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Tetrahedron
Tetrahedron 62 (2006) 5363–5383

Tetrahedron report number 758

Ring C closure as key step in the synthesis of steroids

Florence C. E. Sarabèr and Aede de Groot*

Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

Received 9 March 2006
Available online 5 April 2006

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1. Introduction

Syntheses of steroids can be achieved by partial synthesis, modification of readily available steroidal compounds or total synthesis. The latter is the most applied method and has been widely studied during the 20th century, the first total synthesis of a steroid being reported in 1939 by Bachmann, Cole and Wilds.[1] Steroid total synthesis remains to this day a topic of interest for synthetic organic chemists and the pharmaceutical industry, even though many elegant syntheses have been developed. The efficiency of routes towards adequately functionalised steroid skeletons, which preferably also should be chiral, short and versatile, can, however, be improved, and this explains why research in this area is still ongoing.

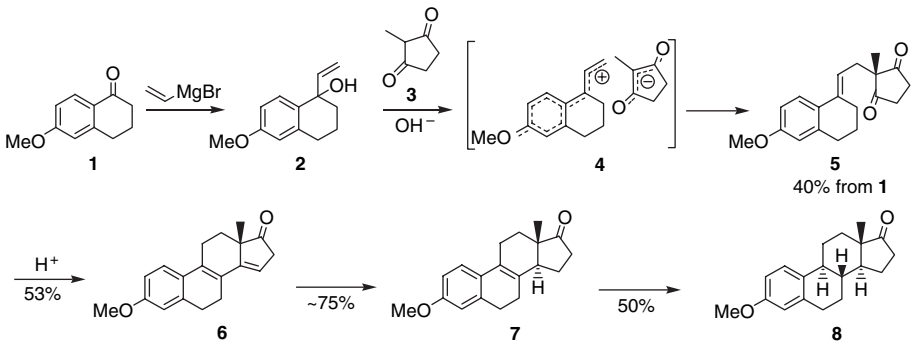
Several reviews have appeared over the years giving a good overview of the complete field of steroid total synthesis.[2–5] This review is focussed on approaches in which the formation of ring C is the crucial step. The review is further subdivided according to the reaction types used for the construction of ring C, thus giving an insight into closing methods used in this corner of steroid total synthesis.

2. Torgov syntheses

The Torgov synthesis has marked an important development in steroid total synthesis.[6–11] The method has proven to be highly versatile and has been extensively used and modified, leading to oestrone and its derivatives, homo steroids, hetero steroids, ring A non-aromatic steroids and also non-steroidal ring structures.[12–26] The method involves the condensation of the reactive alcohol **2**, easily obtained from methoxytetralone **1**, with its hydroxyl group at an allylic and benzylic position, with a 1,3-cyclodione, mostly 2-methylcyclopentane-1,3-dione **3** or 2-methylcyclohexane-1,3-dione. Subsequent cyclisation of the obtained intermediate **5** leads directly to steroid skeleton **6**, which can then be modified further, first by catalytic reduction to alkene **7** and finally

* Corresponding author. Tel.: +31 317 482370; fax: +31 317 484914; e-mail: aede.degroot@wur.nl

0040–4020/$ - see front matter
doi:10.1016/j.tet.2006.03.027



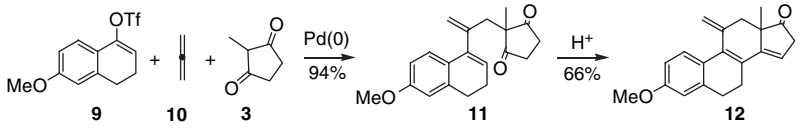
Scheme 1.

to the all *trans* steroid skeleton **8** (Scheme 1). 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 (**4**).[27] Simultaneously, they reported that the condensation and cyclisation steps could be performed in a one-pot reaction, yielding 60% of the tetracyclic steroid skeleton.[16]

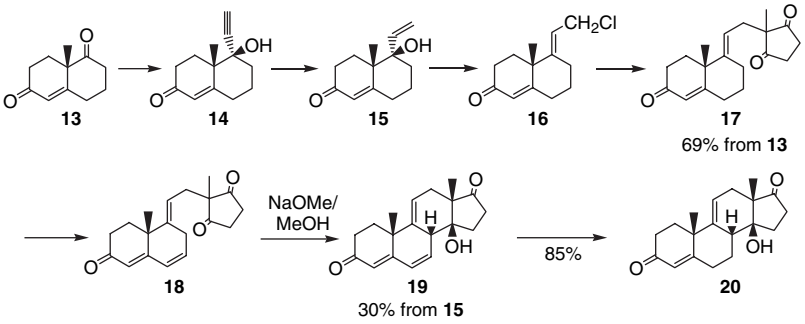
Goré and co-workers published in 1991 a method using carbopalladation of allenic compounds to obtain ring A-aromatic steroids in two steps, with interesting overall yields (40–70%), starting from α-tetralone triflate **9**, allene **10** and cyclopentanedione **3** (Scheme 2).[28,29] The intermediate **11** obtained after the first step resembles the intermediates from the Torgov synthesis, and cyclisation to skeleton **12** was performed accordingly.[21] Unfortunately, this method is limited to ring A-aromatic steroids and, as for the Torgov synthesis, it does not proceed with any stereoselectivity, yielding dienic compounds with Δ^8 and Δ^{14} double bonds.

A comparable approach using a Torgov-like addition step, but with an extended aldol condensation as the final cyclisation step, was used by the groups of Wiechert[30] and Daniewski.[31] This method gave access to non-aromatic ring A steroids bearing a C19 methyl group (Scheme 3). The addition of an acetylide to dione **13**, followed by selective reduction of the triple bond in **14** afforded the Torgov-type intermediate **15**. This intermediate had to transform into the allylic chloride **16** before coupling with cyclopentanedione to **17**. Before the extended aldol condensation can take place, an extra double bond has to be introduced at the Δ^6 position to activate C8 as in compound **18**. Now the aldol-type cyclisation to **19** can be performed in good yield, and reduction of the Δ^6 double bond then leads to **20**. As compound **13** 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,[32] by Taguchi in 1991, yielding two diastereomers of a C10-trifluoromethyl-substituted steroid,[33] and, finally, by Zard in 1993, leading to 19-nor-steroids as single diastereomers in good yields.[14]

The standard Torgov reaction leads to racemic mixtures of the steroid skeletons, but several routes leading to enantiomerically pure compounds have been published over the years. These routes use either chemical[12,19] or enzymatic[15,17,18] resolution, a chiral ring D precursor[22] or a chiral catalyst.[23] The first chemical asymmetric synthesis was published by Bucourt and co-workers[12] and used L-tartaric

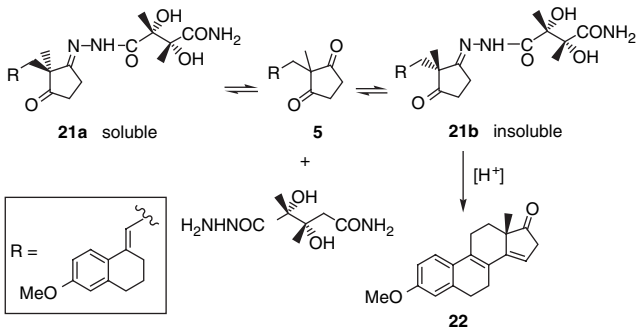


Scheme 2.



Scheme 3.

amide hydrazide to form the steroidal monohydrazones **21a** and **21b**, which could then be separated (Scheme 4).



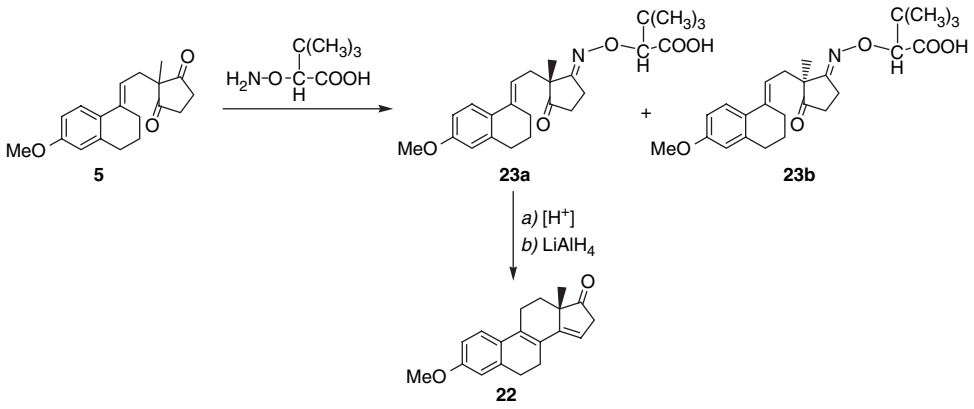
Scheme 4.

In a suitably chosen solvent system, selective crystallisation of the monohydrazone **21b** with a β-configuration on C13 could be achieved and over 75% yield of the pure product could be obtained. Consecutive treatment with acid gave the enantiomerically pure cyclised diene **22** in 80% yield.

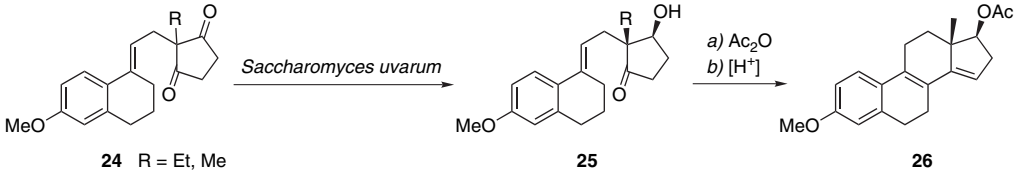
A few years later, a second method using chemical resolution was published by Pappo and co-workers.[19] They derivatised the intermediate seco steroids to the oxime ethers **23a** and **23b** using chiral amino oxycarboxylic acids and could selectively form mainly one of the two diastereomers on C13 via variation of the chemical environment (reaction conditions, used amine, etc.). In this way, compound **23a** was obtained in high optical purity with an overall yield of 36% (Scheme 5).

Gibian and co-workers[15,17,34] made use of enzymatic resolution of the seco steroidal intermediates from the Torgov route. Selective reduction of ketones **24** using *Saccharomyces uvarum* gave the compounds **25**, in 53 to 74% yield, having both a β-alcohol on C17 and a β-methyl or ethyl on C13. After acetylation, they could then cyclise these products in high yields to the acetate **26** and further transform them into known compounds (Scheme 6).

