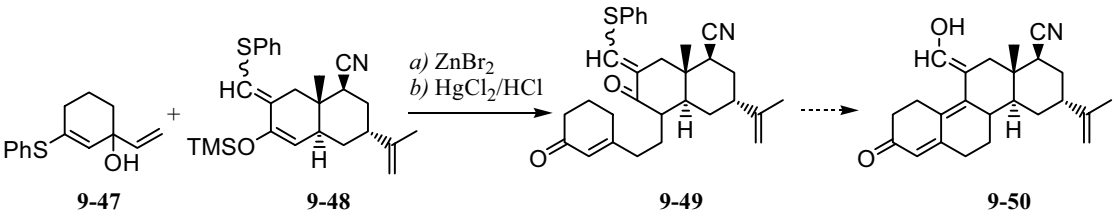


A possible solution for short, enantioselective synthesis of substituted cyclopentanones could come from the use of chiral catalysis. Such attempts are made, for example, by the group of Minnaard and Ferringa[26-30]. Their research is focused on copper and rhodium catalysed additions to cyclic enones using chiral ligands. Although it is possible to introduce alkyl chains on the η-position of cyclopentenones with high enantioselectivity, the introduction of functionalised chains, such as vinyl or allyl, is still troublesome. Furthermore, these additions do not tolerate substituents on the ζ-position and at present no method has been found to introduce an alkyl substituent regioselectively after the addition on the η-position has taken place[31].

Our key reaction, the addition of carbocations to silyl enol ethers, was also used to investigate the possibilities of 1-phenylthio-3-vinyl-3-cyclohexenol **9-47** as a new bis-annelating reagent (scheme 9, and chapter 7). The results showed that reactions of this phenylthio carbocation precursor with silyl enol ethers led to enones in good yields in only two steps. Steric factors decreased the yield but improved the stereoselectivity of the reaction, which is in agreement with the reactions of silyl enol ethers with the Torgov carbocation precursor from chapter 5. One more step cyclises these enones to tricyclic systems, although the most appropriate conditions, leading to high yields of the tricyclic systems, have not yet been found. The conditions mentioned in literature for the cyclisation of similar compounds (*p*-TsOH/AcOH, >80%)[32-34] did not give such high yields in our hands.

The method has been shown to be in principle suitable for the production of steroids. A seco steroid has been synthesised and, although the coupling reaction has to be optimised and the cyclisation of this compound has not yet been attempted, relying on the results obtained with the simple bicyclic compounds, a reasonable yield of a highly functionalised steroidal compound (**9-50**) should be accessible using this method (scheme 9).

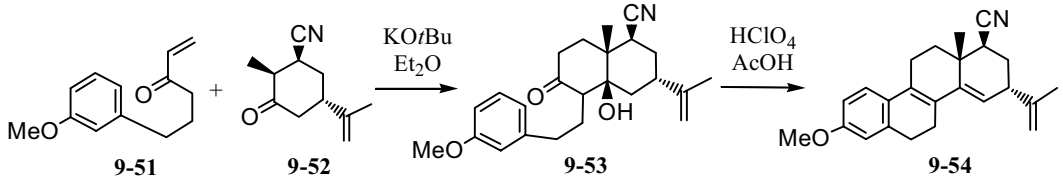
Scheme 9



9-47 **9-48** **9-49** **9-50**

Chapter 8 does not fit in with the preceding chapters in the sense that the key reaction, the addition of a carbocation with a silyl enol ether, present in all these chapter, does not occur in the chemistry described here. It does however solve a problem encountered in two of the preceding chapters (chapters 5 and 7), being the unreactivity of the silyl enol ether of η-cyano carvone towards the addition with carbocations under the conditions used. This unreactivity was explained by the lower nucleophilicity of this silyl enol ether due to the negative inductive effect of the cyano group. This negative inductive effect can however be turned into an advantage when η-cyano carvone is used in a Robinson annelation. The good reactivity of this compound in such a reaction with methyl vinyl ketone (MVK) had been noticed previously[35] and extension of this feature to the use of other η-cyano ketones and enones, eventually leading to polycyclic systems and especially steroid skeletons seemed feasible. Good results were obtained with the use of η-cyano cyclopentanone on one side and ethyl vinyl ketone (EVK) on the other. Moreover, when η-cyano carvone was reacted with 6-(3-methoxyphenyl)hex-1en-3-one, a D-homo steroid precursor was obtained in a good 76% yield (scheme 10). Cyclisation, although also high yielding, afforded an unstable product that quickly transformed to a complex mixture upon purification, which lowered the yield to 35%. Further conversion of the cyclised product prior to purification should lead to a D-homo steroidal product with a good overall yield for this reaction sequence.

Scheme 10



9-51 **9-52** **9-53** **9-54**

In conclusion, the work presented in this thesis has led to several new, short and efficient syntheses of (D-homo) steroid skeletons which present possibilities for further conversions but which could also possess interesting biological properties by themselves. The use of the dienol ether of (*R*)-(-)-carvone in a domino Mukaiyama reaction sequence and the development of short and efficient syntheses of optically pure five-membered ring D precursors for their use in the Torgov related route presented in chapter 5 are interesting options for further development.

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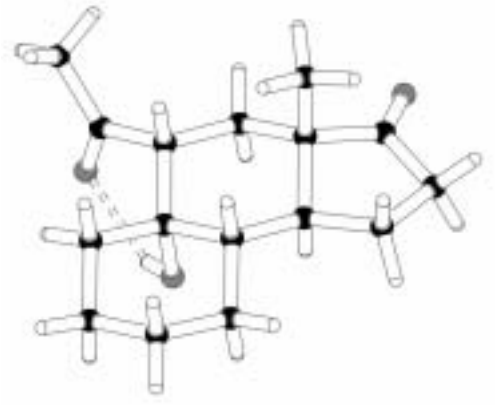
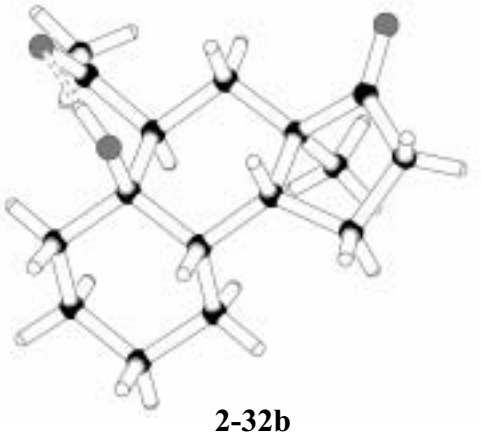
Appendix – Crystal structures



2-32a



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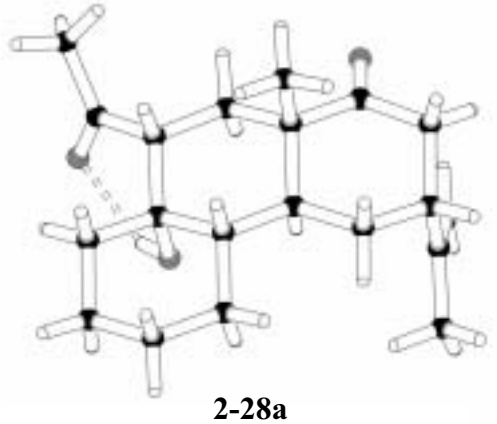

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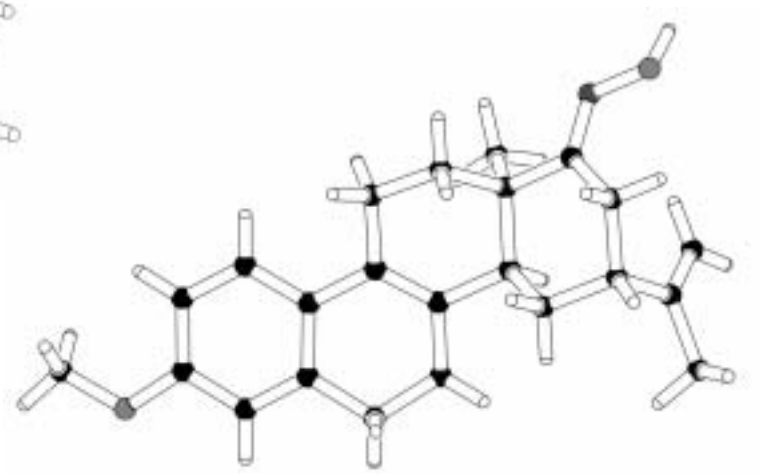

