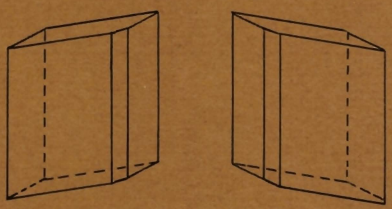
The preparation of heterocyclic steroids via asymmetrically induced ring closure reactions

THE PREPARATION OF HETEROCYCLIC STEROIDS VIA ASYMMETRICALLY INDUCED RING CLOSURE REACTIONS



A. A. Macco

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PROEFSCHRIFT

Ter verkrijging van de graad van Doctor in de Technische Wetenschappen aan de Technische Hogeschool Eindhoven, op gezag van de Rector Magnificus, Prof. Dr. P. v.d. Leeden, voor een commissie aangewezen door het College van Dekanen in het openbaar te verdedigen op vrijdag 6 april 1979 te 16.00 uur

door

ANTONIUS ALOYSIUS MACCO

Geboren te Zuilen

OFFSET KURVER SITTARD B.V.

DIT PROEFSCHRIFT IS GOEDGEKEURD DOOR

DE PROMOTOREN

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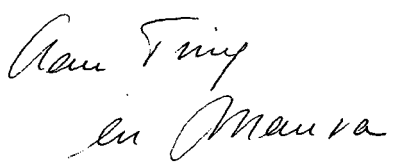


True wit is Nature to advantage dress'd
What oft was thought, but ne'er so well express'd

Alexander Pope (1688-1744)

Contents

Chapter I

General introduction

I.1 *Historical background*

The first asymmetrically induced reaction was observed by *Fischer* in 1894[1] on homologating a sugar *via* the cyanohydrin reaction. This area of organic chemistry knew a slow progress and for a long time it was not completely liberated from the vitalistic theories. It was only in 1950 that a reassessment was made about the mechanisms involved, as one became more interested in steric hindrances in general[2]. The first modern mechanistic rationale of asymmetric reactions was made by *Doering*[3] and *Jackman*[4]. They carried out the asymmetric Meerwein-Pondorf-Verley reduction of a ketone. The mechanism was interpreted in terms of steric interactions in the transition state. *Mosher* and *La Combe*[5] gave an analogous interpretation about their results of studies on asymmetric Grignard reactions. Soon thereafter, a predictive treatment of asymmetric reactions became possible after *Cram* introduced his now well known empirical rule of steric control of asymmetric induction[6]. Since then numerous asymmetric reactions were developed and their mechanisms studied. An excellent review covering the synthetic organic field was recently given by *Morrison* and *Mosher*[7] and a more fundamental treatment by *Izumi* and *Tai*[8].

I.2 *Asymmetric polyolefinic cyclization reactions*

I.2.1 *The in vivo mechanism of the formation of steroids*

One of the most fascinating cyclization reactions is the biochemical conversion of squalene to tetra- and pentacyclic

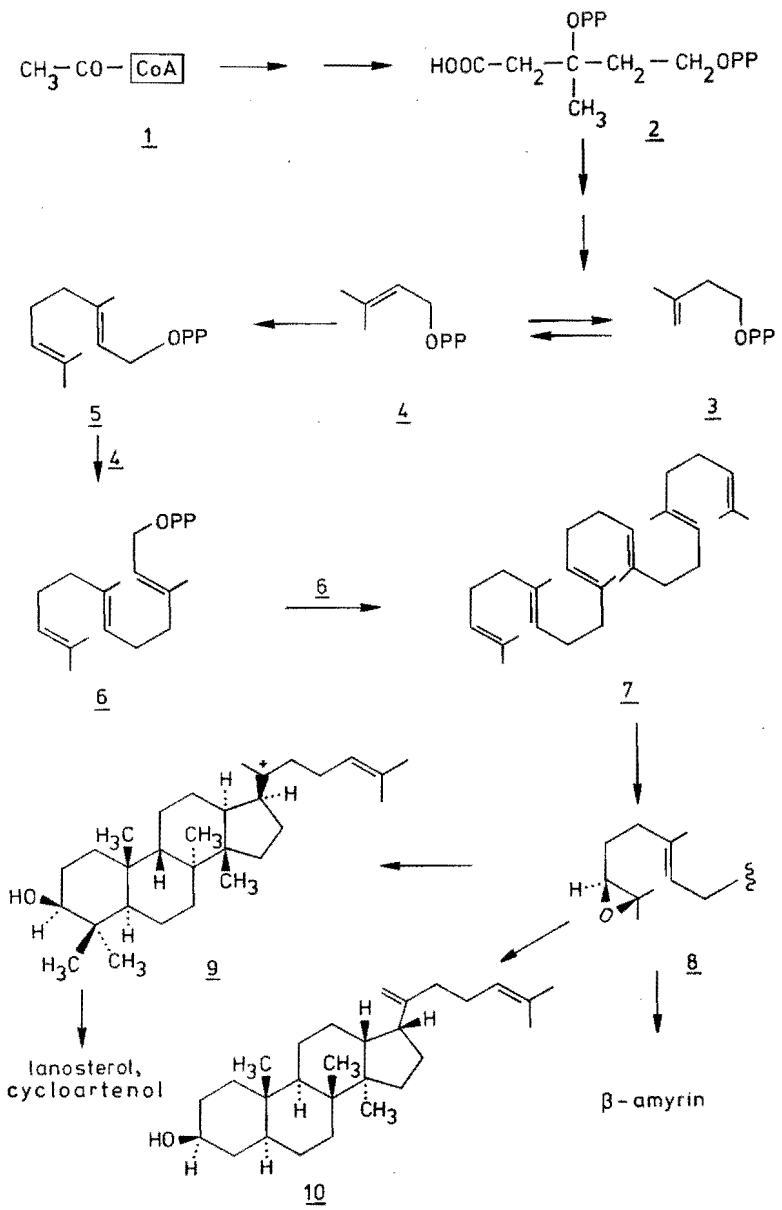


Figure 1.1 The biosynthesis of some steroids

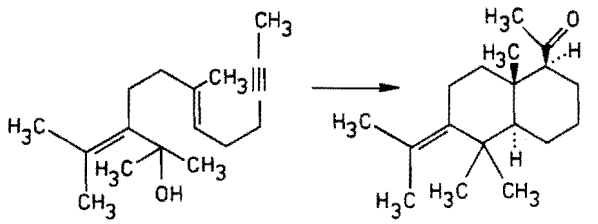
terpenoids. The enzymatic production of squalene is presented in figure 1.1[9]. Acetyl coenzyme-A 1 (Acetyl-CoA) is converted into phosphorylated mevalonic acid 2, which in turn is dehydrated into isopentyl- and dimethylallyl pyrophosphate, 3 and 4 respectively. Coupling of these units gives geranyl (5) and farnesyl pyrophosphate 6, successively. A final head to tail linkage of the latter affords squalene 7. This compound serves as a general precursor for all kinds of tetra- and pentacyclic triterpenoids. In an oxidative cyclization sequence, squalene is initially converted into its (S)-2,3-epoxy derivative 8[10]. Depending on the biomechanism, the epoxy compound is cyclized to a number of steroids like protosterol 9 (the precursor of lanosterol, cholesterol, and cycloartenol), dammaradienol 10, and β-amyrin. Impressive is the stereospecificity in all these ring closures. 2,3-Epoxysqualene with only one chiral center is converted into products containing seven asymmetric centers. The importance of the cyclase enzyme is obvious. The different configurations of the tertiary chiral centers are the result of different approach of the double bonds to each other. So, the cyclization to protosterol 9 is believed to be initiated from a chair-boat-chair conformation of 2,3-epoxysqualene, and dammaradienol 10 from a chair-chair-chair conformation. This essential difference is generally thought to be caused by the enzyme, holding the precursor in a single folded conformation. This aspect is chemically very unlikely. *De Loos* demonstrated[11] how participation of an enzyme site (like the imidazole part of histidine) may well rationalize the stereochemistry of the ring closures and the differences found for cyclizations under *in vitro* conditions. The nucleophilic capture of a bicyclic carbenium ion in dependence of the site location must determine the boat or chair B-ring closure. This theory also accounts for the consecutive rearrangements after cyclization.

I.2.2 *The in vitro cyclizations of polyalkenes*

The *in vivo* cyclizations of squalene proceed highly

stereospecifically, as outlined in the previous section. This prompted the cyclization studies of polyalkenes under non-biological circumstances[12]. The ring closures of E-alkenes appeared to provide *trans*-fused rings. In a few cases, these *trans*-fused rings were also formed on cyclizing the isomeric Z-alkenes. It could be demonstrated, however, that in the latter case a de- and reprotonation was responsible for the formation of the thermodynamically more stable *trans*-fused rings. In 1955, *Stork*[13] and *Eschenmoser*[14] postulated the general concept that (*in vitro*) E-olefins provide *trans*-fused rings and Z-olefins *cis*-fused rings.