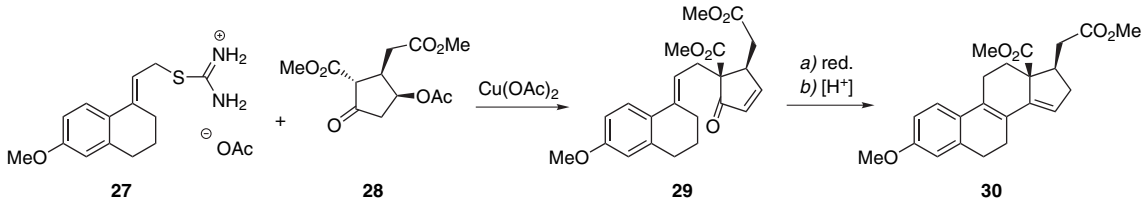
Johnson and Magriotis[22] used a synthesis in which the diketone that served as the ring D precursor in the traditional Torgov route was replaced by a chiral cyclopentanone **28**, derived from *S*-malic acid. This compound was coupled with a modified Torgov steroid precursor **27** to give the seco steroid **29** in an 8:1 diastereomeric mixture on C13, out of which the C13-β-isomer could be isolated in 95% optical purity and with a yield of about 40%. Subsequent cyclisation to compound **30** and further transformation enabled the synthesis of the optically active (+)-18-hydroxyestrone (Scheme 7).



Scheme 5.

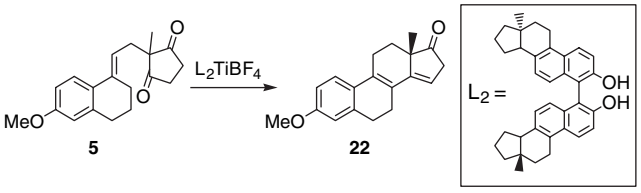


Scheme 6.



Scheme 7.

Finally, Enev and co-workers[23] 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 72% yield of **22** in combination with an ee of 70% (Scheme 8).



Scheme 8.

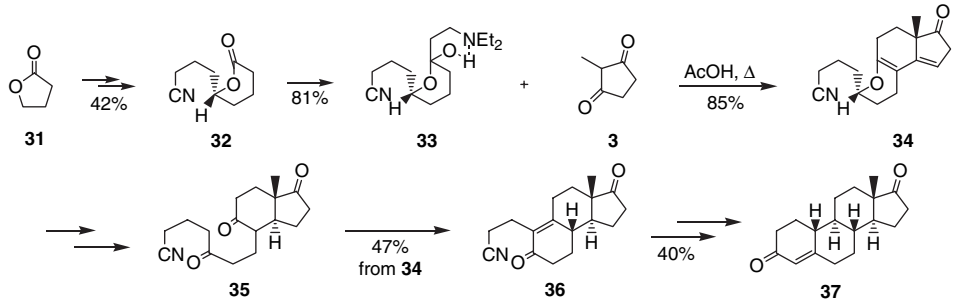
3. Michael additions and cyclisations

A second group of ring C closing strategies relies on Michael-type additions, mostly using 2-methyl-1,3-cyclopentadione **5**. One of the first was developed by Saucy and co-workers and has been referred to as the Hoffmann–LaRoche synthesis (Scheme 9).[35–42] It was used to produce steroid hormones via condensation of a Mannich base with 2-methyl-1,3-cyclopentanedione. The synthesis started with the easy production of lactone **32**, starting from butyrolactone **31**. Ester condensation of **31** and decomposition of the dimer with HCl gave 1,7-dichloro-4-heptanone, which was protected and reacted with cyanide. Deprotection and reduction of the carbonyl group followed by lactonisation afforded **32** in 42% overall yield. A selective reaction of vinylmagnesium bromide with the lactone followed by addition of diethylamine to the adduct gave the required Mannich base **33**. The route could even be applied for the synthesis of optically pure steroids when an optically active variant of the Mannich base **33** was used, leading to intermediate **34** after reaction with 2-methylcyclopentadione **3**. The enantiomerically pure Mannich base **33** was obtained via resolution of its oxalic acid salt derivative.

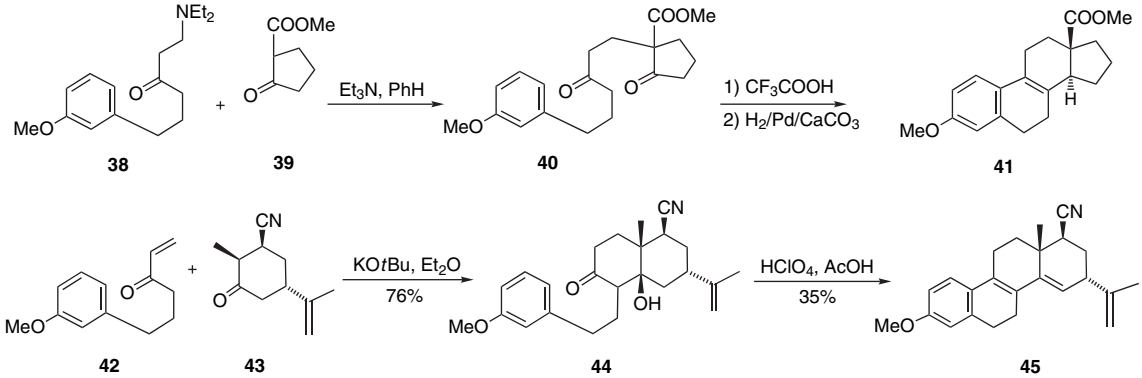
The condensation reaction and cyclisation of ring C took place consecutively in the same reaction vessel and occurred with high asymmetric induction, giving dienol ether **34** with the natural configuration around C13 as the major product. Hydrolysis of the dienol ether and oxidation of the hydroxyl group gave the triketone **35**, in which ring C was closed with an aldol condensation to **36**. Conversion of the nitrile to a methyl ketone and again an aldol condensation finally afforded the 19-nor-steroid skeleton **37**.

A variant, based on the approach of Smith and co-workers,[43] was developed for the synthesis of C18-functionalized steroids, using the reaction of Mannich base **38** with β-keto ester **39** to give the diketone **40**. Cyclisation of **40** and reduction of one double bond afforded the C18 ester **41**, which could be modified easily for the preparation of a variety of other C18-substituted compounds (Scheme 10).[44]

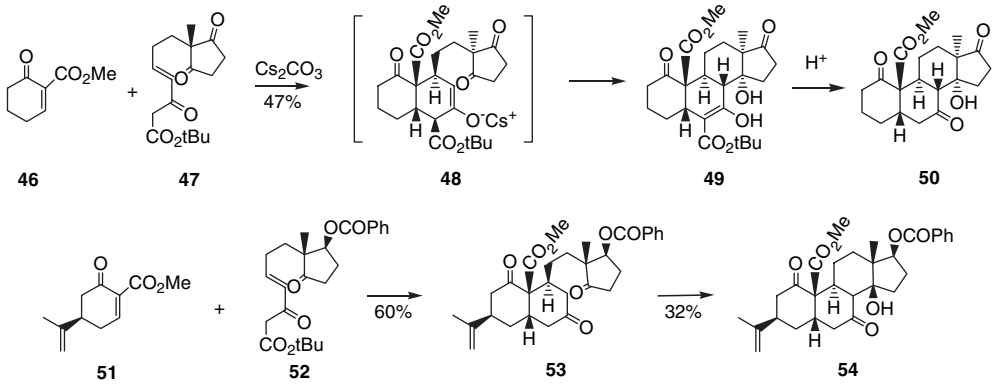
The high reactivity of β-cyanoketones in annelation reactions was demonstrated by the enantioselective synthesis of D-homo steroid skeletons from cyanocarvone **43** and 6-(3-methoxyphenyl)hex-1-en-3-one **42** (Scheme 10).[45] This Michael addition could be achieved under aprotic conditions with KO*t*-Bu in diethyl ether, giving one ketol **44** in



Scheme 9.



Scheme 10.



Scheme 11.

good (76%) yield. A 35% yield of the rather unstable dehydrated compound **45** could be obtained in a one-pot reaction using $HClO_4$ in AcOH.[46]

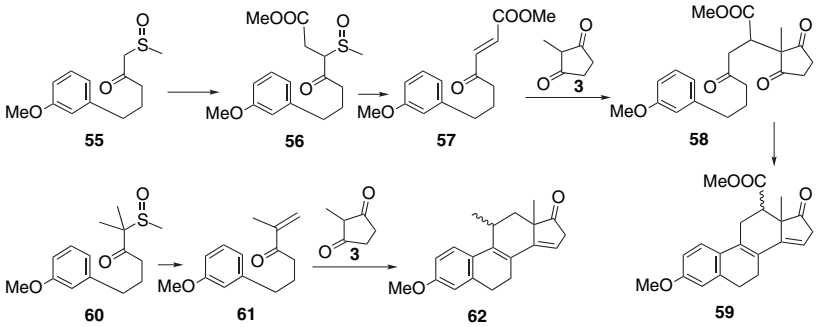
Deslongchamps and Lavallee have developed a one-step stereocontrolled method using an anionic cycloaddition catalysed by caesium carbonate as a polycyclisation reaction and yielding 13,14-*cis*-α-steroids (Scheme 11).[47,48] Addition of the Nazarov-type reagent **47** to 2-carbomethoxy-2-cyclohexenone **46**, intermediately followed by trapping of enolate **48** in situ, yielded the tetracyclic steroid skeleton **49**.