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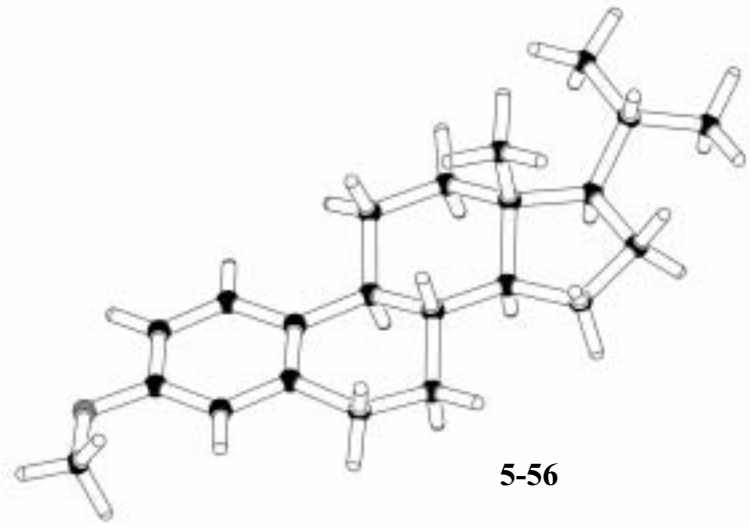


5-56

List of used abbreviations

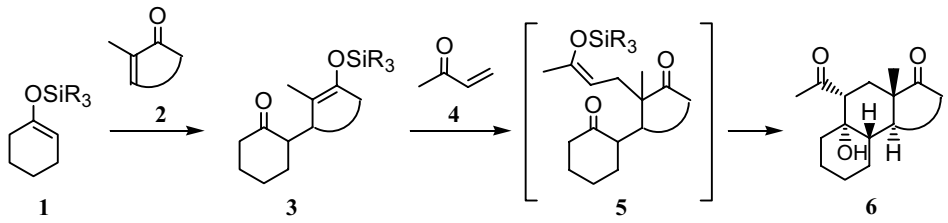
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
*t*BuOMe	*tert*-butyldimethylether
Cp	cyclopentadienyl
DHP	dihydropyran
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
KO*t*Bu	potassium *tert*-butoxide
Me	methyl
MOM	methoxymethyl
PCC	pyridinium chlorochromate
PE	petroleum ether 40-60 / light petroleum
Ph	phenyl
Piv	pivaloyl (= 2,2-dimethylacetyl)
PPTS	pyridinium *para*-toluenesulfonic acid
Pr	propyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate (trifluoromethanesulfonyl)
THF	tetrahydrofurane
THP	tetrahydropyranyl
TMS	trimethylsilyl
$TrSbCl_6$	trityl (= triphenylcarbenium) hexachloroantimonate
p-TsOH	*para*-toluenesulfonic acid

Summary

Steroidal hormones figure amongst the most important natural products involved in the regulation of the delicate balance which is our health. As a consequence, their use is widespread in the pharmaceutical and food (supplement) industry. Due to its versatility, steroid total synthesis has proven most valuable to find new compounds with increased potencies and reduced side effects. Unfortunately, most total synthesis routes to steroids are long and/or low yielding, and often lead to racemic mixtures. This explains why the research in this area, although already in progress for almost 70 years, is still ongoing. The development of new efficient, short, versatile and chiral routes to adequately functionalised compounds is therefore of significant value for this field of research.

Our approaches focus around carbocation additions to silyl enol ethers. These additions can be performed under mild Lewis acidic conditions and lead to high yields of addition products. In our first approach (***chapter 2***), we used a Mukaiyama domino reaction to synthesise tricyclic systems in a one-pot procedure (scheme 1). To develop this method further to steroid synthesis, 6-methoxytetralone and (*S*)-(+)-carvone were tested as starting silyl enol ethers. However, although the first addition step, especially in the reactions with 6-methoxytetralone, was high yielding, the second addition step, with methyl vinyl ketone (**4**), appeared difficult, not giving any desired product.

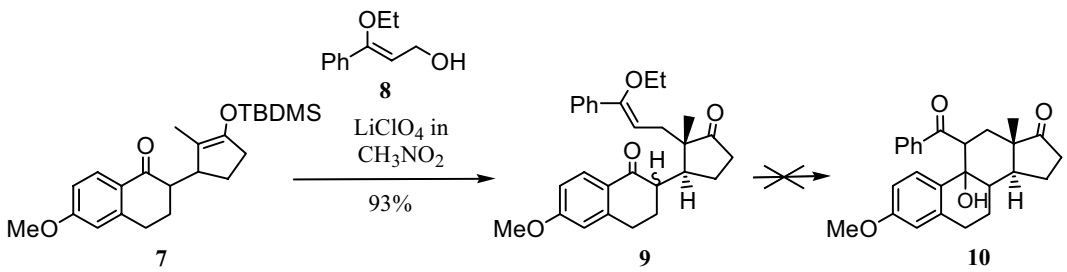
Scheme 1



1 3 5 6

The addition of more reactive carbocation precursors for this second step was tried in the reaction sequences with 6-methoxytetralone and this finally led to a good yield for this addition step (90%) (***chapter 3***). However, the consecutive aldol cyclisation step, leading to closure of ring C, then caused trouble (scheme 2).

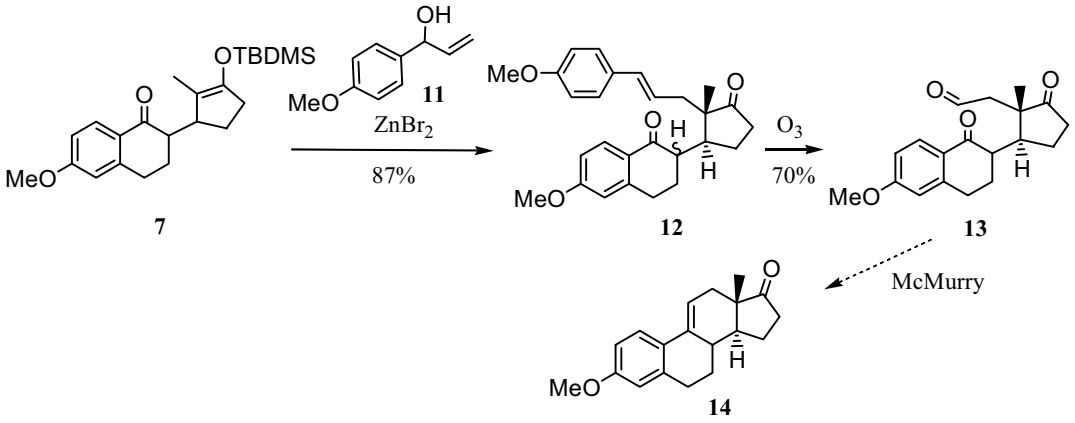
Scheme 2



7 9 10

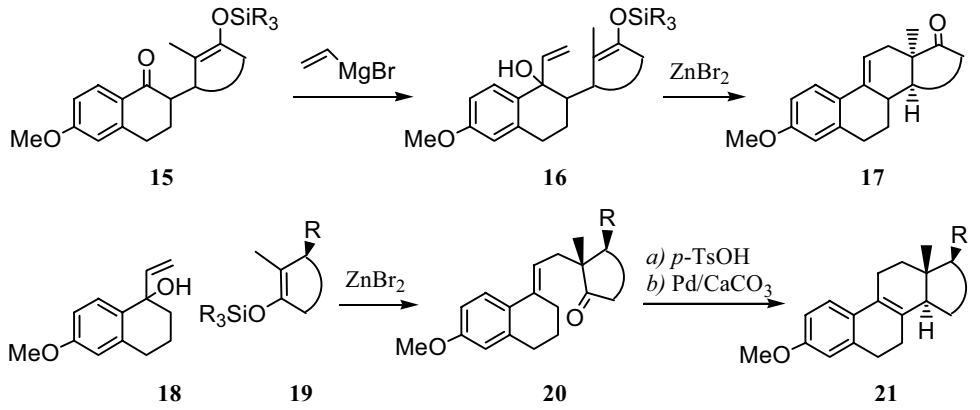
This problem was solved by replacing the aldol cyclisation step with a McMurry reaction. The correct precursor for this reaction (**13**) was obtained by ozonolysis of the double bond in the side chain of the intermediate **9**. A good 70% yield for this reaction was obtained when the alkoxy group in the side chain was moved from its position adjacent to the ozonolysed double bond to the *para* position in the aromatic ring. The presence of this alkoxy group appeared crucial in the preceding carbocation addition reaction, as, without it, no addition occurred.