At first, only small amounts of polycyclic material were formed on ring closure of polyolefins, albeit with high stereospecificities. The indiscriminate protonation and deprotonation occurring in the strongly acidic media employed, was attributed to the low yields of desired cyclizations. *Johnson* and coworkers initiated in 1960 a search for polyolefinic substrates containing a suitable functionality, serving as a nucleofuge under conditions which would only lead to ring closure. The solvolysis of Z- and E-polyolefinic p-nitrosulphonate esters proceeded in accordance to the *Stork* and *Eschenmoser* hypothesis[15]. However, the yields on tricyclic material were still low and the ring closures are accompanied by the loss of ring functionality (the p-nitrosulphonate group)[16]. Studies with other cyclization initiators like (cyclic) allylic alcohols[17] and acetals[18] were very successful. It was found that an appositely placed acetylenic bond (as cyclization terminator) can participate in olefinic ring closure reactions so as to produce a *trans*-fused five-membered ring. The allylic alcohol 11 (see figure 1.2) underwent ring closure to form an enol formate, which was readily hydrolyzed to the bicyclic ketone 12[19]. This model reaction for the formation of the CD-part of steroids was next adapted to a synthesis of d,l-progesterone[20]. Cyclopentenol 13 was cyclized in high yield and stereospecifically to the tetracyclic alkene 14; A-ring opening



11 12

Figure 1.2 Acetylenic bond participation in an olefinic cyclization

by ozonolysis and intramolecular aldol condensation afforded d,l-progesterone 15. However, this type of ring closure undergoes side reactions, probably caused by the low nucleophilicity of the acetylenic bond. The reaction of 16[21] gave besides the desired product 17 also retrosteroid 18 and spiro compound 19 *via* the intermediacy of a bicyclic carbenium ion. Also the 13-*iso* steroid 20 was formed, probably *via* a tricyclic carbenium ion. These side reactions do not occur when an aromatic ring is used as reaction terminator. This led to a short and very elegant biomimetic synthesis of d,l-oestrone[22] (see figure 1.4). The route to precursor 21 has, in a general sense, been used to prepare chiral precursors. Their syntheses are described in full detail in the following Chapters. Ring closure of 21 (Ar=Anisole) provided the *trans-anti*-fused tetracycle 22. α-Epoxidation, followed by a BF_3-catalyzed [1,2]-methyl shift gave d,l-oestrone 23. Recently, *Corvers* applied this method to study the accessibility of heterocyclic steroids, containing thiophene as A-ring[23]. Ring closure of

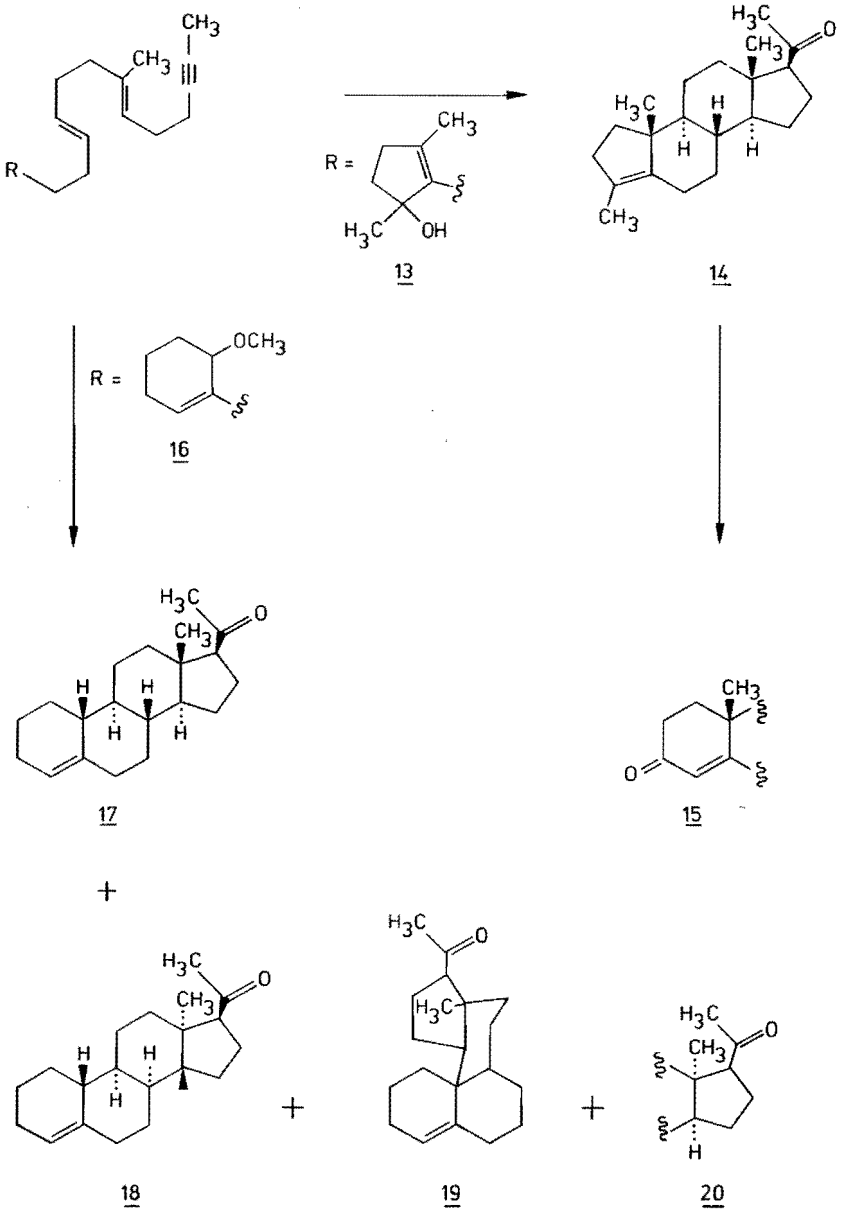
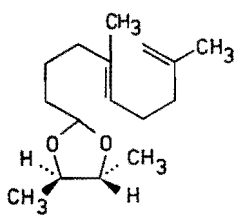


Figure 1.3 Acetylenic bond participation in the synthesis of steroids

the 2-thienyl derivative 24 (Ar=2-thienyl) gave 3-thia-4-noroestratriene 26. The 3-thienyl analogue 25 (Ar=3-thienyl) led to compound 27. No ring closure to the 4-position of thiophene was observed. *Noteworthy is the fact that the isomeric Z-alkenes of 24 and 25 (or their ketonic precursors) did not cyclize under a great variety of reaction conditions.* The tetracycles 26 and 27 were, in analogy to Johnson's work, transformed into the oestrone analogues 23.

I.3 *Application of asymmetric induction to the olefinic cyclization reactions*

The tetracycles obtained on the biomimetic polyene cyclizations, as described in the previous Section, are isolated as racemates. The ring closures take place in two mirror imaged sequences, thus producing two enantiomeric forms. The investigations of chiral induced cyclization reactions, stemming from *intra*molecular interactions, were initiated by *Johnson*. High inductions were observed on cyclizing a chiral dienic acetal[24] (compound 28, containing a chiral acetal function) and on the preparation of 11-substituted progesterones[25]. Both examples are further described in the next Chapter. The presence of a stable chiral center causes in the two no longer "mirror imaged" cyclization sequences a difference in transition state energy, accounting



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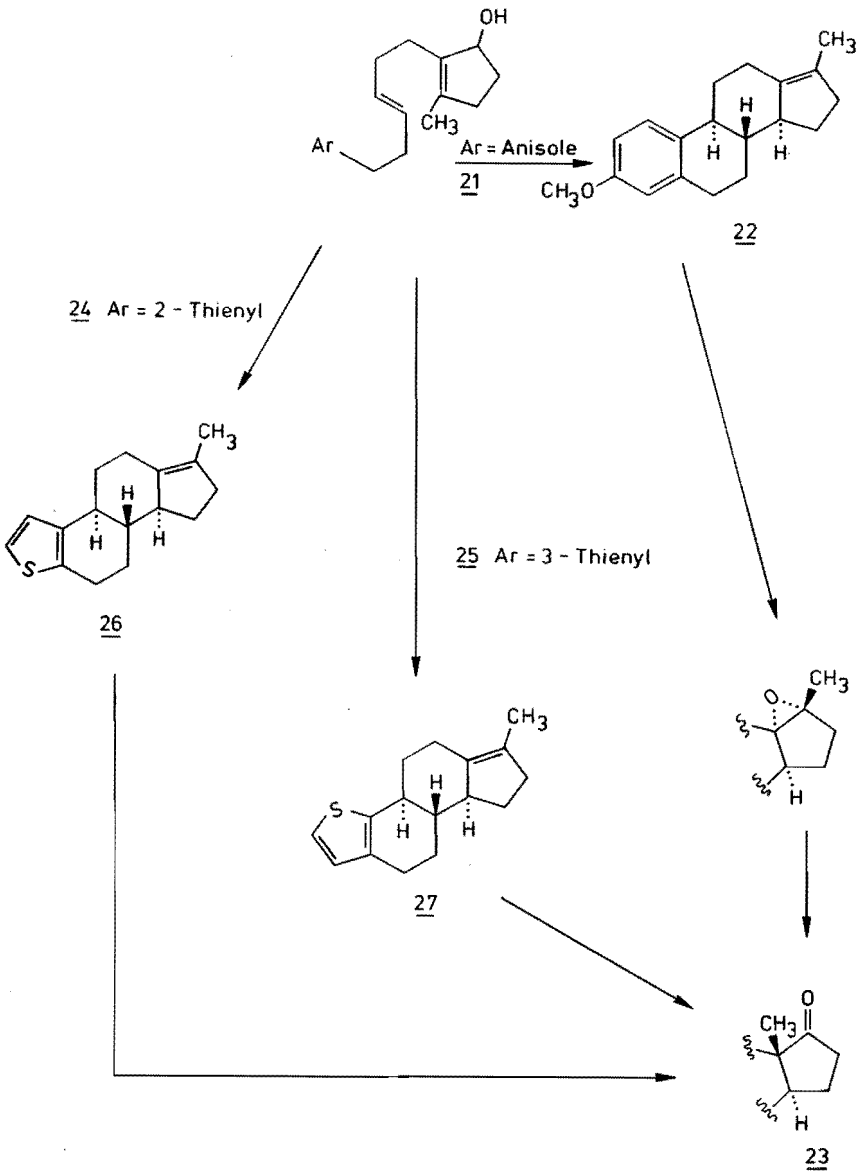

Figure 1.4 The synthesis of oestrone and its 1- or 3-thia-4-nor-analogue *via* polyolefinic cyclization

for differences in the product ratio of the eventually formed diastereomers.

In this thesis the influence of the presence of a chiral center on the ring closures of 24 and 25 is described. The chiral centers were located at a far distance from the reaction initiator (the cyclopentenyl carbenium ion). In Chapter II the dependence of the size of pro-C-6 substituents on the stereospecificity of the ring closure is given. A high degree of steric induction due to small 1,3-interactions led to a dynamic model description for the cyclization. It is assumed that a precoiled conformer in the ionic species preserves all stereochemical information of the final product.

An indication for the existence of 1,3-interactions between the substituent at pro-C-6 and the thiophene ring is given in Chapter III. It was found that the cyclization of a chiral 3-thienyl derivative was terminated not only *via* the 2-position of thiophene but also *via* the 4-position of thiophene.