After selective decarboxylation, 13α-methyl,14α-hydroxy steroid **50** was obtained. Later syntheses, using a similar addition of an optically active Nazarov-type reagent **52** to an optically active 5-isopropylidene-2-carbomethoxy-2-cyclohexenone **51**, developed to obtain stereoselectively the more desired β-configuration on C13 and C14, did not yield directly a steroid skeleton in a one-step procedure, but led to open intermediates like **53**. Cyclisation using an aldol condensation then produced steroid **54** as the sole product, although in a low yield which could not be improved.[49–51]

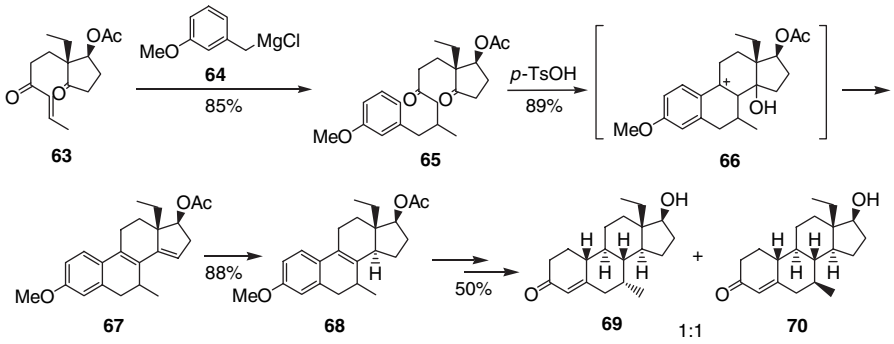
Thermal elimination in the C11 substituted sulfoxide **56**, obtained by alkylation with methyl bromoacetate of **55**, afforded the substituted α,β-unsaturated ketone **57**. After reaction of **57** with cyclopentanedione **3** to the open triketone **58**, aldol-type cyclisation gave the C12-substituted steroid skeleton **59**. In a similar way the C11-substituted enone **61** was obtained via thermal elimination of sulfoxide **60**. The reaction of cyclopentanedione **3** with enone **61**, followed by cyclisation, afforded the C11-substituted steroid skeleton **62**. (Scheme 12).[52,53]

4. Aldol cyclisation

A method in which ring C and ring B are closed simultaneously was reported by the groups of Kurosawa and Zhou.[54,55] This method was actually a modification of a route first reported by Smith in 1963[43,56] and, later, also used and adapted by several other groups.[46,57–67] These routes relied on the formation of a 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 starting enone was obtained in 25% overall yield from acrolein in a sequence of steps involving the conversion of acrolein into a γ-keto-sulfoxide, which was then coupled to 2-ethyl-1, 3-cyclopentadione. A consecutive microbial asymmetric reduction and further conversion then led to compound **63**.[54] The diketone **65**, the substrate for cyclisation, was obtained by conjugate addition of **64** to the enone **63**. The acid-catalysed aldol reaction closing ring C to intermediate **66**, was followed immediately by a Friedel–Crafts-type reaction, closing ring B and then by dehydration to **67**. Reduction of the Δ^{14} double bond then gave **68**, with its trans-coupled C,D ring system. In this way, Zhou and Zhuang[54] synthesised 7α,18- and 7β,18-dimethyl-19-nor-testosterone (**69** and **70**, respectively) in six steps from intermediate **63** (Scheme 13).



Scheme 12.



Scheme 13.

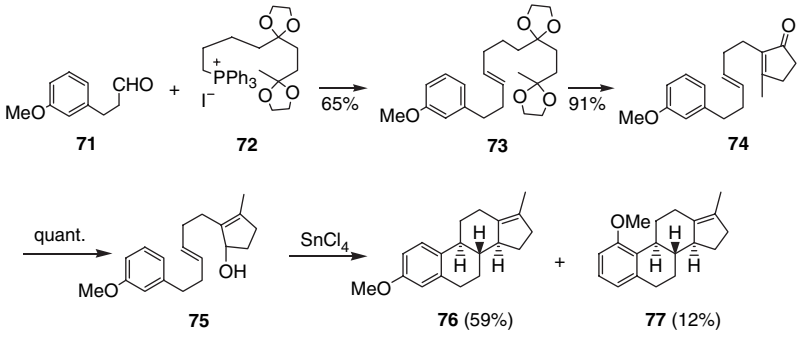
5. Polyene cyclisations

The traditional polyene cyclisations have been investigated and reviewed extensively by Johnson.[68] An example is the cyclisation developed by Bartlett and Johnson, where rings B and C were closed simultaneously (Scheme 14).[69] In contrast with the Smith cyclisations, *ortho* cyclisation can also take place, which leads to products like **77**, and can lower the yield considerably. The method consists of a Wittig–Schlosser condensation of aldehyde **71** with phosphonium iodide **72**, which gave the *trans*-alkene **73** with greater than 98% stereoselectivity. Hydrolysis of the diketal, aldol cyclisation and dehydration gave the enone **74** and after reduction the steroid precursor **75** was obtained. Cyclisation was catalysed by stannic chloride and gave compound **76** in 59% yield. Further conversion led to oestrone in 22% overall yield from **74**.

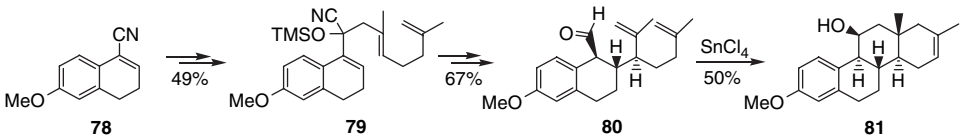
In an additional use of a polyene cyclisation, Ziegler and Wang reported the C/D-cyclisation of the oxo-diene **80**, which leads to the D-homo steroid **81** (Scheme 15).[70,71] The aryl triene **79** was prepared in 49% yield from nitrile **78**,[72,73] and converted into the oxo-diene through a (trimethylsilyl)-cyanohydrin Cope rearrangement, in which the stereochemistry at C8 and C9 is controlled. Acid-catalysed cyclisation then leads to the D-homo steroid skeleton **81**. Using a slightly modified approach, a compound with a five-membered D ring could also be obtained by the same group.[71] Ziegler and Lim additionally investigated a similar route involving a Cope–Claisen rearrangement, but this method showed a low stereoselectivity.[74]

6. Friedel–Crafts cyclisations

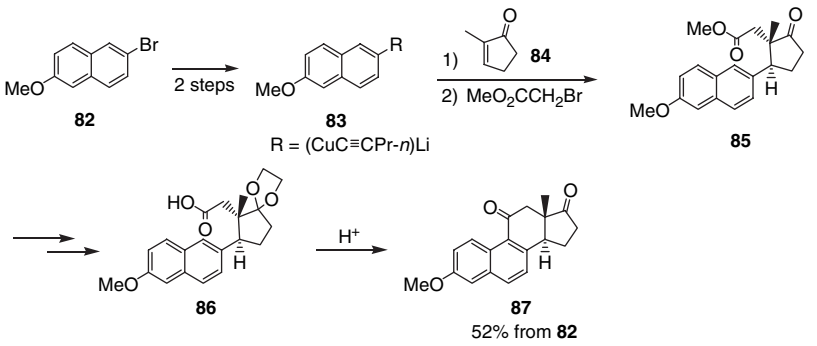
Posner et al. have developed a short and stereoselective synthesis using Friedel–Crafts chemistry where C ring formation is the key step (Scheme 16).[75,76] Using this method, 11-oxoequilenin methyl ether **87** was synthesised in only six steps from the readily available 6-methoxy-2-bromonaphthalene **82** (52% yield). Conjugate addition of the organometallic complex prepared from **82**, to 2-methyl-2-cyclopentenone **84** and trapping of the intermediate with bromoacetic acid led to the ester **85**. Hydrolysis of the ester and protection of the carbonyl group set the stage for the ring-closing Friedel–Crafts reaction in compound **86**. 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 Scheme 18).[77]



Scheme 14.



Scheme 15.

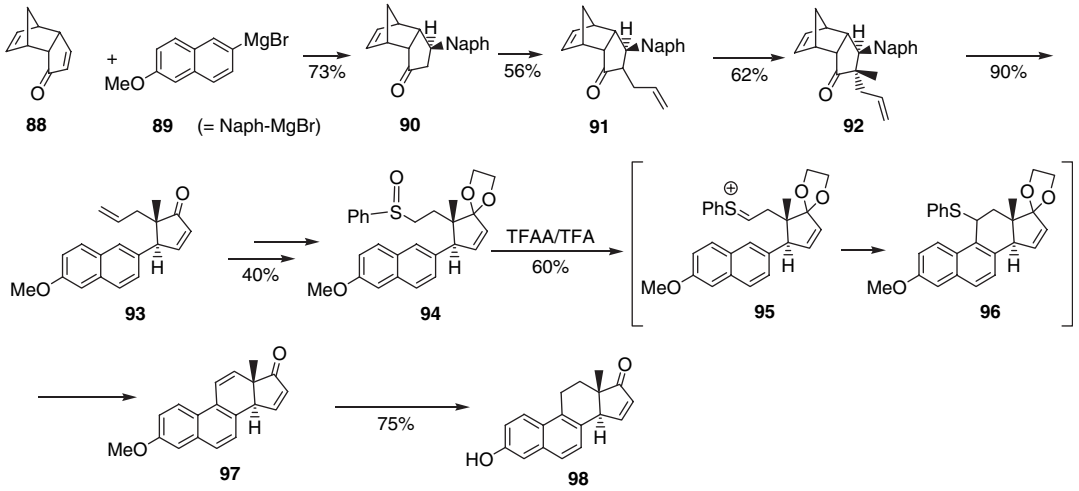


Scheme 16.

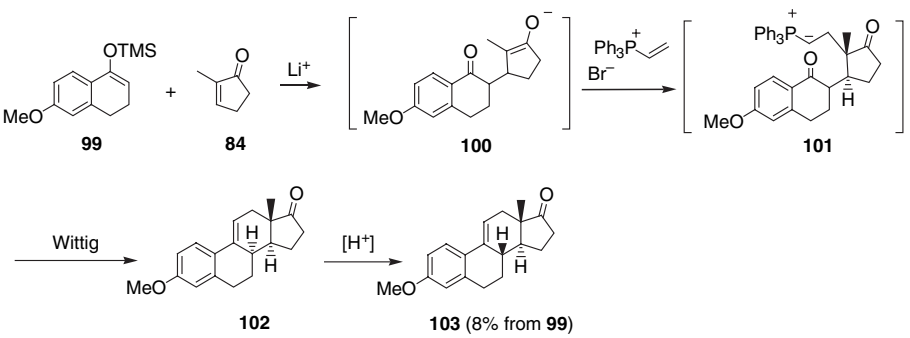
A method was developed by Takano and co-workers using stereoselective introduction of nucleophiles at the β-carbon of a tricyclic dienone **88**, which they had designed for the enantiocontrolled synthesis of natural compounds. They applied this method to the synthesis of (+)-equilenin (Scheme 17).[78] Compound **88** had been previously synthesised by the same group in an efficient conversion from dicyclopentadiene, using kinetic resolution by lipase in the key stage.[79]

The substrate for cyclisation was synthesised starting with the conjugate addition of the organometallic naphthalene derivative **89** to the enone in **88**. Stereoselective alkylation of first an allyl group to **91**, and a methyl group to **92**, followed by pyrolysis afforded **93**. The double bond in the allyl group was converted into the desired sulfoxide **94** in four steps. Closure of ring C was performed using a trifluoroacetic anhydride/trifluoroacetic acid (TFAA/TFA) catalysed cyclisation of this sulfoxide via the intermediate **95** and elimination of thiophenol in **96**, to afford the Δ^{11} unsaturated steroid skeleton **97** in 60% yield. Selective catalytic reduction of the Δ^{11} double bond gave (+)-equilenin methyl ether **98** in 90% yield. Racemic **93** has also been used for the synthesis of racemic equilenin in an earlier work by Horeau and co-workers.[80]

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 the literature making use of a Wittig reaction for the ring



Scheme 17.