Scheme 3



In compound **7,** next to doing a selective reaction on the silyl enol ether moiety, a selective reaction can also be performed on the free carbonyl group of the tetralone moiety. By introducing a vinyl group a carbocation precursor was obtained which could be cyclised in an intramolecular reaction with the silyl enol ether in ring D to C,D-*cis* fused steroid skeleton (scheme 4, **15** Ÿ **17**). Using (*R*)-(-)-carvone as ring D led to an enantiomerically pure D-homo steroid skeleton (***chapter 4***).

Scheme 4

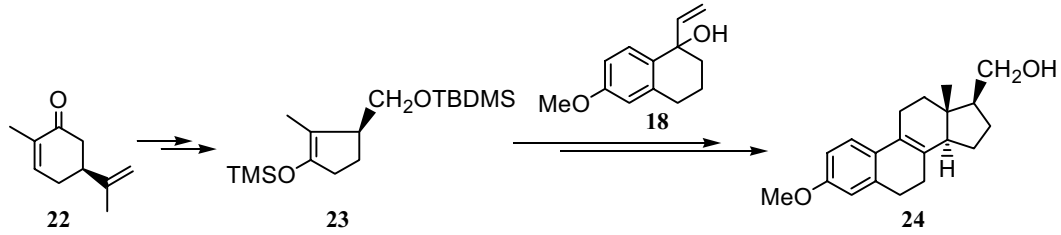


This approach was further developed to an intermolecular variation giving access to a short and flexible route to C,D-*trans* fused steroid and D-homo steroid skeletons (scheme 4, **18** Ÿ **21**)

(***chapter 5***). Especially with five-membered ring D precursors this enabled quick access to a wide variety of C17 substituted steroid skeletons. Substituted silyl enol ethers are easily accessible in various ways and their coupling under Lewis acid catalysed conditions with Torgov reagent **18** was performed in good to high yields. The addition products were cyclised and selective reduction led to a C,D-*trans* fused ring system.

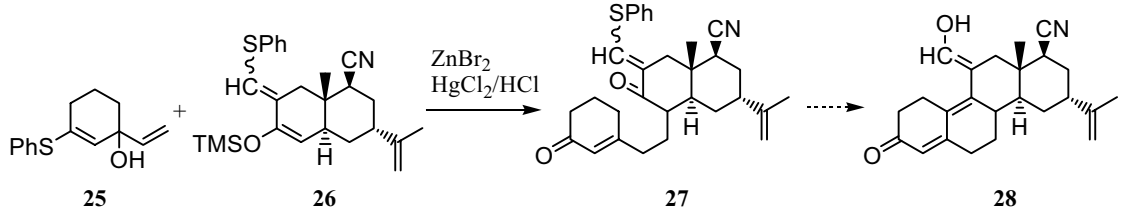
To obtain an optically pure steroid using the chemistry described in chapter 5, a synthesis route to a chiral ring D precursor was devised starting from (*S*)-(+)-carvone. This route led in 10 steps and 10% overall yield to an enantiomerically pure ring D precursor. This precursor was used to synthesise the corresponding dienic steroid skeleton, obtained as mainly one enantiomer. Selective reduction the led to steroid **24** (***chapter 6***).

Scheme 5



During our investigations it appeared that carbocation additions to the silyl enol ether of *η*4cyanocarvone lacked any result but previous results had shown that Robinson annelations with this compound can be carried out in very good yields. This quality was used in two different ways. In the first, a silyl enol ether derived decalone system obtained from the Robinson annelation of *η*4cyanocarvone and methyl vinyl ketone was further reacted with a new bis-annelating reagent, 1-phenylthio-3-vinyl-3-cyclohexenol (scheme 6). From this reagent, again, a carbocation can be generated under mild conditions, which reacts with cyclic silyl enol ethers to tricyclic compounds. The scope and limitations of this new bis-annelating reagent were investigated, showing that enones like **23** can be obtained in good yields in two steps. Steric factors decrease the yield but improve the stereoselectivity of the reaction, which is in agreement with the results described in chapter 5. The reaction of this new reagent with silyl enol ether **23** led to seco steroid **24**. Although the coupling

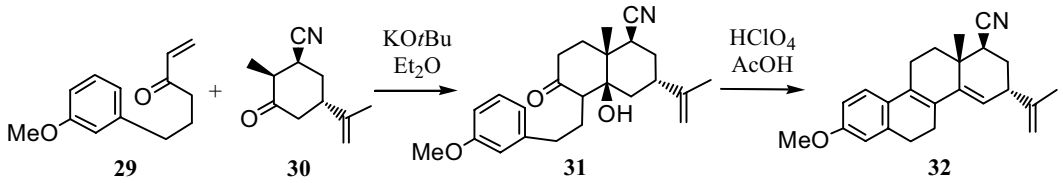
Scheme 6



reaction should be still optimised and the cyclisation of this compound has not yet been attempted, relying on the results obtained with the simple bicyclic compounds, a reasonable yield of the steroidal compound can be expected using this method (***chapter 7***).

The second route involved the Robinson annelation of η4cyanocarvone with 6-(3-methoxyphenyl)hex-1-en-3-one, leading to a D-homo steroid precursor in 76% yield. This compound was then cyclised to a D-homo steroid skeleton (scheme 7). This route was developed within a broader research project evaluating the applicability of cyclic η-cyano ketones like cyanocarvone and cyanocyclopentanone in annelations with enones such as methyl vinyl ketone and ethyl vinyl ketone. This research led to cyano-substituted decalones and indanones which are suitable intermediates for the synthesis of isoprenoid, steroid and D-homo steroid skeletons (***chapter 8***).

Scheme 7



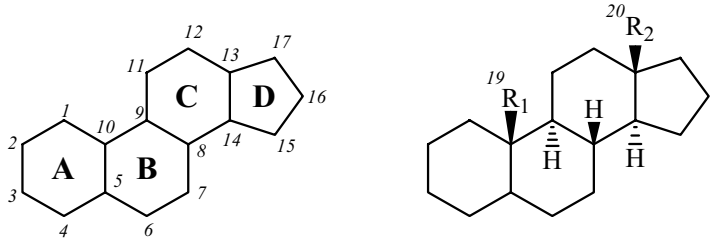
29 **30** **31** **32**

Several new, short and flexible syntheses of steroids and D-homo steroids have been developed within the scope of this thesis research. The synthesised compounds could be further converted into substances of known pharmaceutical interest but the obtained molecules that were as yet unknown could very well also prove to display interesting biological properties by themselves.

Samenvatting

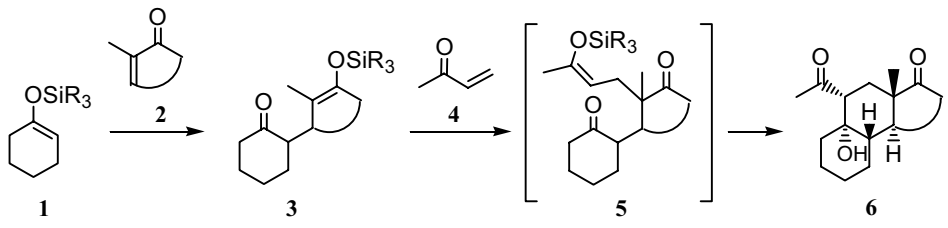
Steroïde hormonen behoren tot de belangrijkste natuurproducten die betrokken zijn bij de regulering van het broze evenwicht dat onze gezondheid is. Hun gebruik is hierdoor wijdverbreid binnen de farmaceutische en voedingsmiddelen (*c.q*. voedingsadditieven) industrie. Steroïde totaal-synthese (d.w.z. het opbouwen van het steroïde skelet uit kleinere eenheden) is, door de veelzijdigheid van deze methode, zeer waardevol gebleken bij het ontwikkelen van nieuwe verbindingen met verhoogde biologische activiteit en verminderde bijwerkingen. Helaas zijn de meeste totaal-synthese routes voor steroïden lang en/of laag in opbrengst en ze leiden vaak tot mengsels van verbindingen (racematen, d.i. verbindingen die erg veel op elkaar lijken omdat het spiegelbeelden van elkaar zijn -zoals, bij voorbeeld, ook onze linker- en rechterhand dat zijn- maar niet identiek! Deze spiegelbeeldverbindingen worden ook wel 'enantiomeren' genoemd). Dit verklaart waarom onderzoek op dit gebied, hoewel al ongeveer 70 jaar in ontwikkeling, nog steeds gaande is. De ontwikkeling van nieuwe efficiënte, korte en veelzijdige routes naar adequaat gefunctionaliseerde verbindingen (d.w.z. met extra groepen op interessante posities in het molecuul) heeft dan ook een grote toegevoegde waarde voor dit onderzoeksveld. De algemene *tetra*cyclische structuur (d.w.z. bestaande uit *vier* gekoppelde ringen) van steroïden staat weergegeven in figuur 1. Hierin staat ook de gebruikelijke nummering voor de koolstofatomen in dit soort verbindingen aangegeven.