The additional steric influence of the cyclopentenyl nucleus on a pro-C-7 substituent before cyclization causes a *cis*-BC-ring fusion *via* the intermediacy of a sulphonium ion, besides the formation of the 7α-substituted *trans-anti*-fused product. The amount of *cis* fusion could be increased by the influence of an additional pro-C-6 substituent (*threo*, *via* additional 1,3-interactions). The existence of the intermediate sulphonium ion could be made plausible by studying the ring closure of the corresponding 3-thienyl analogue, in which the formation of an intermediate sulphonium ion is sterically impossible.

The ring closure of an optically pure substrate must lead to an optically pure tetracycle if complete asymmetric induction occurs. In Chapter V the resolution and determination of absolute configuration (by circular dichroism) of a pro-C-6 substituted precursor is presented, from which is known that its cyclization proceeds with 100% asymmetric induction.

In the last Chapter the ring closure to an optically pure tetracycle is given. Its absolute configuration is confirmed by circular dichroism.

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Chapter II

Asymmetric induction upon cyclization of pro-C-6 substituted E-polyalkenes[1]

II.1 *Introduction*

The first asymmetrically induced polyolefinic cyclization was reported by *Johnson*[2] (see figure 2.1). The reaction of optically pure 1 with stannic chloride in benzene gave two pairs of enantiomers 2a,c and 2b,d (in different yields), in which three new chiral centers have been created. Conversion of 2a,c gave 92% 3a and 8% 3b, while the reverse ratio was obtained from 2b,d. The reaction 1 → 3 proceeds with 84% asymmetric synthesis. Conducting the cyclization in dry pentane or nitromethane lowered the percent asymmetric synthesis to 72% and 48%, respectively. A satisfactory model of the transition state could not be given, although it was suggested that chiral recognition through nonbonded interactions between the substituents of one of the chiral centers and the protons at C-7 should be responsible for the high stereospecificity.

The synthesis of natural polycyclic compounds *via* biomimetic polyene cyclization reactions has proved to be very fruitful[3]. Asymmetric induction on such cyclizations has first found application in the preparation of 11α-substituted progesterones[4] (see figure 2.2). On cyclizing racemic 4 (R= CH_3, OH; R'=CH_3), 100% asymmetric induction occurred in favour of the α-substituted racemic 5a. *Johnson* ascribed the highly stereochemical outcome of the reaction in part to a nonbonded interaction between R and the methyl groups attached to pro-C-10 and possibly pro-C-13[5]. In contrast, *Yarnell*[6] and *Groen*[7] found no induction at all on ring closure of 4 (R'=H).

As mentioned in Chapter I, cyclization of 6 (R=H) leads to

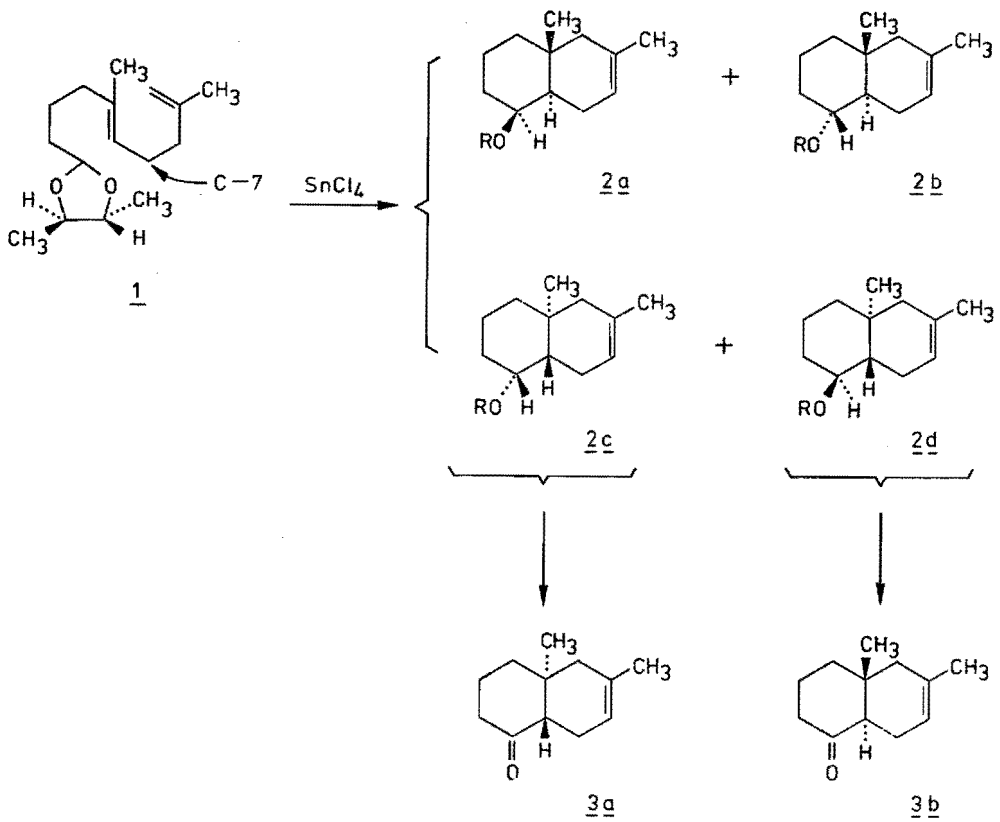


Figure 2.1 Asymmetrically induced cyclization of an olefinic acetal

a racemic mixture of *trans-anti* fused tetracycles 7 (R=H) (see figure 2.3). The chiral hydroxy in the pro-D-ring has no influence on the stereochemical pathway of the ring closure. Recent studies on a similar system showed[8] that complete racemization occurred on cyclizing an asymmetrically reduced ketone. This indicates the ring closure to be initiated after

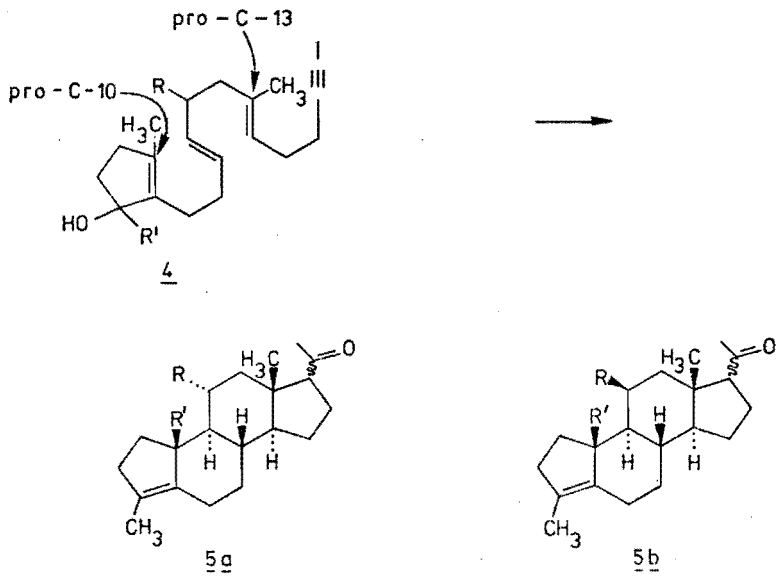


Figure 2.2 Asymmetrically induced cyclization in the synthesis of 11-substituted progesterones

heterolysis of the allylic-O bond.

In order to gain more insight into the stereochemical outcome of such cyclization processes, a chiral center at pro-C-6 (R=D, CH_3, $C(CH_3)_3$) of type 6 was introduced. In *Johnson*'s work (*vide supra*) the interactions responsible for the high asymmetric induction are clearly demonstrable, in contrast to 6 (R≠H), wherein no direct alkyl interaction is possible. Furthermore, the chiral center in 6 is one C-C distance further from the reaction initiator. Thiophene was chosen as reaction terminator, thus affording heterocyclic steroids (see Chapter I). These, containing an extra active site (sulphur), can serve as model compounds for *in vivo* conditions.

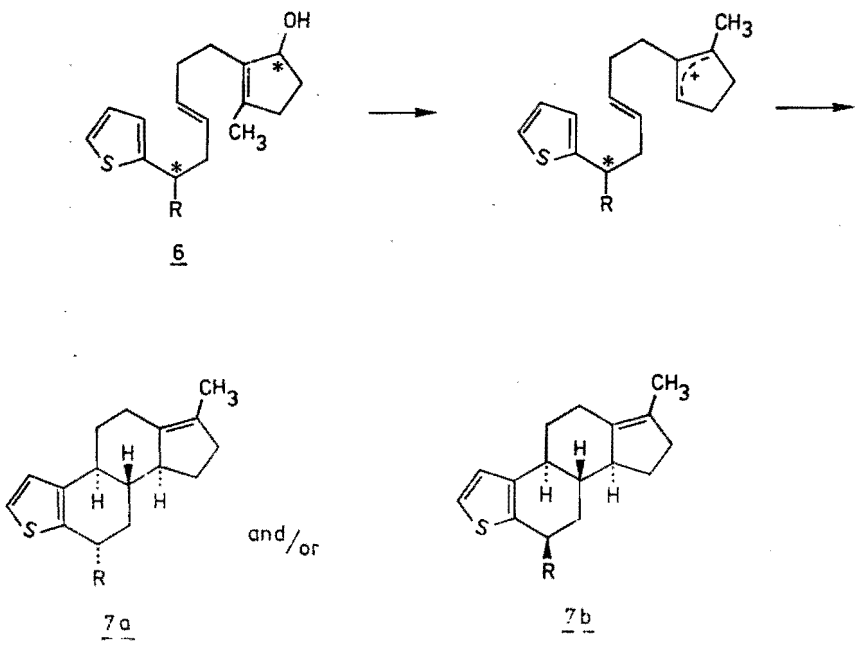


Figure 2.3 Products, possible on ring closure of a heterocyclic chiral polyalkene.

As will be seen in Chapter IV, the cyclization of a pro-C-7 substituted precursor leads to *cis*-BC ring fused tetracycles, brought about *via* the intermediacy of an intramolecular sulphonium ion. *Cis*-fused tetracycles like cycloartenol are also formed under *in vivo* conditions.