Scheme 18.

closure,[77,81] or a McMurry reductive cyclisation[82] as the final step.[74,83–85]

7. Wittig reaction for cyclisation

Posner et al. have published a one-pot synthesis for racemic 9,11-dehydroestrone methyl ether **103**[77] using an intramolecular Wittig reaction for the closure of ring C (Scheme 18). The reaction starts with the trimethylsilyl enol ether of methoxytetralone **99**, which is added to 2-methyl-2-cyclopentenone **84**. After formation of the intermediate adduct **100**, an unsaturated phosphonium salt is added, and in this way, the Wittig reagent **101** is created in situ. This now can react intramolecularly with the carbonyl group of the tetralone moiety to close ring C. The route yielded a steroid system **102** with trans-fusion around C13–C14 and cis-fusion around C8–C9, which could easily be isomerised to the trans-fused system of the oestrone skeletons. Although this reaction sequence to the racemic oestrone methyl ether **103** was short, the overall yield of the reaction sequence was only 8%.

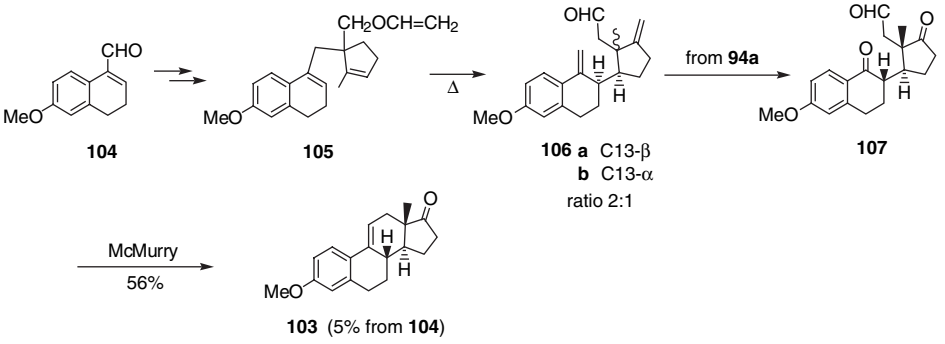
8. McMurry reaction for cyclisation

Shortly after Posner's work, Ziegler and Lim published a synthesis of the same compound, again as a racemic mixture, relying on a Cope–Claisen rearrangement and a McMurry reaction for the closure of ring C (Scheme 19).[74] After the Cope–Claisen rearrangement in compound **105**, obtained from aldehyde **104**, and ozonolysis of the exocyclic double bonds in **106**, the obtained keto aldehyde **107** was subjected to a McMurry radical reaction that gave **103** 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 a mixture of cis- and trans-fusion around C13–C14.

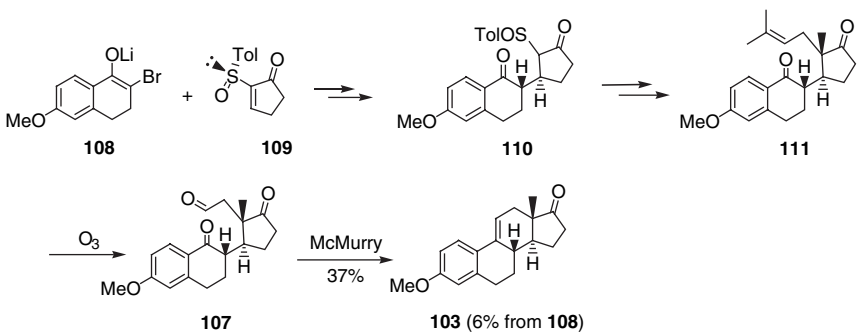
In his asymmetric synthesis of the natural (+)-oestrone methyl ether **103**, Posner also applied the McMurry cyclisation.[83] This sequence used a stereoselective Michael addition of enolate **108** with the enantiomerically pure cyclopentenone sulfoxide **109** to steer the reaction to the adduct **110** (Scheme 20). Introduction of an isopentenyl group in **110** gave **111** and ozonolysis of the double bond then led to Ziegler's triketone **107**. The cyclisation under McMurry conditions, in this case, gave a lower (37%) yield, but the reaction sequence was highly stereoselective, yielding optically pure (+)-oestrone methyl ether **103** in 6% overall yield.

The groups of Mikami[84,85] and Groen[81] both used a route based on a tandem Claisen-ene reaction to obtain the seco tricarbonyl steroid but different methods were used for the closure of ring C. These routes both led to optically pure compounds, starting from *R*-(+)-glyceraldehyde, which is first converted into an optically active and dioxolan protected derivative of 3*S*,4-dihydroxy-methylethylketone and then elongated using a *Z*-selective Still–Wittig olefination to **113a** (Scheme 21).

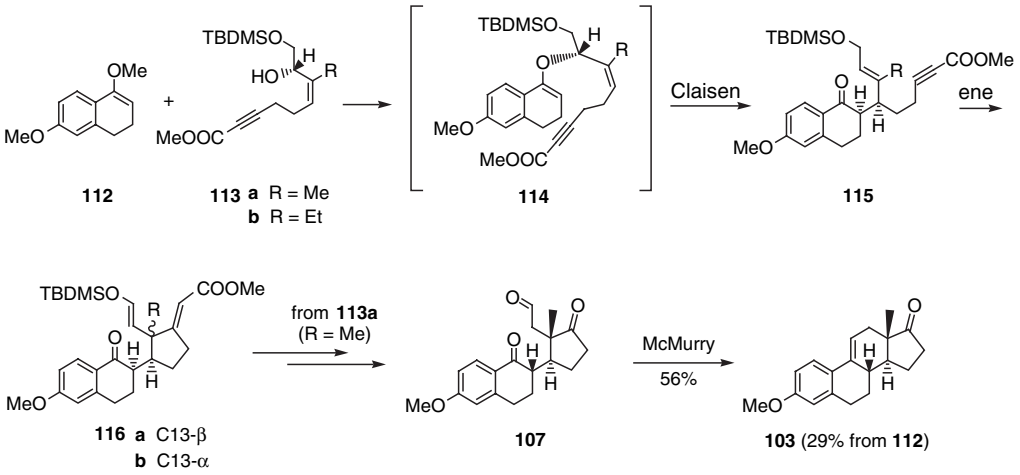
A Claisen-ene reaction of this C,D ring precursor with enol ether **112** as A,B ring precursor now led in a one-pot reaction first to intermediate **114**, which underwent the Claisen



Scheme 19.



Scheme 20.



Scheme 21.

rearrangement to **115** and finally the ene reaction to **116**. Hydrolysis of the *tert*-butyldimethylsilyl (TBDMS) enol ether and ozonolysis of the unsaturated ester then afforded Ziegler's triketone **107**.

While Mikami et al. reported the exclusive formation of the trans-stereochemistry around the C13–C14 bond in the tandem reaction to **116**, Groen et al. obtained an approximately 1:1 mixture of this isomer, together with the 13α-isomer. This difference can be attributed to the replacement of the methyl substituent on C13, in the route of Mikami, by 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 extent that the conformation leading to the unwanted cis configuration (T_1) becomes as probable as that leading to the trans-product (T_2) (see Fig. 1).

After a few more steps, Mikami then cyclised the obtained aldehyde **107** via the McMurry reaction, previously published by Ziegler,[74] again in 56% yield. Groen reduced the obtained C13 ethyl substituted silyl enol ether **117** to the hydroxyl compound **118**, which was converted into the phosphonium salt **119** for the closure of ring C with a Wittig reaction (Scheme 22).

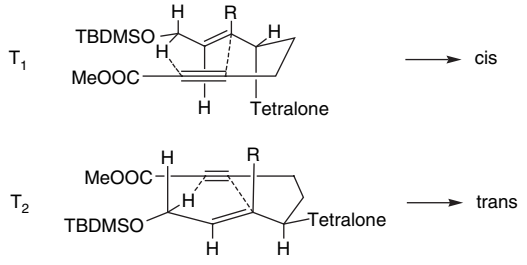


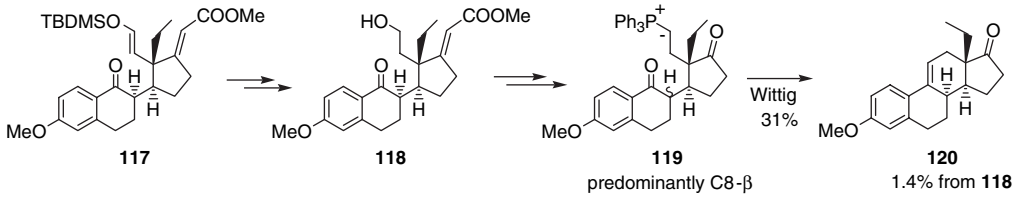
Figure 1.

The yield of the ring-closing reaction could not, however, be enhanced and was unfortunately even lower than the yield reported using the McMurry reaction. The only product **120** had the C8-α configuration, and this low yield could be due to the fact that the ring closure seems only to take place when the seco steroid **119** has this α-configuration around C8, while **119** is mainly present as the C8-β isomer. The exact reason for this behaviour was not explained,[81] but Posner reported similar results when performing his Wittig ring-closing reaction.[77] Surprisingly, the McMurry cyclisation gave significantly higher yields when performed on the 8β-isomer,[74] leading directly to the natural all trans configuration around the steroid ring system.

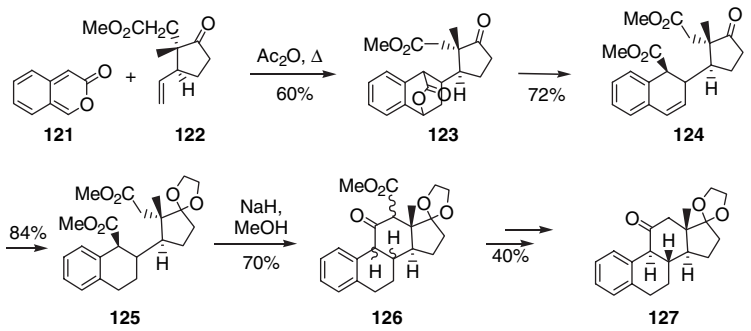
9. Dieckmann cyclisation

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 **127** (Scheme 23).[86,87]

The Diels–Alder reaction between 2-benzopyran-3-one **121** and the readily available Oppolzer olefin **122** appeared to be highly regioselective and gave the right regioisomer **123** for steroid synthesis in 60% yield. Protection of the carbonyl group in diester **124** gave **125**, and now a Dieckmann



Scheme 22.