Figuur 1. Algemene steroïde structuur en nummering



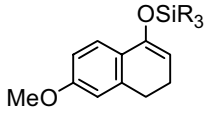
Onze benaderingen concentreren zich rond de addities van carbocationen (dit zijn positief geladen molecuul-ionen), afkomstig bij voorbeeld uit **2** of **4** (schema 1), aan silyl enol ethers, zoals bij voorbeeld verbindingen **1** en **3** (schema 1). Deze addities kunnen onder mild zure condities worden uitgevoerd en geven hoge opbrengsten van de additie producten. In onze eerste benadering

Schema 1



(***hoofdstuk 2***), is een één-pots domino reactie (d.w.z. alle opeenvolgende stappen vinden plaats onder dezelfde omstandigheden en in hetzelfde vat) gebruikt voor de synthese van tricyclische (drie-ring) systemen zoals **6**.

Om deze methode verder te ontwikkelen voor steroïde synthese zijn de silyl enol ethers van 6-methoxytetralon (**7**) en (*S*)-(+)-carvon (**8**) als startverbindingen getest. Hoewel de eerste additie stap, vooral in de reacties met 6-methoxytetralon, goede opbrengsten gaf, was de tweede stap, de additie met methyl vinyl keton (**4**, schema 1), problematisch en gaf deze stap niet het gewenste product.



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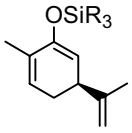
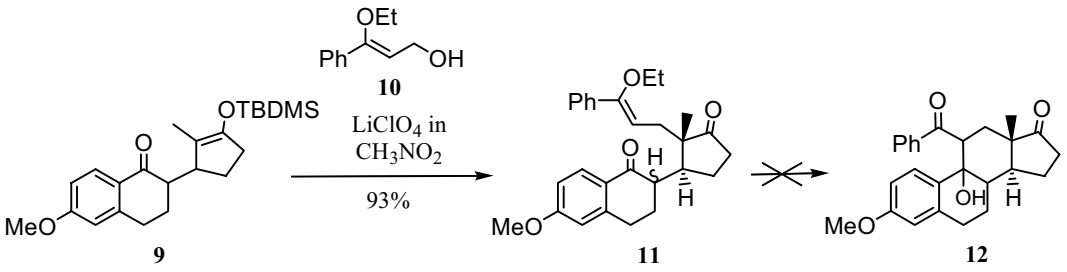


8

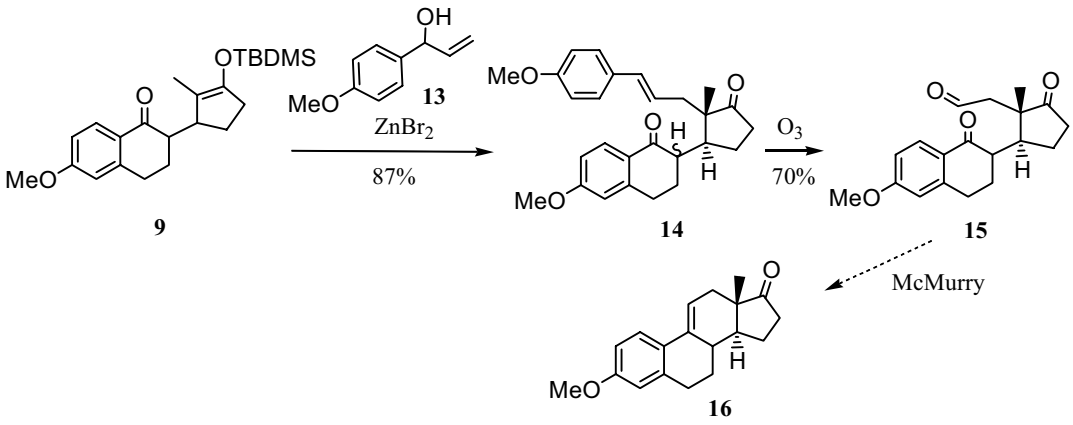
In de reactie sequenties met 6-methoxytetralon is toen voor deze tweede additie stap overgegaan op de additie van meer reactieve carbocation precursoren (***hoofdstuk 3***). Dit leidde uiteindelijk tot een goede opbrengst (93%) voor het additie product **11** (schema 2), maar de opvolgende ringsluiting (naar **12**) *via* het type reactie dat wij hadden gepland, een aldol reactie, gaf daarna problemen.

Schema 2



Een oplossing werd gevonden in de overstap van deze problematische aldol reactie naar een nieuw type reactie, een McMurry reactie, voor het uitvoeren van de ringsluiting (schema 3). De goede

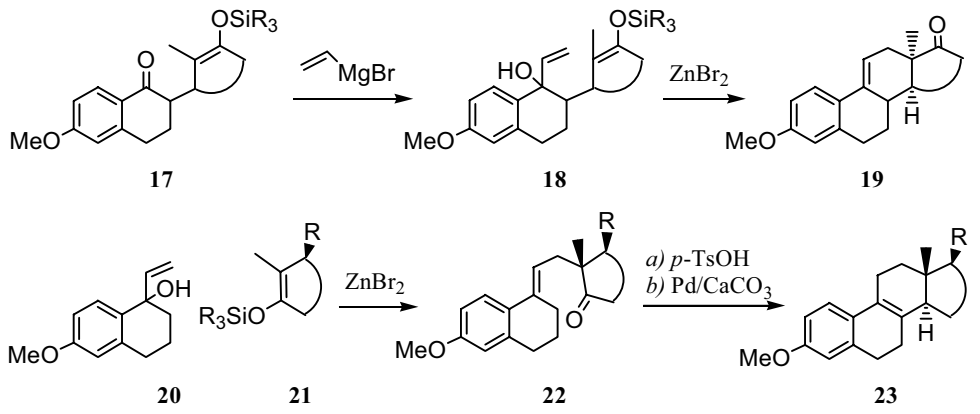
Schema 3



uitgangsstof voor deze reactie (verbinding **15**) werd verkregen door de dubbele band in de zijketen van intermediair **11** (schema 2) te ozonolyseren (met ozon te laten reageren waardoor de dubbele binding in tweeën wordt gesplitst). Voor deze reactie kon een goede 70% opbrengst worden behaald door verplaatsing van de alkoxygroep van zijn positie naast de dubbele binding (OEt in **11**) naar een positie (‘*para’*) in de aromatische ring (OMe in **14**). De aanwezigheid van deze alkoxygroep bleek essentieel voor het goed verlopen van de voorafgaande additie reactie met verbinding **9**, aangezien er, bij afwezigheid van deze groep, helemaal geen additie plaatsvond.

In verbinding **9** kan er naast een selectieve reactie op de silyl enol ether functie ook selectief worden gereageerd op de vrije carbonyl groep van de tetralon eenheid (positie 9, volgens de steroïdnummering). Door introductie van een vinyl groep op deze positie werd stof **18** (schema 4) verkregen waarin een intramoleculaire reactie met de silyl enol ether uit ring D kan plaatsvinden. Deze intramoleculaire reactie zorgt voor ringsluiting tot een C,D-*cis* ringverknoopt steroïde skelet **19** (in de gevallen hier besproken refereren de termen *cis* en *trans* –zie verder- naar de manier waarop ringen aan elkaar gekoppeld zijn. *Trans* geeft een ringsysteem dat min of meer een vlakke structuur heeft, terwijl *cis* verwijst naar een ringsysteem waarin de ringen ongeveer een haakse hoek met elkaar maken). Bij gebruik van (*R*)-(-)-carvon als ring D werd een optisch zuivere D-homo steroïde (d.w.z. met een zeshoekige D ring i.p.v. de gebruikelijke vijfhoek) gevormd (***hoofdstuk 4***). Deze benadering werd verder ontwikkeld tot een intermoleculaire variant die leidde tot een korte en flexibele route naar steroïden en D-homo steroïden met *trans* verknoping tussen de ringen C en D (schema 4, **20** Ÿ **23**) (***hoofdstuk 5***). Vooral bij gebruik van ring D voorlopers **21** afgeleid van cyclopentanon (derivaten van vijfhoekige ringsystemen), gaf dit een snelle toegang tot een grote verscheidenheid aan steroïde skeletten met verschillende groepen op positie C17 (figuur 1). De silyl enol ethers **21** zijn goed te produceren *via* verschillende methoden. Koppeling van deze silyl enol ethers onder mild zure condities met Torgov reagens **20** verliep in goede tot zeer goede