II.2 *The synthesis of pro-C-6 substituted polyenes*

Thiophene alkylation is generally performed by treating thienyllithium with a proper halide, since acid catalyzed alkylations give mixtures of 2- and 3-alkylthiophenes. However, the former method is only useful with primary halides: secondary halides appeared to incommode by base-induced eli-

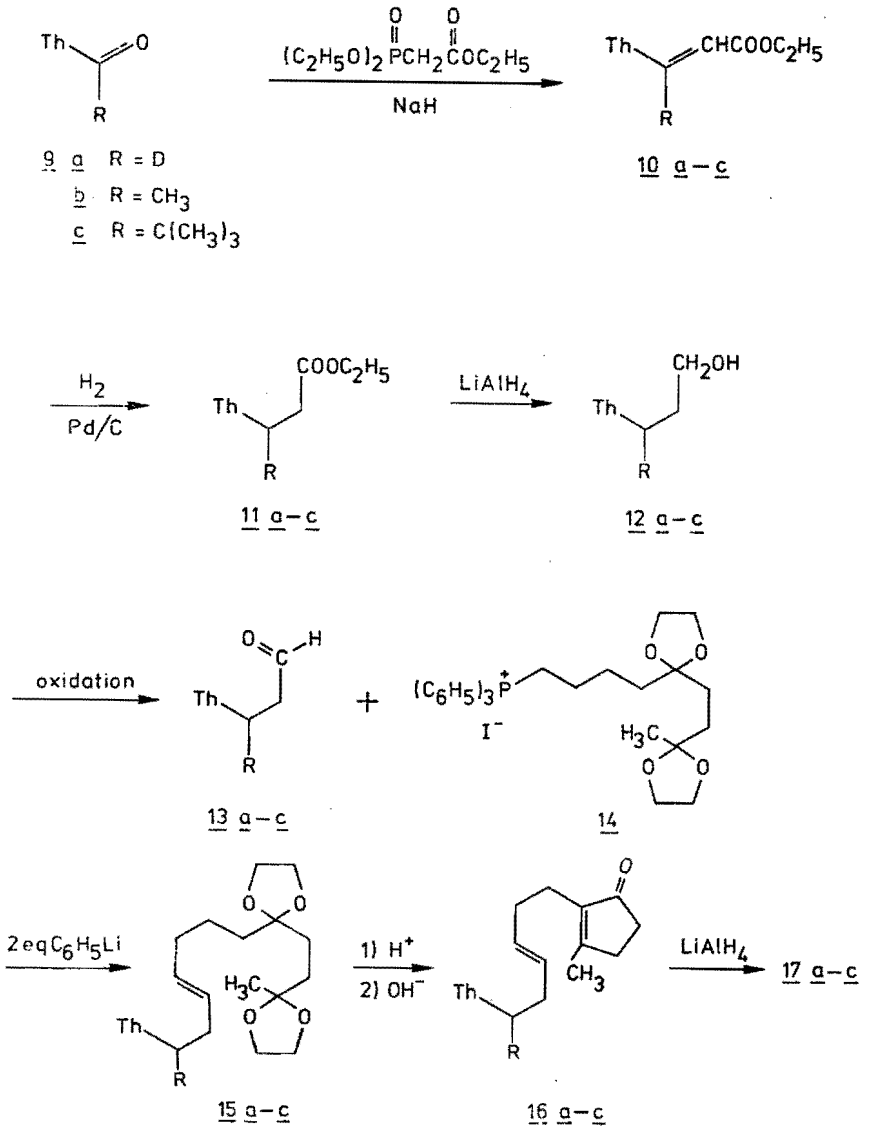


Figure 2.4 The preparation of the cyclization precursors.
Th=2-thienyl

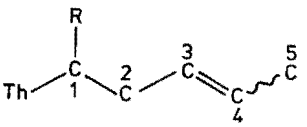
mination. The preparation of the required secondary 2-alkylthiophenes thus had to proceed *via* acylation as is outlined in figure 2.4. Such reactions are known to afford 2-substituted thiophenes exclusively.

2-Thiophenecarboxylic acid, on esterification and reduction with $LiAlD_4$ gave 2-thienyldideuteriomethanol 8. Oxidation of the alcohol with pyridinium chlorochromate[9] in dichloromethane afforded aldehyde 9a. 2-Acetylthiophene 9b[10] and 2-pivaloylthiophene 9c[11] were prepared according to literature methods. The α,β-unsaturated esters 10 were formed on treating 9 with the ylid of triethyl phosphonoacetate (Wadsworth-Emmons). The alkene moiety was hydrogenated with palladium on carbon (10%) as catalyst. The saturated esters, on reduction with $LiAlH_4$, gave the alcohols 12 and subsequent oxidation with pyridinium chlorochromate yielded the aldehydes 13. The Wittig condensation under *Schlosser*[12] conditions of aldehydes 13 with phosphonium salt 14[13] turned out to be the most difficult step. The E-configuration of the alkenes 15 is a prerequisite, since the Z-isomers fail to give any tetracyclic product (see Chapter I). The most effective procedure, giving more than 95% E-alkene, is described in the experimental section II.5. The configuration of the E-alkenes was established by the method of *De Haan* and *Van de Ven*[14]. The differences in chemical shift (Δδ) between the allylic carbon atoms are characteristic for Z and E-isomers. These data are gathered in Table II.1. Acid treatment of 15 effected deketalization and subsequent cyclodehydration of the diketones by base afforded the unsaturated cyclopentenones 16. These, on reduction with $LiAlH_4$ (inverse addition at -30 °C) gave the unsaturated cyclopentenols 17 in quantitative yield. They were used immediately for the cyclization experiments, since they are very susceptible to dehydration.

II.3 *The cyclization results*

Precursors 17 were cyclized in 50% yields, as was found for the unsubstituted alkenes[15]. The significance of these

Table II.1 The ^{13}C NMR chemical shift values of the Z- and E-alkenes[a,b]



Compound	C_2 (E)	C_2 (Z)	Δδ	C_5 (E)	C_5 (Z)	Δδ
15 (R=H)[c]	35.71	30.54	5.17	33.80	28.50	5.30
15a	43.41			33.75		
15b	34.85	30.88	3.97	33.61	28.54	5.07
16 (R=H)	35.55			32.15		
16a	43.38			32.15		
16b	35.25	30.64	4.61	32.09	26.94	5.15

[a]Values in ppm downfield from Me_4Si; [b]Th=2-substituted thiophene; [c]The values for these compounds have been obtained from ref. 15.

comparable yields is rationalized in section II.4. The by-products consisted of polymers[16] (caused by the action of the Lewis acid on thiophene) and Diels-Alder products, generated from the unstable cyclopentenol ring. After purification of the mixture by column chromatography the compositions of the resulting TLC-pure steroid mixtures were determined by several physical methods.

On cyclizing 17a, both enantiomeric pairs of diastereomers 18a and 19a (see figure 2.5) were formed in equal amounts: in ^1H NMR (360 MHz) the integrals of the signals from the C-5-αH and C-5-βH (distinguishable by their coupling constants) at δ 2.74 and 2.84 ppm, respectively, were of equal magnitude

(± 5 %); this cyclization proceeded therefore without any asymmetric induction. This is not surprising considering the small difference in shape between a hydrogen and a deuterium atom. Unexpectedly, the relatively small methyl substituent in 17b sufficed to generate a 97% asymmetric induction to give the α-substituted 18b. The remaining 3%, detectable by HPLC (M^+: 258), was tentatively assigned to 19b. No further experiments were carried out to increase the amount of 19b to study its spectroscopic properties and to corroborate its structure. It could be effected by increasing the reaction temperature, but as will be seen in Chapter IV the temperature dependence on the ratio of diastereomer formation is only

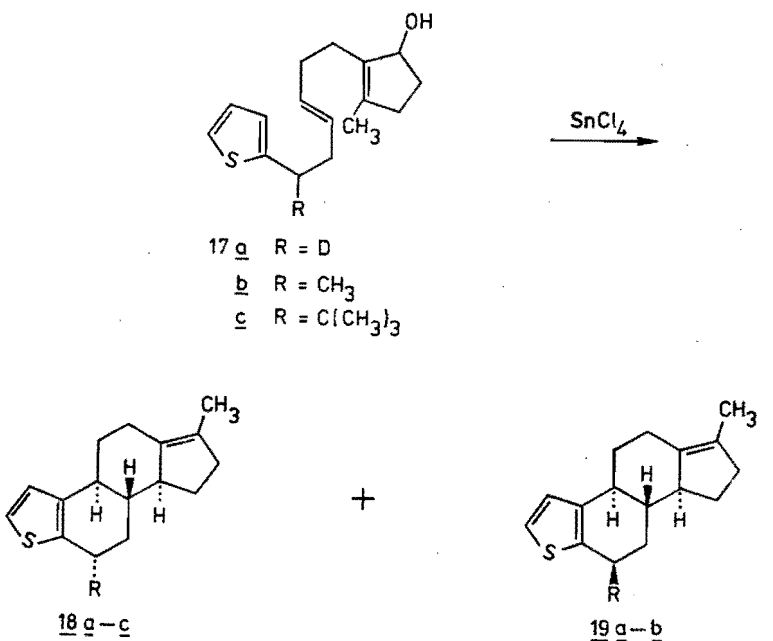
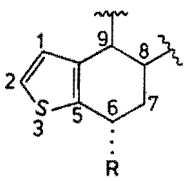


Figure 2.5 The ring closures of the pro-C-6 substituted alkenes

small. The *t*-butyl substituent in 17c generated *complete α-symmetric induction:* no diastereomer (19c) was detected either by NMR, GC, LC, or HPLC. This implies that the reaction on enantiomerically pure 17c would give optically pure 18c (see Chapter VI). The pseudo-equatorial position of R in 18b,c was established by ^{13}C NMR (Table II.2). If R was to occupy the β-position, a γ-gauche interaction would cause an upfield shift of C-8 of the order of 1-3 ppm as compared with 18 (R=H).