Scheme 23.

cyclisation of this diester **125** was used for the closure of ring C. A fair yield (70%) of the C11-functionalized steroid skeleton **126** was obtained. When the methoxy-pyrone homologue of **121** was used as the starting material, the reactions gave similar results and the methoxy analogue of **127** was obtained.

10. Diels–Alder cyclisations

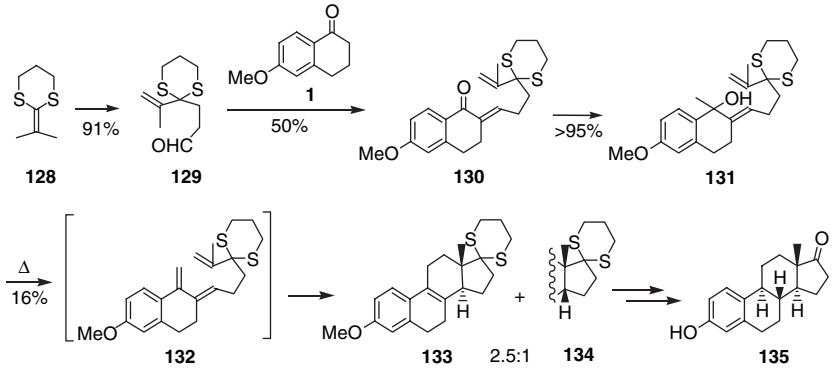
Jung and Halweg published a method using an intramolecular Diels–Alder reaction for ring closure to synthesise oestrone **135** (Scheme 24).[88] The alkene part of the substrate for the Diels–Alder reaction was prepared by alkylation of the ketene bisthioacetal **128** with bromopropionacetal followed by hydrolysis to aldehyde **129**. An aldol condensation of aldehyde **129** with methoxytetralone **1** was used to couple this aldehyde to the potential diene part of the substrate.

Unfortunately, the preparation of the diene from **130** to **132** proved to be extremely difficult. According to these workers, the presence of the 6-methoxy group in the tetralone ring decreased the ketone reactivity considerably, rendering the molecule inert to the normally successful methods such as (silyl-)Wittig reaction or Tebbe reagent. Finally they resorted to thermal dehydration of the tertiary carbinol **131**, giving a yield of 16% of the cyclised compounds **133** and **134**.

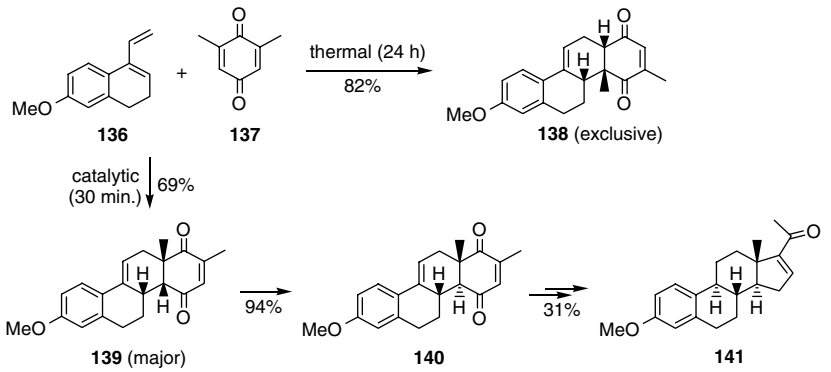
Intermolecular Diels–Alder reactions in steroid synthesis were investigated as early as 1939, but these were very quickly turned down because of failure.[89–91] Indeed, it appeared that the products like **138** did not only have the unwanted configuration, but also mostly had the wrong constitution, the reaction being entirely unselective.[92,93] When several groups tried the use of Lewis acids to catalyse the Diels–Alder reactions, however, these were shown not only to influence the reaction rate positively, but also to greatly improve the stereoselectivity of the addition.

Catalysed intermolecular Diels–Alder reactions of diene **136** and quinones **137** to **139** were used by Valenta and co-workers to obtain D-homo steroid skeletons (Scheme 25). After isomerisation of the configuration at C14, compound **140** was obtained and ring contraction then gave a precursor of oestrone **141** in 13 steps (starting from **136** and **137**) with an overall yield of 22%.[92] This intermediate was converted into oestrone in 31% yield according to a method described previously.[94–96] Similar work was carried out by Quinkert and co-workers, also leading to oestrone.[93,97]

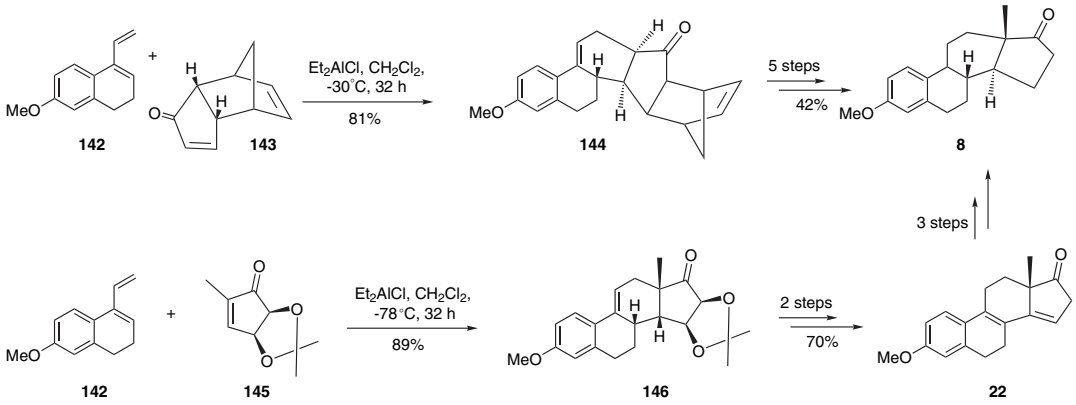
A variation on these syntheses came from Narasimhan and Bapat, who used a silyl ether substituent with intermolecular Diels–Alder chemistry to achieve regioselectivity in their synthesis of equilenin.[98] Two chiral variations on this chemistry have been published by the groups of Takano[99] and Ogasawara[100] (Scheme 26). The regioselectivity of the reaction was investigated by Taticchi and co-workers.[101] The syntheses started with the chiral enones **143** or **145**, which reacted stereo- and regioselectively with diene **142** using Lewis-acid catalysis, to the adducts **144** and **146**, respectively. The adduct **144** has been converted further in several steps using traditional chemistry involving C13



Scheme 24.



Scheme 25.



Scheme 26.

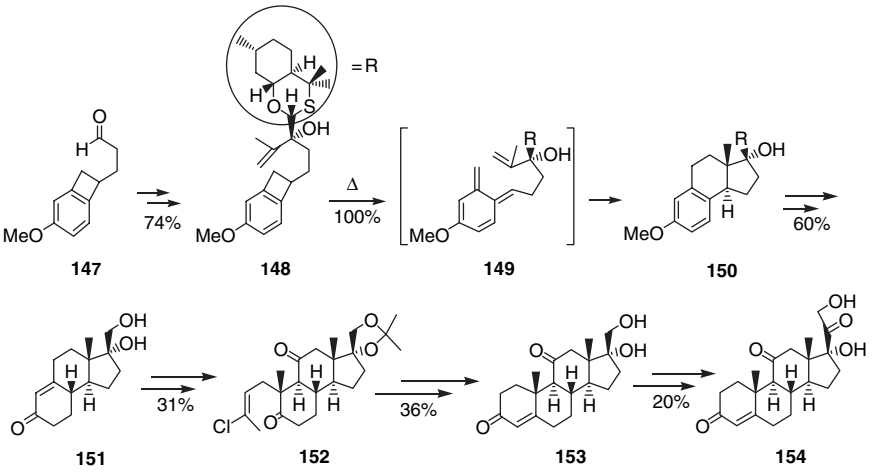
methylation, pyrolysis and reduction of the Δ^{15} double bond to afford (+)-oestrone **8**. In the adduct **146** the acetal first had to be removed using reductive elimination of the oxygen functionality from C16, followed by acid-catalysed elimination and isomerisation of the C15 hydroxyl group to the Δ^{14} double bond as in **22**. In this way also the configuration of C14 can be adjusted, as reduction of the two double bonds in **22** can be carried out in a traditional manner to afford also (+)-oestrone.

Other methods, also using Diels–Alder chemistry, but intramolecular versions, were, for example, developed and reviewed by Kametani, Nemoto and co-workers. This group used the thermolytic chemistry of benzocyclobutenes, giving orthoquinodimethanes, such as **132**, as intermediates,[102] to synthesise oestrone and estradiol,[103] ring-D aromatic steroids,[104,105] pregnanes,[106] (+)-chenodesoxycholic acid,[107] C17 spiro steroids,[108] (+)-11-deoxy-19-norcorticosterone,[109,110] des-A steroids[111,112] and (+)-cortisone.[113] In their synthesis of the last compound (Scheme 27), a chiral auxiliary, readily available in high yield from (+)-pulegon,[114] was coupled to the cyclobutane aldehyde **147**. Reoxidation of the resulting hydroxyl group to a carbonyl group and addition of isopropenylmagnesium bromide now afforded the chiral intermediate **148**.

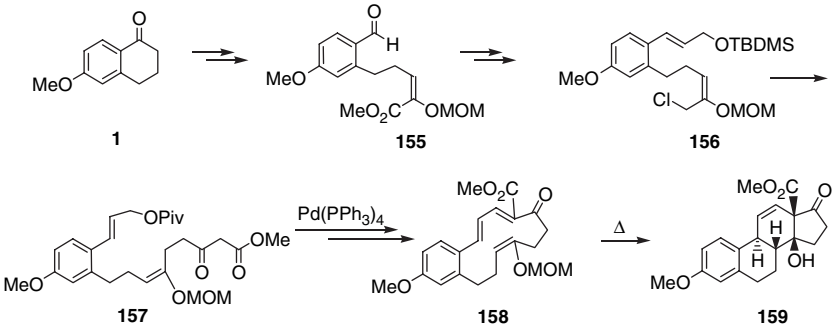
Next the orthoquinodimethane intermediate **149** was generated, in which the intramolecular Diels–Alder reaction led to **150**. The chiral auxiliary was removed, the aldehyde reduced and the aromatic ring converted into enone **151**. After protection of the diol and oxidation of C11, ring A was annelated via **152** and **153** using traditional chemistry. After deprotection of the diol, the side chain could be transformed into one with the C21-hydroxyl and the C20-carbonyl group, which is characteristic for cortisone **154**. In this way, enantiopure steroids have been produced.