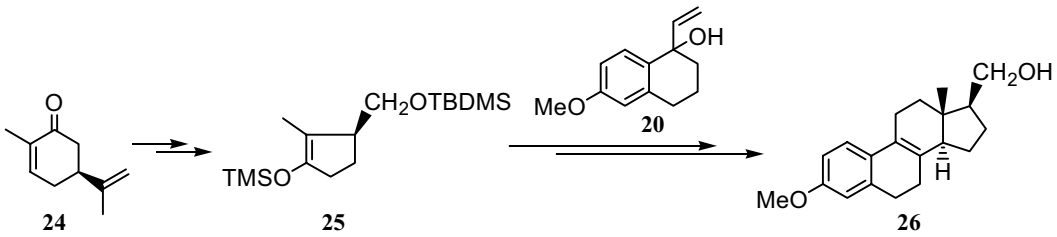
Schema 4



opbrengst. De additie producten **22** werden daarna eenvoudig ringgesloten en omgezet naar verbinding **23** met *trans* verknoping tussen de ringen C en D.

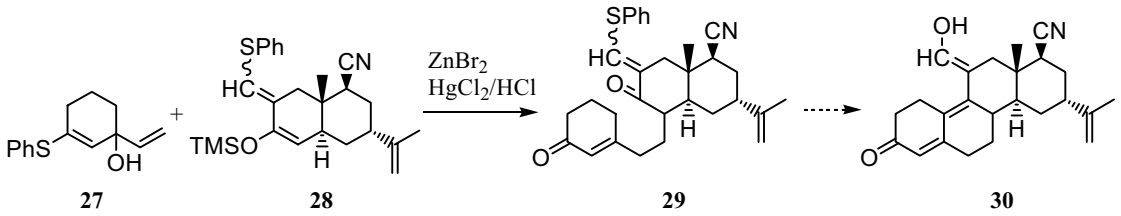
Om via de chemie beschreven in hoofdstuk 5 een optisch zuivere steroïde te verkrijgen is een synthese route ontwikkeld voor ring D uitgangsstof **25** (schema 5) uitgaande van (*S*)-(+)-carvon (**24**). Deze route gaf de gewenste verbinding in 10 stappen en 10% totale opbrengst. Deze verbinding is daarna gebruikt om de overeenkomstige steroïde **26** te synthetiseren als voornamelijk een enkel enantiomeer (d.w.z. als één enkele van de mogelijke spiegelbeelden –zie ook boven-, ook wel naar gerefereerd als 'enantiomeer' of 'optisch' zuiver) (***hoofdstuk 6***).

Schema 5



Gedurende het lopende onderzoek bleek dat carbocation addities aan de silyl enol ether van η4cyanocarvon (η4cyanocarvon is verbinding **32** in schema 7) geen resultaat opleverde. Eerder onderzoek had uitgewezen dat een Robinson annelering (d.i. een bepaald soort koppeling van een nieuwe ring aan een bestaande ring) aan deze verbinding wel in zeer goede opbrengst kon worden uitgevoerd. Deze eigenschap is gebruikt in twee verschillende benaderingen. In de eerste methode werd silyl enol ether **28** (schema 6) (afkomstig van het product verkregen door de Robinson annelering van η4cyanocarvone met methyl vinyl keton **4**, schema 1) gereageerd met een nieuw bis-annelerings reagens (d.i. een verbinding die ervoor zorgt dat er in een keer twee nieuwe ringen aan een bestaande ring kunnen worden gekoppeld), 1-phenylthio-3-vinyl-3-cyclohexenol **27**. Onder mild zure condities kan een carbocation worden gegenereerd uit deze verbinding en deze kan dan reageren met cyclische silyl enol ethers tot tricyclische systemen. De mogelijkheden en beperkingen van het nieuwe bis-annelerings reagens werden onderzocht en dit bewees dat enonen als **29** in goede opbrengst en in enkel twee stappen kunnen worden gemaakt. Sterische factoren (ruimtelijk beperkende factoren) verlagen de opbrengsten maar verhogen de stereoselectiviteit, wat overeenkomt met de resultaten beschreven in hoofdstuk 5. Additie van dit nieuwe reagens aan silyl enol ether **28** gaf steroïde voorloper **29** en hoewel de additie reactie nog zou moeten worden geoptimaliseerd en de cyclisatie van de verbinding nog niet is uitgevoerd, kan een goede opbrengst van het steroïdale eindproduct (**30**) worden verwacht (***hoofdstuk 7***).

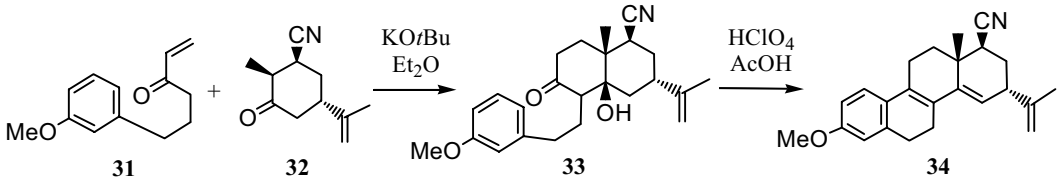
Schema 6



27 **28** **29** **30**

De tweede benadering betrof de Robinson annelering van *m*-cyanocarvon **32** met 6-(3-methoxyphenyl)hex-1-en-3-on **31** (schema 7). Dit leidde tot D-homo steroïde voorloper **33** in 76% opbrengst. In deze verbinding werd daarna ring B gesloten waarbij het overeenkomstige D-homo steroïde **34** ontstond. Deze route werd ontwikkeld binnen een breder onderzoek met als doel de toepasbaarheid van cyclische *m*-cyano ketonen, zoals cyanocarvon and cyanocyclopentanon, in anneleringen met enonen als methyl vinyl keton and ethyl vinyl keton te evalueren. Dit onderzoek leidde tot bicyclische systemen (decalon en indanon ringen) die geschikte intermediairen vormen voor de synthese van isoprenoïde, steroïde en D-homo steroïde skeletten (***hoofdstuk 8***).

Schema 7



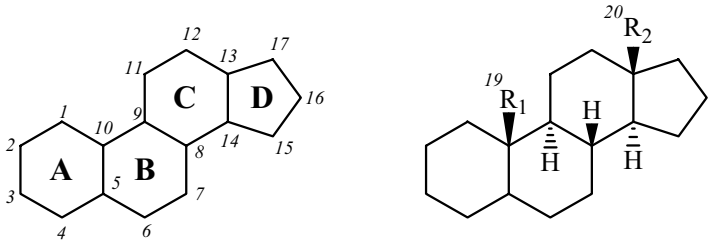
31 **32** **33** **34**

Verschillende nieuwe, korte en flexibele syntheses van steroïden en D-homo steroïden zijn binnen de omvang van dit onderzoeksproject ontwikkeld. De gesynthetiseerde verbindingen kunnen worden omgezet in stoffen van bekend farmaceutisch belang, maar de verkregen moleculen die tot nu toe nog onbekend waren zouden zeer goed zelf ook interessante biologische activiteit kunnen vertonen.