Table II.2 ^{13}C NMR chemical shift values of the α-substituted steroids[a]



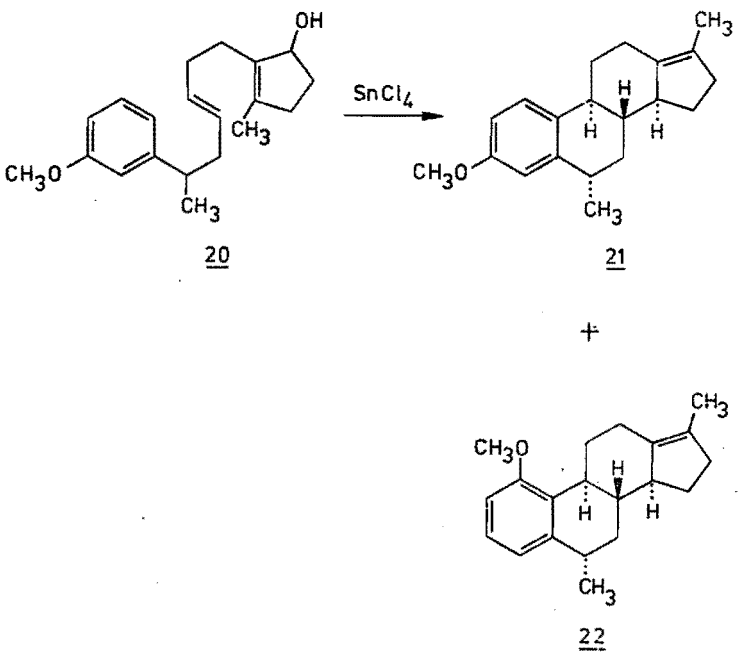
Compound	C-6	C-7	C-8	C-9
18 (R=H)[b]	26.29	29.29	42.48	49.76
18b	33.22	39.22	42.70	50.33
18c	48.72	33.45	42.35	50.05

[a]Values in ppm downfield from Me_4Si; [b]The values of this compound were obtained from ref. 15.

A similar effect amounts to 6.3 ppm in methyl substituted cyclohexanes, where the axial position of a methyl substituent has been firmly established[17]. This effect is not observed. It was concluded therefore, that the compounds formed had R in the α-position. The small downfield shift of C-9 is also in accordance with the α-position of R.

Recently, *Groen* and *Zeelen*[18] reported their results on the conversion of the anisole analogue 20 to the oestrone deri-

vatives 21 and 22 as is outlined in figure 2.6. The cyclization proceeded with 90% asymmetric induction, also in favour of the 6α-products. Here the α-configuration of the C-6 methyl group could be firmly established by comparison of the physical properties of the products with natural derived material.



20 21 22

Figure 2.6 Asymmetrically induced cyclization of an anisole derivative

II.4 *Precoiling as model description for the cyclization*

The fact that the *t*-butyl group effectuates a total asymmetric synthesis is, considering its bulkiness, not very surprising. However, the 97% specificity induced by a relatively small methyl substituent far from the cyclization initiator is striking. These results imply a concerted path-

way[19], starting from the allylic cation *via* a distinct product-like transition state in which the nonbonded interactions between the alkyl group at pro-C-6 and the hydrogen atoms at pro-C-8 and pro-C-10 favour the α-isomer. Apparently the initially formed ion pair of the allylic cation, resulting from heterolysis of the allylic-O bond, manifests itself *via* a conformational equilibrium, in which the precoiled conformer, given in chart 2.1 (illustrated for methyl at pro-C-6 in pro-α-position) is the most favourable one. This conformer leads to the thermodynamically most stable tetracyclic product.

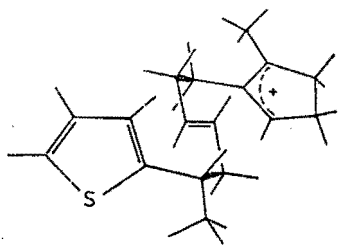


Chart 2.1 Precoiling, minimizing the 1,3-diaxial interactions

The proposed precoiled structure is also based on the following: cyclization of an achiral cation leads to a pure *trans-anti* fused tetracycle. The stereochemical outcome is the result of initiation of the stereospecific process by equal amounts of backside and frontside attachments of the double bond to the allylic cation. A substituent R (R≠H) will inequalize these processes by its sterical influence. However, model studies showed that R *cannot* interact with the pro-D ring before cyclization, but only with the protons attached to pro-C-8 and pro-C-10. These interactions must be present already from the beginning before cyclization in such a way

that one of the attachments of the double bond is selected.

The asymmetric induction in the cyclization process is brought about in the C-D ring closure. Once the C-D closure has taken place, the configuration of R is irreversibly embedded. If all possible C-D ring closures would take place, only half the B-C ring closures can result in the obtained high stereospecificities. A lowered yield of desired product is obtained and as a consequence the process cannot be called asymmetrically induced. This might well explain the importance of agreement in yields upon cyclization of the chiral and achiral cations.

II.5 *Experimental*

General remarks

The ^{1}H NMR data were obtained on a Varian EM 360A spectrometer using TMS as internal standard (δ=0.00). The ^{13}C NMR data were recorded on a Varian HA 100 equipped with a Digilab FTS-NMR-3. Microanalyses were carried out in our laboratories by Messrs. P. van den Bosch and H. Eding. HPLC and GC analyses were carried out by Messrs. G.J. Bezemer and Ir. W.J.J. Leunissen; the GC-MS spectra were recorded by Dr. P.A. Leclercq, J.A. Bakker, Ir. A. de Jong, and G.J. Scherpenzeel. 2-Acetylthiophene (9b)[8] and pivaloylthiophene (9c)[9] were prepared according to the literature.

► 2-Thienyldideuteriomethanol (8)
To 1.4 g of $LiAlD_4$ in 50 mL of ether 7.5 g (53 mmol) of 2-thiophenecarboxylic acid methyl ester was added dropwise at 0^{o} C. After 2 h refluxing 1 N NaOH was added. Filtering and extracting with ether, followed by distillation yielded 6 g of 8 (100%), bp 96-98 ^{o}C (12 mm); NMR (CCl_4) δ 4.53 (s,1,OH), 6.69-7.18 (m,3,ThH).

► 2'-Thienyl-1-deuteriocarbaldehyde (9a)
A solution of 4 g (35 mmol) of 8 in 25 mL of dichloromethane was rapidly added to a suspension of 11.4 g (53 mmol) of pyridinium chlorochromate[7] in 50 mL of dichloromethane at room temperature. After 3 h of stirring no alcohol could be monitored by TLC. A fivefold excess of ether was added and the partially concentrated solution filtered over Florisil. Distillation afforded 3.7 g of aldehyde 9a (94%): bp 67-68 (13 mm); NMR (CCl_4) δ 7.00-7.67 (m,3,ThH).

► 3-(2-Thienyl)-3-deuterioprop-2-enoic acid ethyl ester (10a)
To a solution of 3 g (100 mmol) of sodium hydride (80 wt % in paraffin) in 100 mL of dimethoxyethane (under a nitrogen atmosphere) was added below 20 °C 21.2 g (100 mmol) of triethyl phosphonoacetate. After the solution was stirred for 1 h 11.3 g (100 mmol) of aldehyde 9a was added and refluxed for 16 h. The mixture was poured into water and the product extracted into ether. After the combined ether layers were dried with $MgSO_4$, the solvent was stripped off. Distillation gave 14.5 g of 10a (79%), bp 155-159 °C (25 mm); NMR (CCl_4) δ 1.21 (t,3,CH_3), 4.18 (q,2,CH_2), 6.17 (s,1,CH), 6.17-7.38 (m,3,ThH).

► 3-(2-Thienyl)but-2-enoic acid ethyl ester (10b)
Prepared as for 10a (61%). This product was obtained as a mixture of Z- and E-isomers (Z/E ∿ 3/10), bp 147-154 °C (14 mm); NMR (CCl_4) δ 1.06-1.50 (2t,3,CH_2CH_3), 2.25-2.54 (m,3,C=CCH_3), 3.84-4.39 (2q,2,CH_2CH_3), 5.73 and 6.12 (m,1,C=CCH), 6.76-7.66 (m,3,ThH).

► 3-(2-Thienyl)-4,4-dimethylpent-2-enoic acid ethyl ester (10c)
This compound was prepared analogous to 10a. Only the E-isomer was obtained, bp 99-103 °C (0.25 mm), yield: 60%; NMR (CCl_4) δ 0.99 (t,3,CH_2CH_3), 1.12 (s,9,$C(CH_3)_3$), 3.86 (q,2,CH_2CH_3), 5.99 (s,1,CH), 6.54-7.20 (m,3,ThH).

► 3-(2-Thienyl)-3-deuteriopropanoic acid ethyl ester (11a)
A mixture of 10 g of 10a (54.6 mmol) was hydrogenated at 50 psi in 75 mL of ethanol with 3 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 8.5 g (84%) of 9a: bp 102 °C (9 mm); NMR (CCl_4) δ 1.21 (t,3,CH_3), 2.48-3.17 (m,3,$CDHCH_2$), 4.03 (q,2,CH_2CH_3), 6.70-7.11 (m,3,ThH).

► 3-(2-Thienyl)-butanoic acid ethyl ester (11b)
Prepared as for 11a (89%), bp 123 °C (12 mm); NMR (CCl_4) δ 1.13 (t,3,CH_2CH_3), 1.31 (d,3,CH_3), 2.15-2.85 (m,2,CH_2CHCH_3), 3.15-3.70 (m,1,CH), 3.96 (q,2,CH_2CH_3), 6.55-7.05 (m,3,ThH).

► 3-(2-Thienyl)-4,4-dimethylpentanoic acid ethyl ester (11c)
Analogous to 11a, yield 75%, bp 79-80 °C (0.25 mm); NMR (CCl_4) δ 1.00 (t,3,CH_2CH_3), 0.95 (s,9,$C(CH_3)_3$), 2.48-2.65 (m,2, CH_2CO_2), 3.12-3.38 (m,1,$CHCH_2$), 3.88 (q,2,CH_2CH_3), 6.63-7.04 (m,3,ThH).