At approximately the same time as Kametani and Nemoto, Oppolzer's group developed a synthesis route using similar chemistry, with orthoquinodimethane intermediates again being used, but these were produced via an alternate approach.[115,116] Thermal elimination of sulfur dioxide from sulfones yielded the dimethanes, after which further conversion into steroids could take place. Over the years, a few other groups have published similar methods involving orthoquinodimethane intermediates for the synthesis of steroids.[117–120]

The group of Deslongchamps has recently published a transannular Diels–Alder strategy (Scheme 28).[121,122] The sequence started from 6-methoxytetralone **1**, in which first ring B was reduced, dehydrated, ozonolysed and elongated to **155**. Further chain elongations first gave **156** and finally in overall 12 steps to the precursor **157**. A palladium-catalysed cyclisation and dehydration then led to the macrocyclic triene **158**, which was cyclised to the steroid skeleton **159**.



Scheme 27.

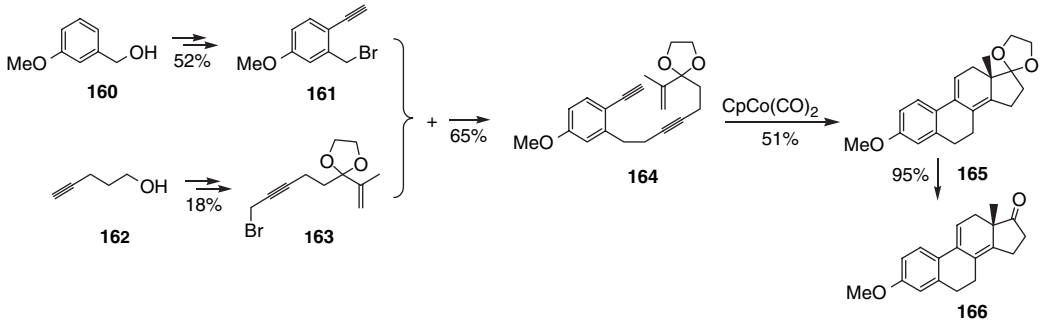


Scheme 28.

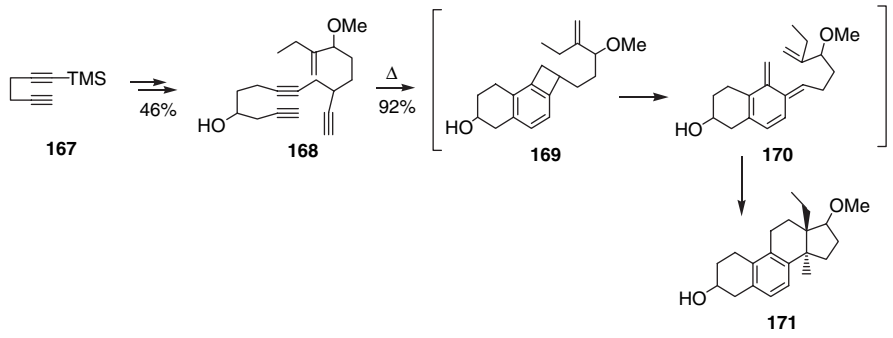
11. Electrocyclisations

The main drawback of the orthoquinodimethane chemistry was the fact that the stereochemical course of these reactions was highly dependent on the substituents used.[123–125] To circumvent this problem, Vollhardt and co-workers explored a new route using a cobalt-catalysed cyclisation of enediyne **164** to the diene intermediate **165** (Scheme 29).[126–129] The enediyne steroid precursor was prepared by coupling compounds **161** and **163**, which were prepared from **160** and **162**, respectively. Deprotection of **165** gave diene **166**, which is an intermediate in the Torgov synthesis of oestrone and can be converted into this compound in two steps.[9]

Developing this method further, the same workers used oligomerisation of the three acetylenic units present in compound **168**. This precursor was prepared in six steps from trimethylsilyl-1,5-hexadiyne **167** via alkylation of its 3,6-dilitio derivative followed by further transformations of the introduced chains. The trimerisation of the three acetylenic units in the presence of a cobalt carbonyl catalyst first led to the benzocyclobutene intermediate **169** and then via the orthoquinodimethane **170** to the B ring aromatic steroid **171**, (Scheme 30).[130] 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 29.

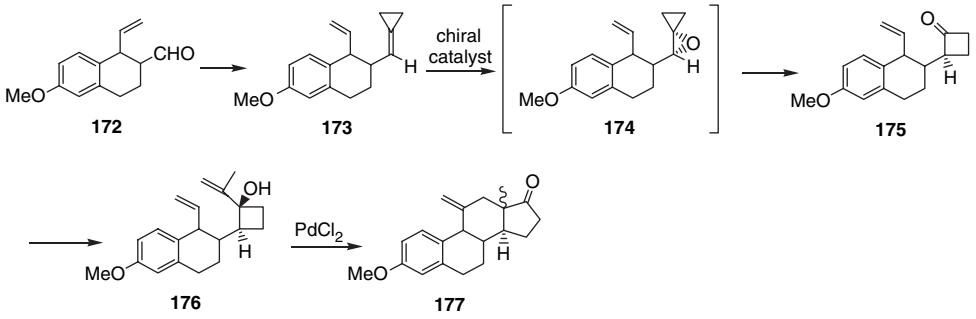


Scheme 30.

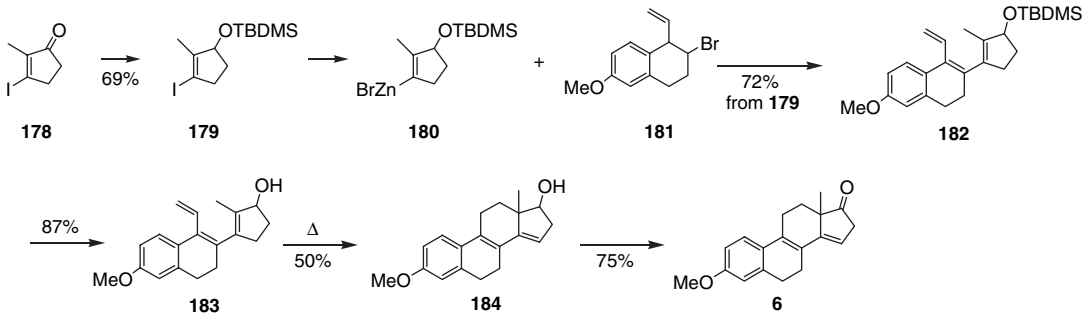
Another method published by the group of Nemoto, also utilising a cyclobutane intermediate, relies on a palladium-catalysed rearrangement leading to the formation of rings C and D (Scheme 31).[131,132] The substrate for the reaction was prepared starting from aldehyde **172**, which was reacted with cyclopropylidene-triphenylphosphorane to **173**. The epoxidation to the chiral intermediate **174** with 5 mol % of (*RR*)-(salen)Mn^{III} complex and sodium hypochlorite and the ring expansion to the cyclobutanone **175** followed by addition of isopropenylmagnesium bromide afforded the chiral substrate **176** for the cyclisation reaction. The palladium-catalysed cyclisation led to a mixture of diastereomers **177**, which was separated and further converted to enantiomerically pure (+)-equilenin.

Gilchrist and co-workers described an approach making use of an electrocyclic ring closure of trienic systems to close ring C (Scheme 32).[133] The trienes were prepared using a palladium(0)-catalysed cross-coupling reaction of vinylzinc bromides (**180**) and aryl halides (**181**). The protected vinyl iodide **179** was prepared starting from 3-iodo-2-methyl-2-cyclopentenone **178**. In this way, the starting triene **182** was obtained in good overall yield (72%). Deprotection of the hydroxyl group to **183** and thermal cyclisation then gave the steroid skeleton **184**. This group prepared several known steroidal compounds of the oestrone family (**6**), using this chemistry.[133–136]

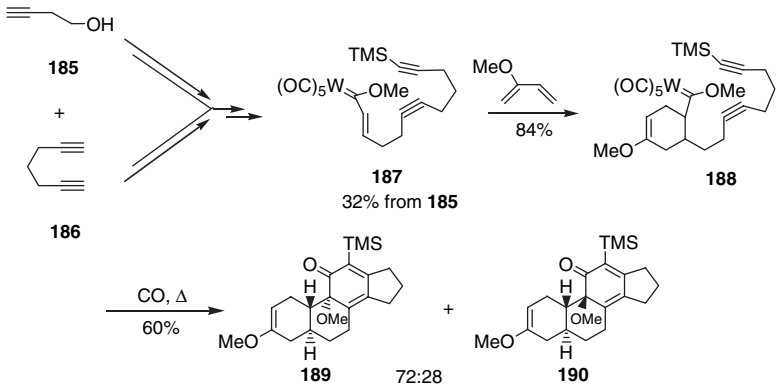
Wulff and co-workers used a tandem coupling of a Diels–Alder reaction of Fischer carbene complexes with a double intramolecular two-alkyne annelation to synthesise steroidal ring systems in which rings A and C are aromatic. In seven steps the linear precursor complex **187** was synthesised starting from the alkynes **185** and **186**. A Diels–Alder reaction of **187** with 2-methoxy-1,4-butadiene for the construction of ring A, then first leads to intermediate **188**, and next, in



Scheme 31.



Scheme 32.



Scheme 33.

a one-pot tandem reaction sequence, accessed the tetracyclic ring systems **189** and **190**, but the product bears no methyl on C13 (Scheme 33).[137]

12. Radical cyclisation

Finally, radical cyclisation was used by Malacria et al. to synthesise a steroid skeleton in a one-pot procedure, giving only two diastereomers **196** in 3:10 ratio, but unfortunately, both had the less desirable 13α-configuration and the usual methyl substituent on this position was missing.[138]

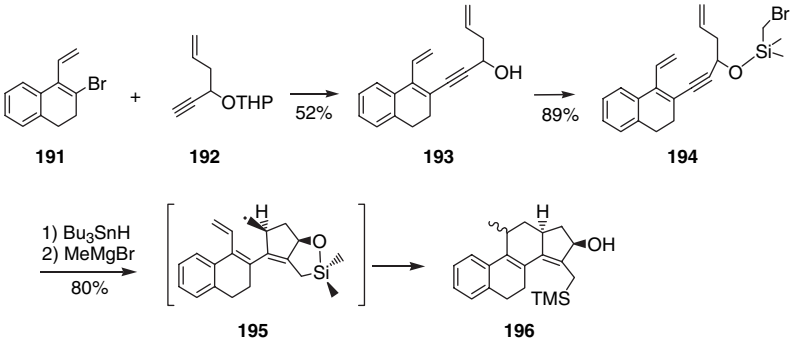
The key step of this reaction sequence consists of a tandem radical cyclisation of compound **194** (Scheme 34), which was obtained using a palladium-catalysed coupling reaction between the alkyne **192** and the aryl bromide **191**. The bromomethyldimethylsilyl group was introduced in compound **194** to initiate the radical cyclisation reaction. This first led to intermediate **195** with closure of ring D, and next to the closure of ring C to the two isomers of **196**.