Résumé

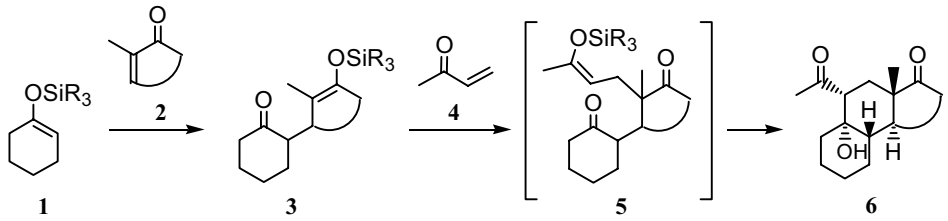
Les hormones stéroïdiennes figurent parmi les produits naturels les plus impliqués dans la régulation de l'équilibre précaire qui est à la base de notre santé. Par conséquent leur utilisation est largement répandue dans l'industrie pharmaceutique et alimentaire. Grâce à son universalité, l'utilisation de la synthèse totale de stéroïdes (c-à-d. la construction du squelette stéroïdien à partir de molécules plus petites) a prouvé être essentielle dans le développement de nouveaux composés à activité biologique accrue et aux effets secondaires réduits. Malheureusement la plupart des synthèses totales de stéroïdes sont longues ou ont un rendement global relativement faible. De plus, ces voies de synthèse mènent souvent à des produits racémiques (c-à-d. des produits très semblables, étant l'image l'un de l'autre -comme le sont notre main gauche et celle de droite- mais pas identiques! Ces produits-images sont aussi appelés des énantiomères). Ceci explique pourquoi, alors qu'ayant débuté il y a environ 70 ans, la recherche dans ce domaine est toujours en cours à ce jour, le développement de méthodes efficaces, courtes et polyvalentes pour la synthèse de composés adéquatement fonctionnalisés (c-à-d. ayant des groupes supplémentaires sur des positions intéressantes), étant de grande valeur ajoutée. La structure générale tétracyclique (c-à-d. étant formée de 4 cycles interconnectés), commune à tous les stéroïdes, ainsi que la numérotation (des atomes de carbone) utilisée pour ces structures, sont représentées ci-dessous.

Figure 1. Structure générale et numérotation des stéroïdes



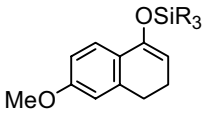
Nos approches se concentrent autour de réactions entre des carbocations (c-à-d. un ion moléculaire chargé positivement), originaires par exemple des molécules **2** ou **4** (schéma 1), et des énols d'éther silyls, comme par exemple les composés **1** et **3**. Ces additions s'effectuent sous des conditions acides (Lewis) douces et donnent des rendements élevés de produits d'addition. Dans notre première approche (***chapitre 2***) une réaction domino Mukaiyama 'one-pot' (c-à-d. plusieurs étapes

Schéma 1



consécutives sont effectuées sous les mêmes conditions et dans un récipient unique), fut utilisée pour la synthèse de produits tricycliques.

Pour étendre cette méthode vers la synthèse de stéroïdes les énols d'éther silyls de 6-méthoxytétralone (**7)** et de (*S*)-(+)-carvone **(8)** furent testés comme produits de départ. Alors que la première étape, surtout pour les réactions impliquant la 6-méthoxytétralone, donnèrent de bons rendements, la deuxième étape, étant l'addition avec la methylvinylcétone (**4**), s'est avérée problématique, ne donnant pas le produit désiré.



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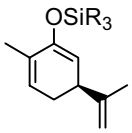
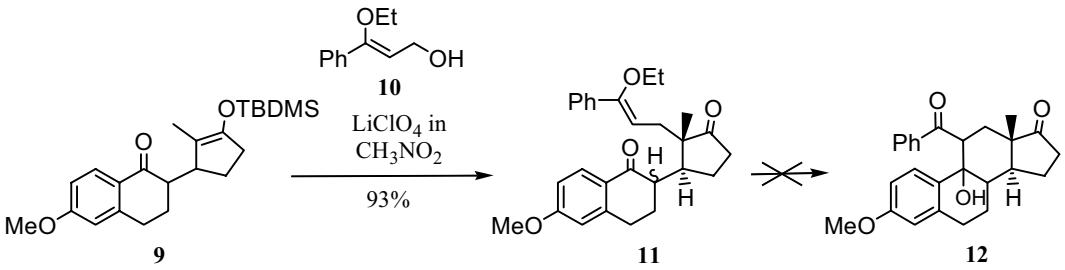


8

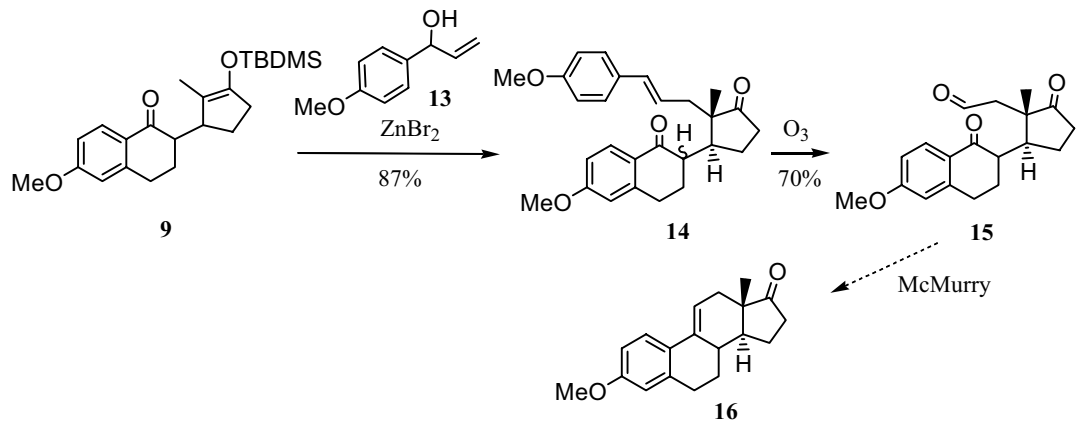
Dans les séquences de réaction avec la 6-méthoxytétralone la deuxième étape d'addition fut remplacée par l'addition de précurseurs de carbocations plus réactifs (***chapitre 3***). Ceci mena finalement à un bon rendement (93%) pour la réaction d'addition (schéma 2), menant à **11**, mais la cyclisation consécutive par le type de réaction que nous avions choisi, la réaction d'aldolisation (étant censée donner **12**), posa alors problème.

Schéma 2



Pour résoudre ce problème la réaction d'aldolisation fut remplacée par une réaction de type 'McMurry' pour la fermeture du cycle C (schéma 3). Pour obtenir le précurseur requis (**15**) pour

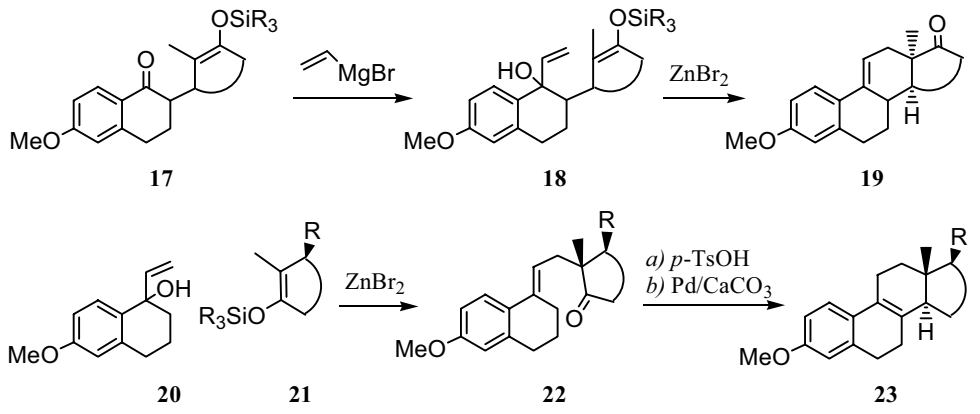
Schéma 3



cette cyclisation, la double liaison dans la chaîne latérale de l'intermédiaire **11** devait être ozonolysée (c-à-d. la molécule est traitée avec de l'ozone ce qui a comme conséquence le partage en deux de la double liaison). Un bon rendement (70%) fut obtenu pour cette réaction quand le groupement éther fut déplacé de sa position adjacente à la double liaison (OEt dans **11**) vers la position *para* du cycle aromatique (OMe dans **14**). La présence du groupement éther parut être essentielle pour un bon déroulement de la réaction d'addition précédente avec l'intermédiaire **9**, vu que, en cas d'absence de ce groupe, l'addition n'eut pas lieu.