► 3-(2-Thienyl)-3-deuteriopropanol (12a)
A solution of 3.7 g (20 mmol) of 11a in 10 mL of ether was added dropwise to a solution of 20 mmol (0.76 g) of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing, 1 N sodium hydroxide was added. Filtering, drying and distillation yielded 2.30 g (80%) of 12a: bp 85 °C (4 mm); NMR (CCl_4) δ 1.77 (q,2,CH_2CH_2OH), 1.72 (t,1,CDH), 3.50 (t,2,CH_2OH), 4.80 (s,1,OH), 6.68-6.90 (m,3, ThH).

► 3-(2-Thienyl)butanol (12b)
Prepared as for 12a (90%), bp 121 °C (12 mm); NMR (CCl_4) δ 1.23 (d,3,$CHCH_3$), 1.72 (m,2,$C\underline{H}_2CH_2OH$), 2.80-3.50 (m,1,$CHCH_3$), 3.43 (t,2,CH_2OH), 3.96 (s,1,OH), 6.70-7.10 (m,3,ThH).

► 3-(2-Thienyl)-4,4-dimethylpentanol (12c)
Analogous to 12a (99%), bp 82-85 °C (0.01 mm); NMR (CCl_4) δ 0.88 (s,9,$C(CH_3)_3$), 1.50-2.08 (m,2,$C\underline{H}_2CH_2OH$), 2.61-2.87 (m,1, CH), 3.28 (s,1,OH), 3.18-3.42 (m,2,CH_2OH), 6.60-7.03 (m,3, ThH).

► 3-(2-Thienyl)-3-deuteriopropanal (13a)
This compound was prepared analogous to 9a: yield 95%; bp 60 °C (0.8 mm).

► 3-(2-Thienyl)butanal (13b)
Prepared as for 9a (91%), bp 104 °C (13 mm); NMR (CCl_4) δ 1.33 (d,3,$CHCH_3$), 2.20-3.05 (m,2,CH_2CHO), 3.20-3.87 (m,1, $CHCH_3$), 6.42-7.06 (m,3,ThH), 9.49 (t,1,CHO).

► 3-(2-Thienyl)-4,4-dimethylpentanal (13c)
Prepared as for 9a (67%), bp 84 °C (0.03 mm); NMR (CCl_4) δ 0.88 (s,9,$C(CH_3)_3$), 2.58-2.70 (m,2,CH_2CHO), 3.17-3.40 (m,1, $C\underline{H}CH_2CHO$), 6.69-7.05 (m,3,ThH), 9.39 (t,1,CHO).

► 2.5-Bis(ethylenedioxy)-12-(2-thienyl)-12-deuterio-(E)-dodec-9-ene (15a)
To 20.23 g (32 mmol) of phosphonium salt 14[11] in 75 mL of tetrahydrofuran (THF) 16 mL of phenyllithium (2 N solution) was added at 0 °C under a nitrogen atmosphere. At -70 °C 5.0 g (32 mmol) of 13a in 5 mL of THF was added, followed by a second equivalent of phenyllithium. The mixture was maintained between -30 and -50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 4.7 g (40%) of 15a. NMR (CCl_4) δ 1.23 (s,3,

diox CH_3), 1.65 (s,4,$O_2CC\underline{H}_2C\underline{H}_2CO_2$), 3.79 (s,8,4 OCH_2), 5.20-5.50 (m,2,C<u>H</u>=C<u>H</u>), 6.61-7.04 (m,3,ThH).

► 2,5-Bis(ethylenedioxy)-12-(2-thienyl)-(<u>E</u>)-tridec-9-ene (<u>15b</u>)
Analogous to <u>15a</u>; NMR (CCl_4) δ 1.23 (s,3,diox CH_3), 1.27 (d,3, $CHCH_3$), 1.62 (2,4,$O_2C\underline{H}_2C\underline{H}_2CO_2$), 2.67-3.27 (m,1,$CHCH_3$), 3.88 (s,8,4 OCH_2), 5.10-5.47 (m,2,C<u>H</u>=C<u>H</u>), 6.54-7.45 (m,3,ThH).

► 2,5-Bis(ethylenedioxy)-13,13-dimethyl-12-(2-thienyl)-(<u>E</u>)-tetradec-9-ene (<u>15c</u>)
Analogous to <u>15a</u> (41%); NMR (CCl_4) δ 0.92 (s,9,$C(CH_3)_3$), 1.23 (s,3,diox CH_3), 1.61 (s,4,$O_2C\underline{H}_2C\underline{H}_2CO_2$), 1.61-2.75 (m,9,aliphatic H), 3.79 (s,8,4 OCH_2), 5.00-5.37 (m,2,C<u>H</u>=C<u>H</u>), 6.60-7.18 (m,3,ThH).

► 2-[6-(2-Thienyl)-6-deuterio-(<u>E</u>)-hex-3-enyl]-3-methylcyclopent-2-enone (<u>16a</u>)
A mixture of 2.75 g (7.5 mmol) of diketal <u>15a</u>, 30 mL of 0.5 N HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere during 1.5 h, whereupon the solution was rendered alkaline with 1 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane, chromatography yielded 1.7 g (88%) of pure product <u>16a</u>; NMR (CCl_4) δ 1.30-2.52 (m,13, aliphatic H), 2.52-3.04 (m,1,CDH), 5.20-5.47 (m,2,C<u>H</u>=C<u>H</u>), 6.45-7.20 (m,3,ThH). Anal. Calcd for $C_{16}H_{19}DOS$: C, 73.51; H, 8.10. Found: C, 73.45; H, 7.82.

► 2-[6-(2-Thienyl)-(<u>E</u>)-hept-3-enyl]-3-methylcyclopent-2-enone (<u>16b</u>)
Prepared as for <u>16a</u> (86%), bp 142-143 °C (0.01 mm); NMR (CCl_4) δ 1.25 (d,3,$CHCH_3$), 1.50-2.57 (m,13,aliphatic H), 2.57-3.26 (m,1,$CHCH_3$), 4.97-5.40 (m,2,C<u>H</u>=C<u>H</u>), 6.45-7.20 (m,3,ThH). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.09. Found: C, 74.51; H, 8.15.

► 2-[7,7-Dimethyl-6-(2-thienyl)-(E)-oct-3-enyl]-3-methyl-cyclopent-2-enone (16c)

Prepared as for 16a (70%), bp 156-157 °C (0.01 mm); NMR (CCl_4) δ 0.90 (s,9,$C(CH_3)_3$), 1.89 (s,3,cyclopent.CH_3), 1.98-2.67 (m,11,aliphatic H), 5.00-5.22 (m,2,CH=CH), 6.58-7.05 (m,3,ThH). Anal. Calcd for $C_{20}H_{28}OS$: C, 75.90; H, 8.92. Found: C, 75.70; H, 8.15.

► 2-[6-(2-Thienyl)-6-deuterio-(E)-hex-3-enyl]-3-methylcyclopent-2-enol (17a)

► 2-[6-(2-Thienyl)-(E)-hept-3-enyl]-3-methylcyclopent-2-enol (17b)

► 2-[7,7-Dimethyl-6-(2-thienyl)-(E)-oct-3-enyl]-3-methyl-cyclopent-2-enol (17c)

At -30 °C 2 mmol of $LiAlH_4$ was added in small portions to a solution of 2.0 mmol of unsaturated ketone 16a, 16b or 16c in 5 mL of ether. After 1 h 0.5 N sodium hydroxide was added. The mixture was filtered, dried and concentrated at low temperature. Due to their susceptibility to dehydration, the cyclopentenols were used immediately for the cyclization experiments.

► 6-Deuterio-17-methyl-3-thia-4-noroestra-1,5 (10), 13 (17)-triene (18a, 19a)

To a solution of 500 mg of unsaturated alcohol 17a in 10 mL of dichloromethane at -95 °C, 1.2 equivalents of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product extracted with dichloromethane. Chromatography yielded 230 mg of product (50%). Anal. Calcd for $C_{16}H_{19}DS$: C, 78.31; H, 8.62. Found: C, 78.47; H, 8.67. NMR (CCl_4) δ 1.60 (s,3,CH_3), 1.80-2.65 (m,14, aliphatic H), 6.66-6.95 (AB,2,ThH). The ^1H NMR showed that the mixture consisted of an equal amount of 11α and 11β epimers.

► 6α,17-Dimethyl-3-thia-4-noroestra-1,5 (10), 13 (17)-triene (18b)

Analogous to 18a (50%). Anal. Calcd for $C_{17}H_{22}S$: C, 69.01;

H, 8.58. Found: C, 78.86; H, 8.48; NMR (CCl_4) δ 1.27 (d,3, $CHCH_3$), 1.60 (s,3,C=CCH_3), 1.00-3.30 (m,14,aliphatic H), 6.66-6.95 (AB,2,ThH). HPLC analysis showed this product to be 97% diastereomeric pure.

► 6α-t-Butyl-17-methyl-3-thia-4-noroestra-1,5 (10), 13 (17)-triene (19c)

Prepared as for 18a. Yield: 50%. Anal. Calcd for $C_{20}H_{28}S$: C, 79.94; H, 9.39. Found: C, 80.07; H, 9.60; NMR (CCl_4) δ 1.00 (s,9,$C(CH_3)_3$), 1.58 (s,3,C=CCH_3), 1.80-2.90 (m,14, aliphatic H), 6.70-6.95 (AB,2,ThH). This product was diastereomeric free.

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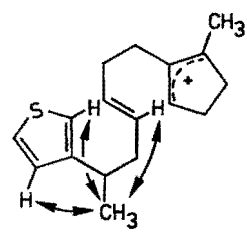
Chapter III

The influence on the cyclization of chiral interactions with the reaction terminator[1]

III.1 *Introduction*

In section II.4 the chiral influence on the cyclization of pro-C-6 substituted olefins is described. In case of a methyl substituent an asymmetric induction of 97% was found in favour of the 6α-isomer. Two pre-cyclization 1,3-diaxial interactions between the pro-C-6 substituent and the pro-C-8 and -10 protons in the precoiled conformer were responsible for the highly stereospecific cyclization. To obtain more insight in the ring closure process, particularly in the influence of the interaction with the aromatic proton, the acid-promoted cyclization of the 3-thienyl analogue 1 was studied. In figure 3.1 the 1,3-interactions appearing in this molecule are indicated. Comparison with the 2-thienyl analogue shows



1

Figure 3.1 1,3-Diaxial interactions in the pro-C-6 substituted 3-thienyl derivative

that there exists in 1 an extra interaction with the C-4 proton of thiophene.