13. Mukaiyama chemistry in ring C construction

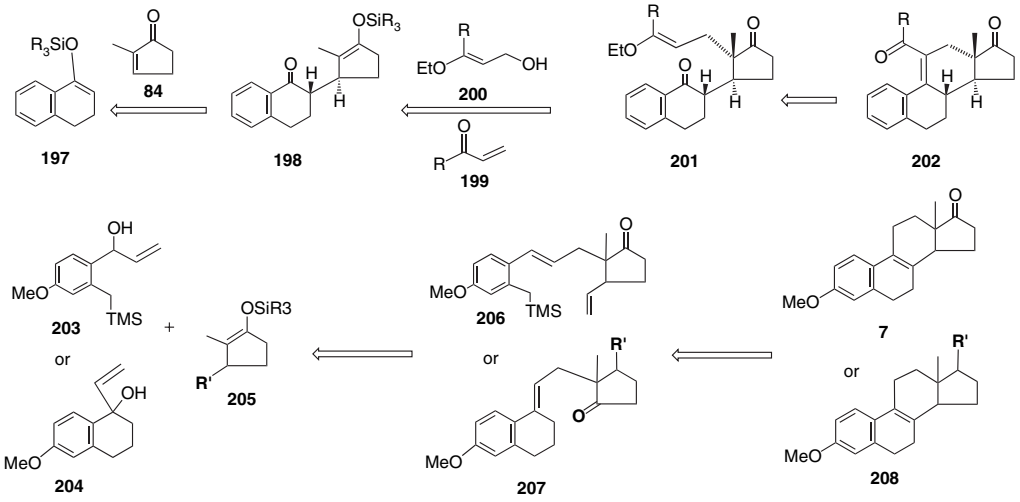
Two elements of the Mukaiyama reaction have been applied in the construction of ring C in steroid synthesis. The first element is the Mukaiyama–Michael reaction with transfer of the silyl group from the starting silyl enol ether, e.g., **197**, to the carbonyl group of the receiving enone, e.g., **84**.[139–147] In this way, a second silyl enol ether **198** is obtained, which enables either a selective reaction with the silyl enol ether in ring D, or a selective reaction with the unprotected carbonyl group in ring B. The second element is the reaction of a silyl enol ether in ring D, e.g., **198** or **205**, with a second enone, e.g., **199**, or with a reactive carbocation precursor, e.g., **200**, **203** or **204**, to construct the C12–C13 bond as in **201**, **206** or **207** (Scheme 35).[148–150] Different types of ring closure reactions then should lead to steroid skeletons like **202**, **7** or **208**.

A first example of the construction of the C12–C13 bond via the reaction of a carbocation precursor with a silyl enol ether was presented by the group of Magnus,[149] who reacted the carbocation precursor **209**, which was synthesised in three steps from *p*-methoxybenzoic acid, with silyl enol ether **210** to obtain the coupled product **211** in 88% yield (Scheme 36). Epoxidation of the $\Delta^{10,11}$ double bond to **212** set the stage for a caesium fluoride-catalysed elimination of the trimethylsilyl group combined with ring opening of the epoxide. In this way, the orthoquinodimethane intermediate **213** was formed for an intramolecular Diels–Alder reaction to **214**. Oxidation of the hydroxyl group then gave the C11-functionalized steroid skeleton **215**.

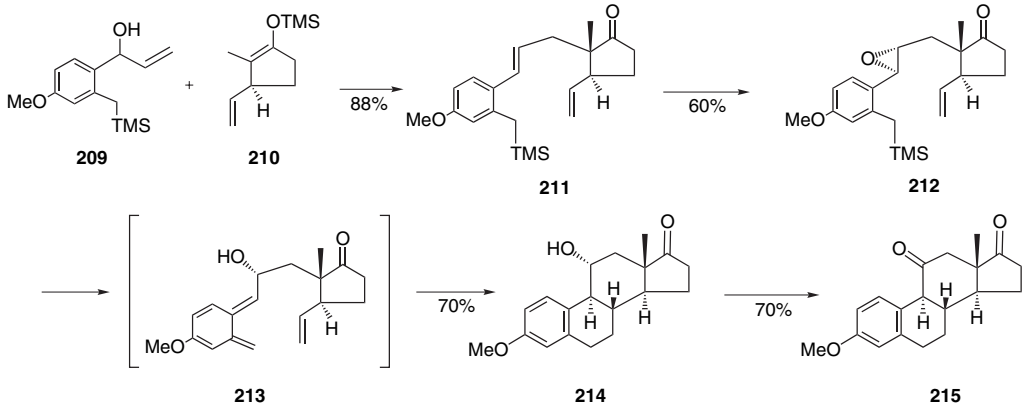
An original method for steroid synthesis was published in 1998 by Grieco and co-workers.[150] This method involved both of the above-mentioned elements of Mukaiyama chemistry. First, a Mukaiyama reaction with transfer of the silyl group from **216** to the second silyl enol ether **217**, followed by a reaction with the reactive carbocation precursor **218**, yielded compound **219** with the correct trans-stereochemistry at C13 and C14 (Scheme 37).



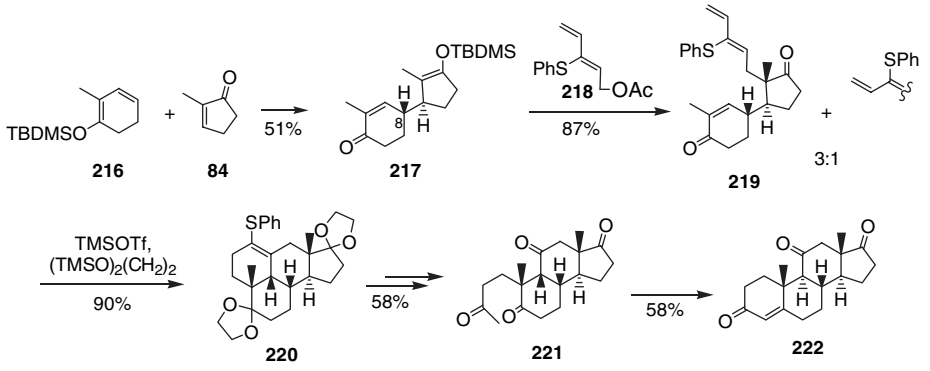
Scheme 34.



Scheme 35.



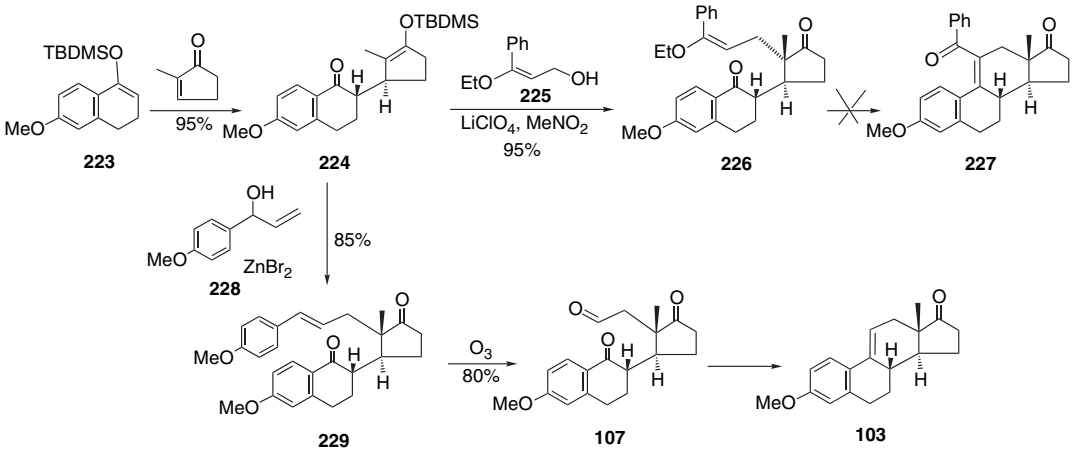
Scheme 36.



Scheme 37.

A tandem intramolecular Diels–Alder cycloaddition/olefin isomerisation then leads to the tetracyclic compound **220**. This intermediate could be converted into adrenosterone **222** via replacement of the thiophenyl group by a methyl, followed by ozonolysis to **221** and ring closure under basic conditions.

Several new routes for the syntheses of cis- and trans-C, D-coupled (D-homo) steroids have been developed by De Groot et al. that rely on a combination of Mukaiyama and Torgov chemistry as illustrated in Scheme 35. A Mukaiyama–Michael reaction with transfer of the silyl group from a silyl enol ether derived from 6-methoxy-1-tetralone **223** to 2-methyl-2-cyclopenten-1-one leads in high yield to the adduct **224**, which can take part in a second Mukaiyama addition. This second Mukaiyama reaction with methyl vinyl ketone did not, however, take place.[151] On the other hand, carbocations, obtained from reactive allylic



Scheme 38.

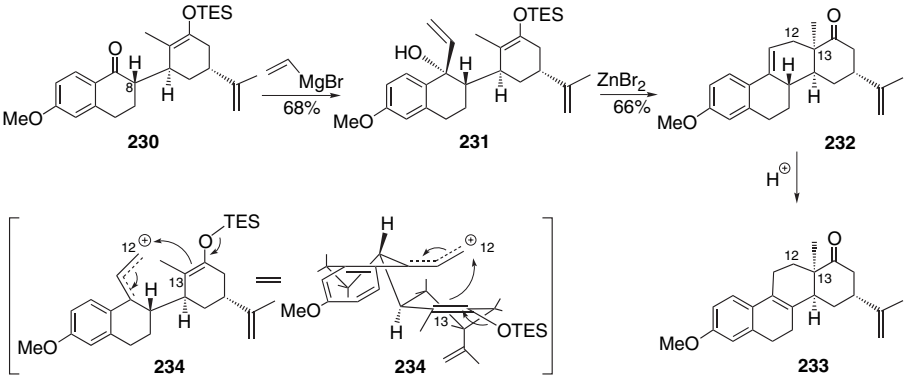
alcohols like **225**[148,152,153] or **228**,[154] did react with silyl enol ethers like **224** under mild Lewis acid conditions in good to excellent yields (Scheme 38).[155–157] An Aldol-type ringclosure of **226** to **227** could also not be accomplished, probably due to the low reactivity of the carbonyl group in the tetralone moiety of the molecule.[158]