A part la réaction sélective sur la fonction énolique d'éther silyl dans le composé **9**, une réaction sélective put aussi être effectuée sur le groupe carbonyle présent dans l'unité originaire du tétralone (position 9, selon la numérotation stéroïdienne). Par l'introduction d'un groupement vinyl sur cette position un précurseur de carbocation (produit **18**) fut créé (schéma 4), qui, par reaction intramoléculaire avec l'énol d'éther silyl du cycle D, ferma le cycle C. Ceci donna le squelette stéroïdien **19** avec fusion *cis* entre les cycles C et D (dans les cas discutés ici, *cis* et *trans* –voir plus loin- sont de dénominations utilisées pour désigner la manière avec laquelle les cycles sont accrochés l'un a l'autre. *Trans* donnant un bicycle plus ou moins plat, alors que *cis* donne un bicycle dont les deux cycles sont positionnés plus ou moins en angle droit). Par l'utilisation du (*R*)-(-)-carvone comme cycle D, un D-homostéroïde (c-à-d. avec un cycle D hexagonal au lieu de l'habituel pentagone) enantiomeriquement pur fut obtenu (***chapitre 4***). Une variation intermoléculaire de cette approche mena à une méthode courte et polyvalente permettant l'acces aux stéroïdes et D-homostéroïdes ayant une fusion *trans* entre les cycles C et D (schéma 4, **20** Ÿ **23**) (***chapitre 5***). Surtout avec les précurseurs dérivés de la cyclopentanone (cycles pentagonaux), cette méthode permit un accès rapide aux squelettes stéroïdiens avec une grande variété de substitutions sur la position C17 (figure 1). Des énols d'éther silyl substitués (**21**) sont facilement accessibles par diverses méthodes. Leur addition avec le produit Torgov **20** donna de bons rendements et les produits **22** obtenus furent facilement cyclisés. Une réduction sélective mena à

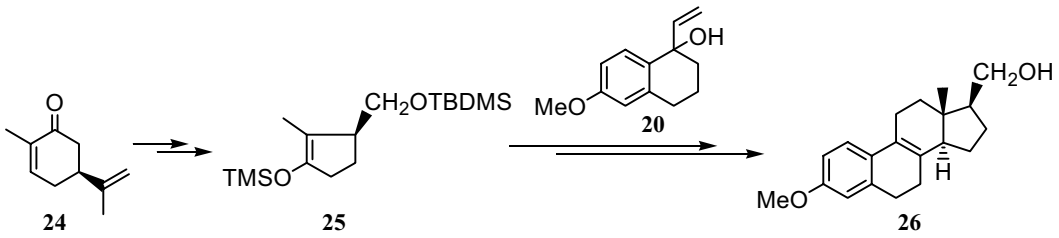
Schéma 4



des systèmes stéroïdiens avec fusion *trans* entre les cycles C et D.

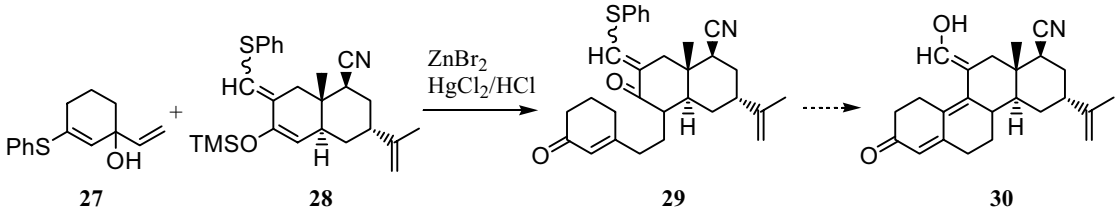
Pour obtenir un stéroïde optiquement pur en utilisant la chimie décrite dans le chapitre 5, une synthèse de précurseur chiral pour le cycle D (**25**, schéma 5) fut conçue à partir du (*S*)-(+)-carvone (**22**). Cette synthèse donna le composé désiré en 10 étapes avec un rendement total de 10%. Ce précurseur fut alors utilisé pour la synthèse du diène stéroïdien correspondant, obtenu principalement comme un seul énantiomère (c-à-d. obtenu comme une seule de ses images –voir plus haut-, aussi qualifié 'enantiomeriquement' ou 'optiquement' pur). La réduction sélective de ce diène mena au stéroïde **26** (***chapitre 6***).

Schéma 5



Au cours de nos recherches l'addition de carbocations à l'énol d'éther silyl de la η4cyanocarvone (la η4cyanocarvone correspond à la structure **32** dans le schéma 7) ne donna pas de résultat. D'autre part, des recherches antérieures avaient prouvé que l'utilisation de la η4cyanocarvone donnait de très bons rendements dans la réaction d'annélation Robinson (c-à-d. un certain type de réaction ayant comme résultat l'accrochage d'un nouveau cycle à un cycle préexistant). Cette caractéristique fut alors utilisée dans deux approches différentes. Dans la première, un nouveau réactif de bis-annélation (c-à-d. un composé qui permet l'accrochage d'un *bi*cycle dans une seule réaction), le 1-phenylthio-3-vinyl-3-cyclohexenol **27** (schéma 6), fut mis réagir avec l'énol d'éther silyl **28** dérivé du produit obtenu par la réaction Robinson de la η4cyanocarvone avec la méthylvinylcétone (**4**, schéma 1). Un carbocation peut à nouveau être formé à partir de ce nouveau réactif sous des conditions acides douces. La réaction de ce cation avec des énols d'éther silyls cycliques mena à des composés tricycliques. Les possibilités et les limitations du réactif de bis-annélation (**27**) furent évaluées et ceci montra que des énones comme **29** peuvent être obtenues en seulement deux étapes avec de bons rendements. Des facteurs stériques (c-à-d. des facteurs limitant spacialement) diminuent les rendements mais améliorent la stéréosélectivité, ce qui est en accord avec les résultats mentionnés dans le chapitre 5. L'addition de ce réactif à l'énol **28** mena au sécostéroïde **29** et, bien que la réaction d'addition n'ait pas été optimisée et que la réaction de cyclisation n'ait pas encore été effectuée, un bon rendement du produit stéroïdien final (**30**) peut être attendu (***chapitre 7***).

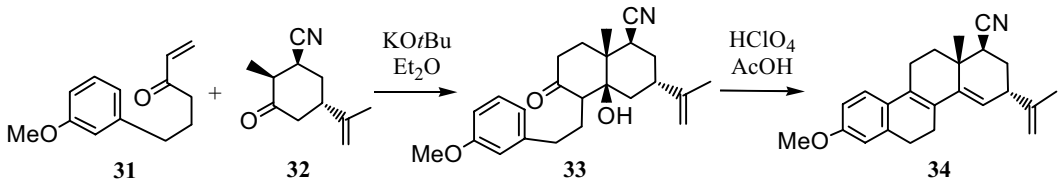
Schéma 6



27 **28** **29** **30**

La deuxième approche concerna la réaction d'annélation Robinson de la η4cyanocarvone **32** avec la 6-(3-methoxyphenyl)hex-1-en-3-one **31** (schéma 7), résultant dans la formation du précurseur du D-homostéroïde **33** avec un rendement de 76%. Ce composé fut alors cyclisé donnant le D-homostéroïde **34** correspondant. Cette méthode fut élaborée au sein d'un project de recherche plus large ayant pour but l'évaluation de l'applicabilité des η-cyanocétones, comme la cyanocarvone et la cyanocyclopentanone, dans des réactions d'annélation avec des énones comme la méthylvinylcétone et l'éthylvinylcétone. Cette recherche mena à des systèmes bicycliques (décalone et indanone) qui forment des intermédiaires utilisables dans la synthèse de produits naturels tels les isoprénoïdes, les stéroïdes et les D-homostéroïdes (***chapitre 8***).

Schéma 7



31 **32** **33** **34**

Au sein du projet de recherche décrit dans cette thèse, plusieurs nouvelles synthèses courtes et flexibles de stéroïdes et D-homostéroïdes ont été développées. Les composés synthétisés peuvent être convertis en différents produits d'intérêt pharmaceutique reconnu, mais les substances obtenues et encore inconnues jusqu'à présent, pourraient aussi très bien aussi présenter d'intéressantes propriétés biologiques intrinsèques.

Dankwoord

En dan is het toch zo ver. Na 5 jaar ploegen, je soms afvragen of je de eindstreep wel zult halen, dan toch doorbijten, en het ook nog allemaal op een redelijke wijze op papier zien te krijgen, ligt er uiteindelijk een boekje en is een datum gepland. Die eindstreep haal je echter nooit alleen, ook al sta je uiteindelijk alleen die commissie te woord. Ik wil dan ook alle mensen, die van dichtbij of veraf mijn 'ups' en 'downs' hebben meegemaakt en, elk op hun eigen manier, mij daarin hebben gesteund, hierbij bedanken. Aan een aantal mensen kan ik niet voorbijgaan zonder ze met naam te noemen.