III.2 *Synthesis and cyclization results of the 3-thienyl substituted precursor*

The preparation of the cyclization precursor 12 is depicted in figure 3.2. As stated in section II.2, the alkylthiophenes are best accessible *via* acylation. The chiral 3-alkylthiophene 12 thus had to be prepared *via* acylated 4. Since direct acetylation of thiophene with a Lewis acid occurs exclusively and almost quantitatively at the 2-position[2], the route 2 → 4 was chosen. Thus, 3-thienyllithium, prepared from 3-bromothiophene 2 and butyllithium, was allowed to react with acetaldehyde giving hydroxycompound 3. Subsequent oxidation with lead tetraacetate in pyridine afforded 3-acetylthiophene 4 in excellent yield, which was then converted into the cyclization precursor 12 as the 2-thienylanalogue, described in section II.2. Again the E-configuration of alkene 10, obtained on Wittig-Schlosser condensation, was confirmed by ^{13}C NMR spectroscopy.

On cyclization of 12 and the usual work-up of the reaction mixture, an analytical pure mixture of steroids was obtained. The ^{1}H NMR and ^{13}C NMR data revealed approximately 70% of the mixture to consist of a compound in which the ring closure had occurred at the most reactive 2-position of thiophene leading to 13 (see figure 3.3). The proton spectrum showed the expected AB pattern around 6.75 ppm and the ^{13}C NMR spectrum showed the normal aromatic pattern for a 2,3-annellated thiophene derivative. The chemical shift differences of C-8 and C-9 with the C-6 unsubstituted analogue demonstrated clearly an α-configuration of the 6-methyl substituent. For the remaining 30% of the mixture a singlet at 6.70 ppm was found in the proton spectrum. This corresponds to a structure in which the ring closure has taken place at the 4-position of thiophene. The ^{13}C chemical shift values, as tabulated in table III.1, also agree with structure 14. The configuration

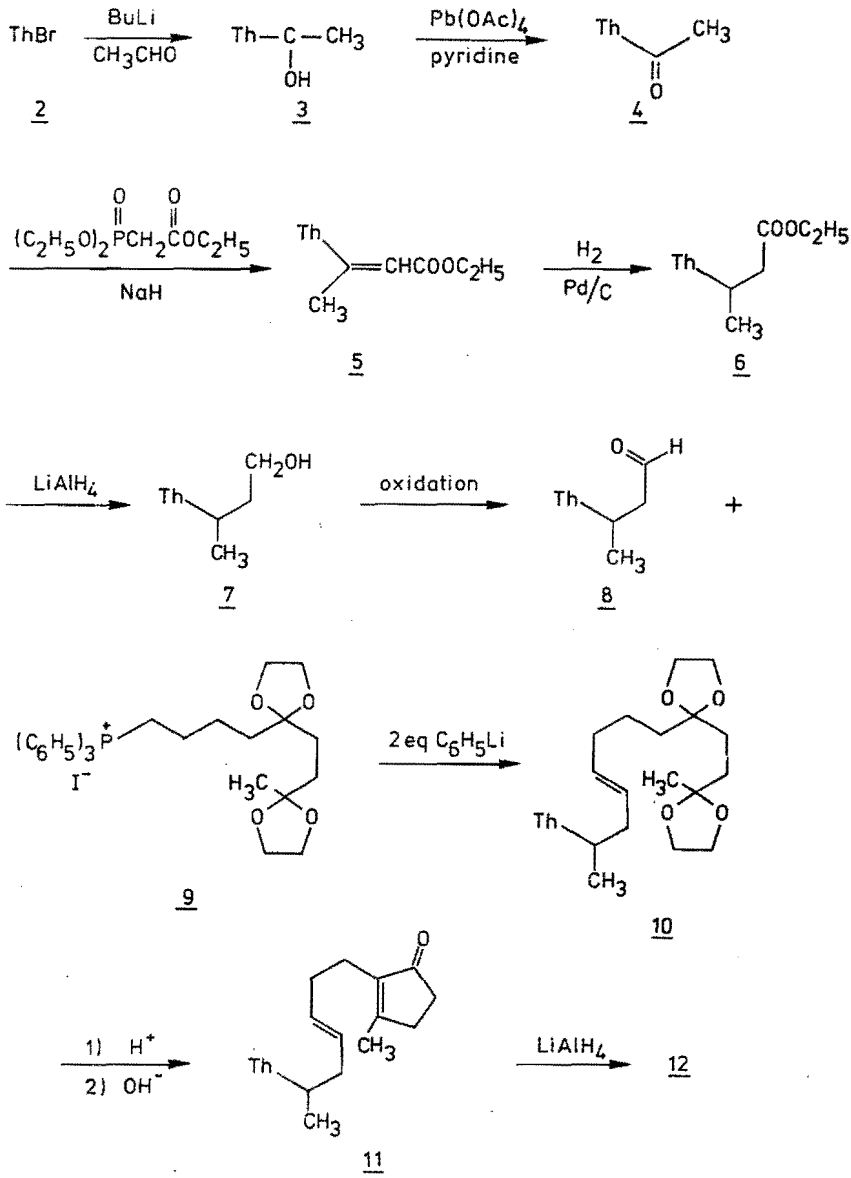


Figure 3.2 The synthesis of the chiral cyclization precursor. Th=3-thienyl

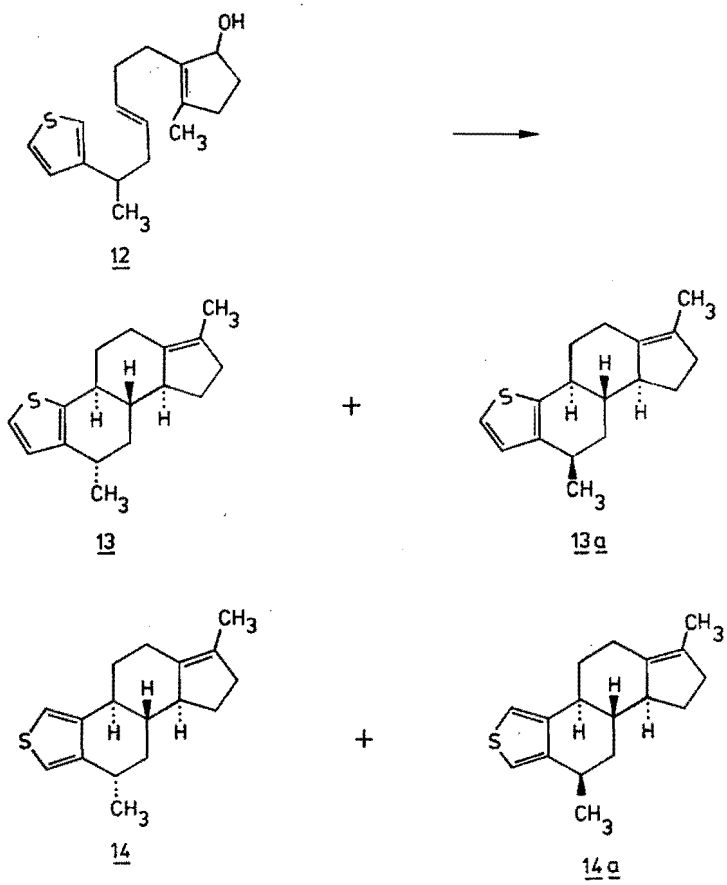


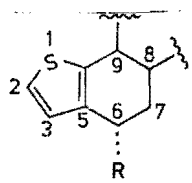
Figure 3.3 Ring closure of the chiral 3-thienyl derivative

of the 6-methyl group in 14 could not be determined. However, the similarities of asymmetric induction suggest a pseudo-equatorial α-configuration. Analytical HPLC, GC and GC-MS pointed out that the mixture consisted in fact of two main- and two by-products, all with the correct mass (M^+: 258) for structure 13 and/or 14. The mass spectra of each component showed a two by two specific fragmentation pattern, indicating

a structural relationship of each minor fraction to one of the main products. The amount of the diastereomers 13a and 14a (3%), probably the C-6 epimers, was determined by GC.

In summary then it can be stated that the cyclization of 12 leads to C-6α substituted 13 (70%) and 14 (30%), each with 97% asymmetric induction.

Table III.1 The ^{13}C NMR chemical shifts of the obtained steroids[a]



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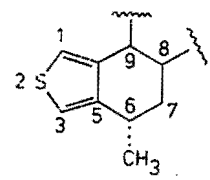

14

Compd	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10
13 (R=H)[b]		122.63	128.16	135.25	26.78	28.89	42.52	50.42	141.16
13		122.73	126.73	141.16	32.28	38.91	42.83	50.68	140.63
14	119.20		118.40	142.97	33.22	39.10	43.27	49.98	144.38

[a]Values in ppm downfield from Me_4Si; [b]The values of this compound are obtained from ref. 3.