A better alternative seemed to be offered by constructing the C9–C11 bond via cyclisation of Ziegler's triketone **107**, which has been reported previously to proceed in reasonable yields (see Schemes 19, 20 and 21).[149,150,159] A short synthesis of triketone **107** could be achieved via the addition of the carbocation precursor **228**, synthesised by the Grignard addition of vinylmagnesium bromide to anisaldehyde,[160] to silyl enol ether **224**, which gave an 85% yield of the adduct **229**. Ozonolysis of this adduct proceeded in good yield and, in this way, provided for a short and efficient synthesis of Ziegler's triketone **107** in 70% overall yield in four easy steps.[158]

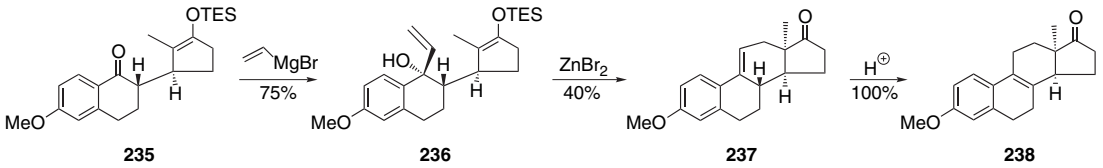
The Mukaiyama–Michael reaction with transfer of the silyl enol ether of methoxytetralone to the carbonyl group of the receiving enone is again an important element in a route leading to CD-cis-fused (D-homo) steroids. In the adduct **230**, a selective Grignard reaction of vinylmagnesium bromide with the unprotected carbonyl group of the methoxytetralone moiety leads to a Torgov-type intermediate **231** (Scheme 39). This can be converted easily into a carbocation, which then reacts intramolecularly with the silyl enol ether under formation of the C12–C13 bond to complete the synthesis of the (D-homo) steroid skeleton **232**.[159] With *R*-carvone as receptor, enantiomerically pure D-homo steroids with the natural steroid configuration at C14 are obtained as an enantiopure product in just five steps, starting from methoxytetralone, in 40% overall yield.

The oxime derived from **233** could be obtained in crystalline form and the X-ray structure[161] revealed the cis coupling of the C,D rings, as indicated in Scheme 39. This stereochemistry can be explained by a selective approach of the bulky silyl enol ether to R-(−)-carvone from the top face, opposite to the isopropenyl group. The carvone ring ends up in a favourable axial position next to the carbonyl group in the tetralone portion of the molecule and, consequently, the addition of vinylmagnesium bromide occurs from the top face. The closure of ring C via the intermediate carbocation **234** then leads to a cis-fused-CD ring system in the steroid skeleton. The TMS enol ethers and the TBDMS enol ethers reacted in a similar manner, ultimately giving the same final product **233** in 45% overall yield.

The Mukaiyama–Michael reaction of the TES enol ether of 3-methoxytetralone with 2-methylcyclopentenone gave diastereomeric mixtures of the new silyl enol ether **235** in



Scheme 39.



Scheme 40.

quantitative yield (Scheme 40; only one stereoisomer is indicated). The addition of vinylmagnesium bromide to **235** also went smoothly, but the cyclisation of the adducts **236** with $ZnBr_2$ gave a lower yield of the diastereomeric mixture of the steroid skeleton **237**, with dehydration as the major side reaction. Finally, acid-catalysed isomerisation of this mixture gave the known racemic **238**[162] in about 30% overall yield, starting from **235**.

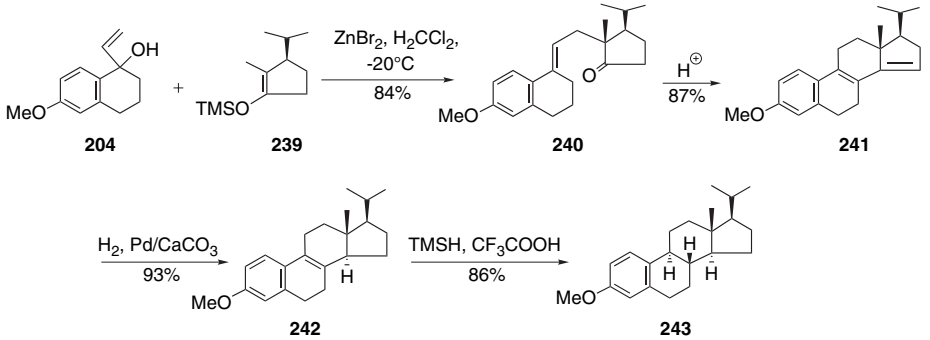
A second approach to CD-trans-fused (D-homo) steroid skeletons has been developed, in which the C12–C13 bond was formed in the second step of the sequence using an *intermolecular* Lewis acid-catalysed reaction of the Torgov-type reagent **204** with a silyl enol ether containing ring D precursor **205**, to give the seco steroid **207**.[163] A cyclisation reaction then gives the C8–C14 bond to close ring C, now as the last step (Scheme 35). This method gives a quick access to a wide variety of C17-substituted steroid skeletons with a similar set of double bonds in the C and D rings as in the products from the traditional Torgov reaction. Selective catalytic reduction then yields the CD-trans-fused (D-homo) steroid skeletons.

A wide variety of silyl enol ethers **205** has been obtained by conjugate addition followed by capture of the enolate with a silylating agent, via Mukaiyama–Michael reactions on enones with transfer of the silyl group from the starting enol ether to the enol of the adduct, or by direct silylation of ketones. The reaction of the Torgov reagent **224** with silyl enol ethers of cyclopentanones to seco steroids **207** proceeded in excellent yields, and also when the silyl enol ether had an ethyl group at C2. Similar reactions with silyl enol ethers derived from cyclohexanones, leading to D-homo steroid skeletons, gave more diverse results and steric hindrance quickly lowered the yields. The double bonds in the C and D rings in the steroid and D-homo steroid skeletons can be reduced catalytically to C,D-trans-fused steroid skeletons according to well-known literature procedures.[22,54,120,162,164] A specific example of the whole sequence is shown in Scheme 41, where the isopropyl substituted silyl enol ether **239** has been reacted with the Torgov reagent **204** to the ring C-open adduct **240**. Acid-catalysed ring closure to diene **241**, reduction of the Δ^{14} double bond to **242** and finally reduction of the Δ^{9} double bond gave the C17 substituted all *trans* steroid **243** in a high overall yield.

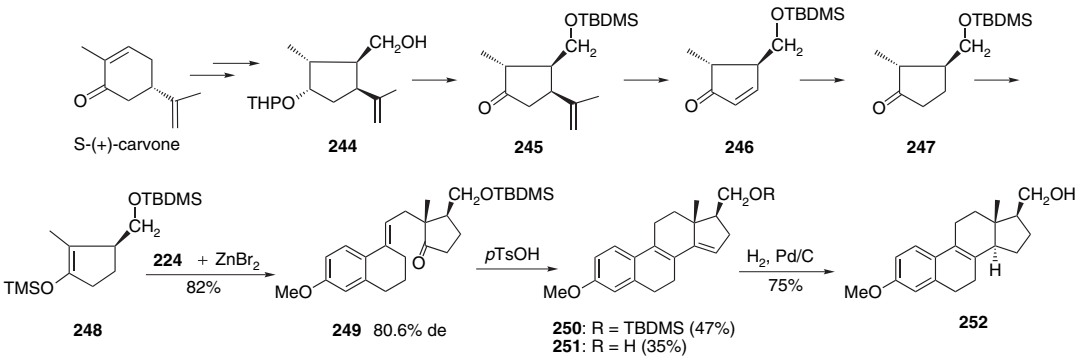
The approach mentioned in Schemes 35 and 41 is very suitable for the synthesis of *chiral* steroid skeletons, provided that chiral ring D precursors are available or easily accessible. Silyl enol ether ring D precursors have been used previously in other routes to steroids by the groups of Magnus[149] and Wicha,[141,165–167] and, on one occasion, a chiral ring D precursor has been used.[167] A synthesis of a suitable ring D precursor was developed starting from carvone, because a good procedure for the ring contraction of carvone, using a Favorskii rearrangement leading to compound **244**, was known from the literature (Scheme 42).[168]

Deprotection, selective reprotection of the primary alcohol and oxidation then gives the cyclopentanone **245**. Regioselective removal of the isopropenyl group to **246**, catalytic reduction of the double bond to **247**, and formation of the thermodynamic silyl enol ether finally affords the desired chiral ring D precursor **248**. When placed into a reaction with the Torgov reagent **204**, seco steroid **249** is obtained in 82% yield as a mixture of two C13 diastereomers, with a diastereomeric excess of 81%. Cyclisation of **249** gives the steroidal diene **250** in 47% yield, next to a 35% yield of the deprotected compound **251**.[169] Selective reduction of the diene **251** gave a 75% yield of **252**, the remainder being unreduced starting material. Thus complete deprotection of the alcohol moiety in the side chain directly after the cyclisation, followed by selective reduction, is the best procedure.

Although the overall yield of the optically active steroid ring D precursor **248** from (*S*)-(+)-carvone is only 10% and



Scheme 41.



Scheme 42.

requires 11 steps, the applicability of this approach for the preparation of enantiomerically pure steroid skeletons has been shown. The development of straightforward, easy and high-yielding syntheses for *chiral* steroid ring D precursors is, however, essential to make this route into a good method for the synthesis of optically active steroid skeletons.

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Biographical sketch

Dr. ir. Florence C. E. Sarabèr was born in 1977 in Rotterdam, The Netherlands. She graduated in 2000 with distinction in Molecular Sciences from Wageningen University, after a stay of 7 months at Nottingham University, in the group of Dr. N. R. Thomas. In 2005, she completed her Ph.D. thesis on the total synthesis of steroids, entitled 'Steroids from Carvone', at Wageningen University under the supervision of Prof. dr. Aede de Groot. Her field of interest remains the total synthesis of natural compounds, although she currently holds a position as Regulatory Affairs Scientist at Organon N.V., Oss, The Netherlands.

Professor Aede de Groot received his M.Sc. in Organic Chemistry and Technical Chemistry in 1964 from the University of Groningen in The Netherlands. He did his Ph.D. in Organic Chemistry in 1967 under the supervision of Prof. dr. Hans Wijnberg, also in Groningen, and he was a post doctoral fellow with Prof. dr. E. E. van Tamelen where he got his first training in synthesis of natural products. From 1969 to 1971 he gained industrial experience at the Dutch State Mines (DSM) on electro-organic synthesis, and after that he was an assistant professor at the Technical University of Eindhoven. In 1972 he was appointed as full professor in Bio-organic Chemistry at Wageningen University. He has retired from this position in 2004. His research interests concentrated on total syntheses of natural products, especially sesqui- and diterpenes with physiologically active properties in the field of crop protection (antifeedants, repellents, pheromones), flavour and fragrance and pharmaceuticals (steroids), and on syntheses starting from terpenes, which are abundantly available from Nature.