Allereerst wil ik graag mijn promotor bedanken. In de loop van mijn promotietijd namen er steeds meer mensen afscheid van de 'synthesegroep' en uiteindelijk vormden wij een tweemanschap, waarbij we zelfs gezamenlijk op het lab hebben gestaan. Aede, ik heb deze tijd als zeer bijzonder en waardevol ervaren en prijs me gelukkig de keuze te hebben gemaakt bij jou te komen promoveren. Bedankt voor alles! Ook wil ik Ben en Marinus hier graag noemen. Ben, door jouw gedegen begeleiding in het eerste jaar en je latere bereidheid altijd mijn vragen te beantwoorden, heb ik, toen je eenmaal weg was, zelfstandig verder kunnen werken in het lab. Marinus, jouw onuitputtelijke kennis op het gebied van steroïden (synthese) heeft mij vaak vol bewondering doen staan. Ik kon echt altijd met vragen bij je terecht en kreeg ook altijd meteen een overvloed aan waardevolle informatie terug. Ik ben je heel dankbaar dat je destijds geaccepteerd hebt als copromotor op te treden bij dit project!

Van de 'oude' synthesegroep wil ik verder nog Patrick, Marjon en Yvonne bedanken. Jullie hebben mij meteen opgenomen in jullie midden en daar is een goede vriendschap uit voortgekomen. Het doorbijten tijdens de 'AIO-dippen' heb ik duidelijk van jullie geleerd… En Patrick, ik vind het erg leuk dat we nu opnieuw collega's zijn! There are also a few people I would like to thank for their direct cooperation in my project: Eva, Tanya, Arkady, Olya, Serghei and Enrique. You all came from abroad to participate in steroid total synthesis. I hope you enjoyed your stay here in the Netherlands and want you to know I am really grateful for all your help and friendship! Geke, jij was mijn enige afstudeervak student, maar ik had me niet beter kunnen wensen! Wat je ook besluit te gaan doen, en of het nu hier, Zuid-Afrika of Singapore wordt, ik weet zeker dat het je allemaal gaat lukken! Vergeet alleen niet op tijd rust te nemen…

Het laboratorium voor Organische Chemie bestaat niet uit enkel de synthese groep (en gelukkig maar, want anders was het de laatste tijd wel erg rustig geworden…). Ook dankzij een hoop andere mensen heb ik me echt thuis gevoeld bij OC. Zonder iedereen bij naam te noemen wil ik toch zeker Hannie, en het 'koffieclubje', bedanken voor de stomende kop koffie met het goede gesprek die elke ochtend klaar stonden. De beste manier om daarna vol energie met een dag werk te beginnen. Melle, de laatste maanden dat ik op de leerstoelgroep rondliep, hebben wij kamer en lab gedeeld. Ik vond het erg gezellig, net zoals onze gezamenlijke lunches samen met Geb! Ik wil Beb, Barend en Maarten bedanken voor hun hulp met NMR en HRMS! Ronald, jou wil ik graag bedanken voor al je hulp met het vinden van de benodigde chemicaliën, glaswerk en aanverwanten, en het, bij tijd en wijlen, aanhoren van mijn gemopper. Ook Han wil ik graag bedanken voor het uitvoeren van de computerberekeningen die zijn opgenomen in dit proefschrift. Verder alle AIO's natuurlijk. Ik realiseer me nu dat het er toch eigenlijk best veel zijn, te veel om allemaal bij naam

te noemen, maar ik wil jullie wel allemaal bedanken voor de gezellige tijd, de Aio-reizen, de Aio-dates en de borrels. And this goes of course also for all our foreign PhD students: thanks for all the fun times we spent together!

Niet behorende tot de leerstoelgroep, maar mensen die wel altijd precies wisten waar ik het over had wat betreft onderzoeksfrustraties, zijn de 'Bornse'meiden. Tina, Marga, Anneriet en Silvia, onze regelmatige etentjes waarbij we allemaal wel eens ons ei kwijt moesten vond ik heerlijk. We moeten ze er absoluut in houden, ook al worden de te overbruggen afstanden misschien wat groter! Een gedeelte van ons staat ook tegelijkertijd voor een nieuwe fase in onze carrière. Ik ben benieuwd hoe het ons zal vergaan…

Anderen die zich, denk ik, juist vaak afvroegen waar ik überhaupt aan begonnen was, en ook waarom, zijn de meiden van 'Faja Lobi'. Anita, Lies, Sjouk, Sandra, Ariëlle, Jannie en ook Sita: sorry dat ik het de laatste tijd wel eens heb laten afweten bij dates en zo. Hopelijk kunnen jullie, bij het zien van dit boekje, een beetje begrip daarvoor opbrengen en ik beloof dat die tijd nu weer voorbij is! *Wie è pesa faja djie makandara!*

Anita, jij staat, samen met Frédérique, op 10 mei aan mijn zijde. Daar ben ik jullie beide heel dankbaar voor, maar dat jij, Anita, helemaal uit de VS overvliegt om naast mij op het podium te staan vind ik echt ongelofelijk! Verder hebben jullie allebei een poging gewaagd om de Nederlandse samenvatting leesbaar te maken voor leken. Dat is volgens mij een onbegonnen taak voor een synthese onderwerp maar hopelijk is het toch enigszins gelukt!

Maud et Agnès, je vous remercie toutes les deux pour vos corrections de la version française de mon résumé. Mes connaissances en terminologies chimiques en français se sont tellement détériorées ces dix dernières années que sans votre aide ce résumé n'aurait sûrement pas ressemblé à grand-chose… Ma belle-famille mérite aussi des remerciements pour leur soutien à distance. J'espère que ce résumé en français vous donnera une petite idée de ce que j'ai fait ces cinq dernières années.

Rest nog de mij meest dierbare mensen te bedanken voor hun steun en geduld. We zien elkaar minder vaak dan ik graag zou willen maar ik wil wel dat jullie weten dat jullie allemaal erg belangrijk zijn in mijn leven. Hélène, Maurice, Martine, Myrna en Frans, jullie zijn allemaal, stuk voor stuk, een voorbeeld voor mij en ik ben trots dat ik jullie kleine (schoon)zusje ben! Dit geldt ook voor Roëlle, weliswaar niet mijn echte zusje, maar toch wel een beetje… En, ook al hebben jullie waarschijnlijk de indruk dat je afhaakt bij een uitleg van wat ik nou precies doe of heb gedaan, mochten jullie toch nog een keertje willen weten wat er nou precies in dit boekje staat, vraag maar raak. Ik ben altijd bereid te proberen het uit te leggen! Myrna, bedankt dat je je in het geheel hebt willen verdiepen om een mooie afbeelding voor de omslag te creëren. Ik vind 'm super!

Pap en mam, jullie komt eigenlijk de meeste eer toe. Zonder jullie onvoorwaardelijke steun en vrijheid in mijn keuzes die jullie me altijd hebben gegeven zou ik nu niet staan waar ik sta. Mijn dank is niet onder woorden te brengen. Ik hou van jullie!

En dan uiteindelijk nog mijn lieve Paul. Ik kan alleen maar hopen dat ik het je de afgelopen tijd niet te moeilijk heb gemaakt en dat ik net zo 'n goede steun en toeverlaat voor je ben als jij voor mij. Zullen we weer op weg gaan, tussen de uren en de uitvindingen?

Floor

Curriculum Vitae

Florence Charlotte Eileen Sarabèr was born on 30 January 1977 in Rotterdam, the Netherlands. Moving to the Belgian Ardennes at the age of five, she followed both primary and secondary school education at French speaking schools. After receiving her diploma in 1995 at the 'Athenée Royal de Stavelot', she started undergraduate studies in 'Molecular Sciences' at Wageningen University. During these studies she spent half a year in the group of Prof. dr. ir. I.M.C.M. Rietjens at the Laboratory of Biochemistry on a research project concerning the biochemical production of the food flavour methylanthranilate (grape flavour). She then moved to the University of Nottingham for a six-months stay in the group of Dr. N. R. Thomas, working on a synthetic organic subject on the development of new antibiotics. In 2000, the author graduated with distinction from Wageningen University as a M.Sc. in Molecular Sciences. In the same year she started as a Ph.D.-student at the Laboratory of Organic Chemistry of Wageningen University, in the group of Prof. Ae. de Groot and under further supervision of Dr. B. J. M. Jansen and Prof. Dr. M. B. Groen (Organon/VU). The result of this assignment is described in this thesis. In April 2005 the writer started as a Regulatory Affairs Scientist at Organon (N.V.) in Oss, the Netherlands.

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The painting on the front cover of this thesis was especially painted for this thesis and is of the hand of Dutch artist Myrna Rasker (*www.rasecht.info*).