III.3 *Discussion*

The formation of 14 represents an unusual mode of cyclization in the thiophene series. Cyclization of 3-thienyl compounds, possessing a substituent at the carbon atom next to the ring are not known. In figure 3.4 some cyclizations of 3-substituted thiophene derivatives are reflected. On

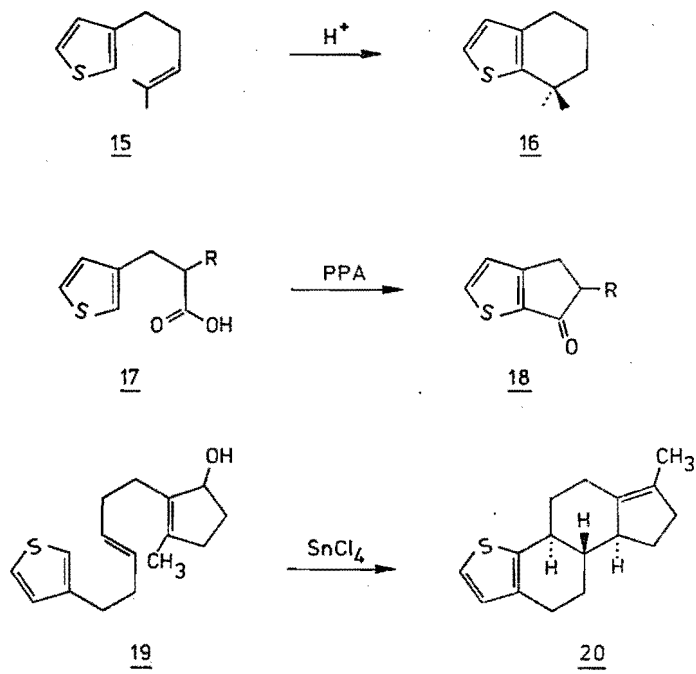

Figure 3.4 Examples of the cyclization of 3-thienyl derivatives, proceeding to the 2-position of thiophene exclusively

conversion of 15[4], 17[5], and 19[4,6] only the 2,3-annellated compounds 16, 18, and 20, respectively, were formed in good yields. The last reaction 19 → 20 proceeded under comparable conditions and with the same yield as for 12 → 13+14. Moreover, it is well-known that the 4-position of 3-alkyl thiophenes is the least reactive one towards electrophilic substitution reactions[7]. Substitution of the 4-position has never been found. All this clearly demonstrates how the 1,3-interactions in 12 influence the cyclization. It means that the rotation as given in figure 3.5 must be strongly hindered or even stopped.

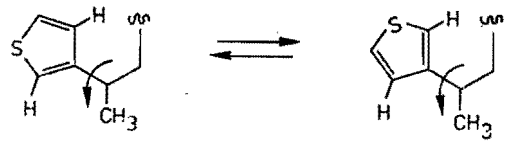

Figure 3.5 The sterically hindered rotation

A similar reaction procedure is outlined recently by *Groen* and *Zeelen*[8]. Upon reacting 21 (R=H), the compounds 22 and 23 are formed in a ratio of about 3:1, respectively (see figure 3.6). However, a pro-C-6 methyl substituent ($R=CH_3$)

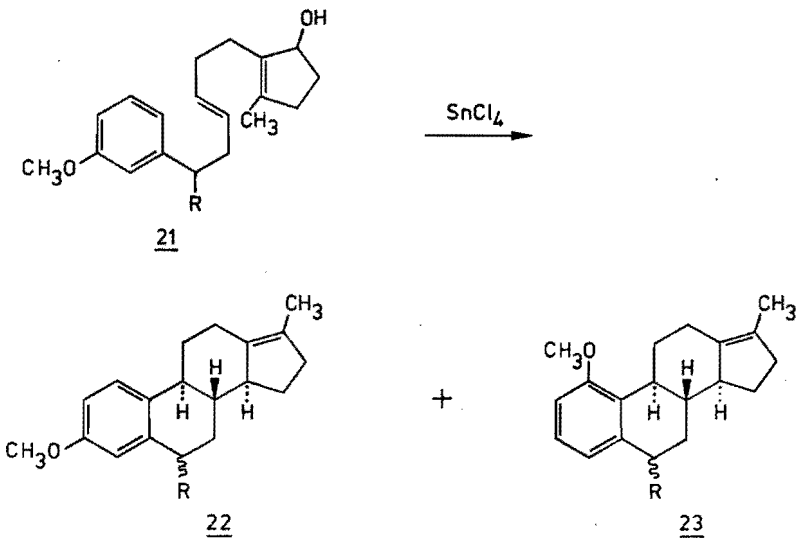

Figure 3.6 The preparation of 6-substituted oestrone analogues *via* an asymmetrically induced ring closure

altered the ratio in the advantage of 22 (22/23 ~ 5). A chemical explanation also for this case is not obvious. It is evident, with respect to the analogy with the thiophene system described, that a hindered rotation of the anisole ring during the reaction must be one of the causes, the more so as the last ratio seemed to be temperature dependent.

III.4 *Experimental*

► 1-(3-Thienyl)ethanol (3)
To a solution of 20 g (123 mmol) of 3-bromothiophene in 150 mL of ether at -78 °C, 80.9 mL of butyllithium (15% in hexane) in 50 mL of ether was added dropwise. After 1 h 20 mL (350 mmol) of acetaldehyde in 100 mL of ether was added. After 4 h stirring at -78 °C, the mixture was poured into water and the product extracted into ether. The combined ether layers were dried with $MgSO_4$ and concentrated. The alcohol was oxidized to 3-acetylthiophene immediately; NMR (CCl_4) δ 1.27 (d,3,CH_3), 3.72 (s,1,OH), 4.70-5.00 (m,1,$CHCH_3$), 6.76-7.22 (m,3,ThH).

► 3-Acetylthiophene (4)
To a solution of 4.8 g (38 mmol) of 3 in 100 mL of pyridine, 20 g of lead tetraacetate was added in small portions at such a rate that the temperature did not exceed 35 °C. After 60 h the mixture was poured into a solution of 150 g of K_2CO_3 in 800 mL of water and the product extracted into benzene. Chromatography yielded 4.6 g of 4 (95%), mp 57.0-57.8 °C; NMR (CCl_4) δ 2.39 (s,3,CH_3), 6.90-8.03 (m,3,ThH).

► 3-(3-Thienyl)but-2-enoic acid ethyl ester (5)
To a solution of 0.315 g (10.5 mmol) of sodium hydride (80% in paraffin) in 2 mL of benzene (under a nitrogen atmosphere) was added 2.35 g (11 mmol) of triethyl phosphonoacetate at a temperature below 20 °C. After the solution was stirred for 1 h 1.32 g (10.5 mmol) of 3-acetylthiophene was added and refluxed for 60 h. The mixture was poured into water and the product extracted into ether. After the combined ether layers

were dried with $MgSO_4$, the solvent was stripped off. The product (1.9 g) was obtained as a mixture of Z- and E-isomers (Z/E ∿ 3/7); yield 92%; NMR (CCl_4) δ 1.02-1.43 (2t,3,CH_3), 2.13-2.52 (m,3,C=CCH_3), 3.80-4.40 (2q,2,CH_2), 5.70 and 6.07 (m,1,CH), 7.02-7.40 (m,3,ThH).

► 3-(3-Thienyl)butanoic acid ethyl ester (6)
A mixture of 3.3 g of 5 (16.8 mmol) was hydrogenated in 125 mL of ethanol with 3 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 2.96 g (89%) of 6: bp 125 °C (18 mm); NMR (CCl_4) δ 1.15 (t,3,CH_3), 1.27 (d,3,$CHCH_3$), 2.35-2.55 (m,2,$CHCH_2$), 3.03-3.63 (m,1,CH), 3.98 (q,2,CH_2CH_3), 6.70-7.18 (m,3,ThH).

► 3-(3-Thienyl)butanol (7)
A solution of 2.96 g (149 mmol) of 6 in 10 mL of ether was added dropwise to a suspension of 150 mmol of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing, 1 N sodium hydroxide was added. Filtering, drying and distillation yielded 2.09 g (90%) of 7: bp 126-129 °C (15 mm); NMR (CCl_4) δ 1.20 (d,3,$CHCH_3$), 1.51-1.91 (m,2,CH_2CH_2OH), 2.63-3.17 (m,1,$CHCH_3$), 3.40 (t,2,CH_2OH), 3.95 (s,1,OH), 6.72-7.18 (m,3,ThH).

► 3-(3-Thienyl)butanal (8)
A solution of 1.26 g (8.1 mmol) of 7 in 10 mL of dichloromethane was added rapidly to a suspension of 2.60 g (12.1 mmol) of pyridinium chlorochromate in 10 mL of dichloromethane at room temperature. After 3 h no alcohol could be monitored. A fivefold excess of ether was added and the solution filtered over Florisil. Distillation afforded 1.12 g of aldehyde 8: bp 112 (16 mm).

► 2,5-Bis(ethylenedioxy)-12-(3-thienyl)-(E)-tridec-9-ene (10)
To 5.12 g (8.1 mmol) of phosphonium salt 9 in 75 mL of tetrahydrofuran (THF) 4.1 mL of phenyllithium (2 N solution) was

added at 0 °C under a nitrogen atmosphere. At -70 °C 8.1 mmol of 8 in 5 mL of THF was added, followed by a second equivalent of phenyllithium. The mixture was maintained between -30 and -50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 1.29 g (42%) of 10; NMR (CCl_4) δ 1.22 (d,3,$CHCH_3$), 1.23 (s,3,diox. CH_3), 1.62 (s,4,$O_2CC\underline{H}_2C\underline{H}_2CO_2$), 2.48-3.17 (m,1,$CHCH_3$), 3.88 (s,8,4 OCH_2), 5.20-5.40 (m,2,C<u>H</u>=C<u>H</u>), 6.77-7.28 (m,3,ThH).

► 2-[6-(3-Thienyl)-(E)-hept-3-enyl]-3-methylcyclopent-2-enone (11)

A mixture of 1.25 g (3.3 mmol) of diketal 10, 30 mL of 0.5 N HCl and 25 mL of ethanol was refluxed under a nitrogen atmosphere during 1.5 h, whereupon the solution was rendered alkaline with 1.3 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane, chromatography yielded 714 mg of pure product 11; yield 79%; NMR (CCl_4) δ 1.18 (d,3,$CHCH_3$), 1.67-2.52 (m,13, aliphatic H), 2.52-3.00 (m,1,$CHCH_3$), 5.12-5.37 (m,2,C<u>H</u>=C<u>H</u>), 6.72-7.17 (m,3,ThH). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.08. Found: C, 74.25; H, 8.18.

► 2-[6-(3-Thienyl)-(E)-hept-3-enyl]-3-methylcyclopent-2-enol (12)

At -30 °C 12 mmol of $LiAlH_4$ was added in small portions to a solution of 1.2 mmol of ketone 11. After 0.5 h 1 N of sodium hydroxide was added. The mixture was filtered, dried and concentrated at low temperature. Due to its susceptibility to dehydration, the cyclopentenol was used immediately for cyclization experiments.

► The cyclization of 12 to a mixture of 13 and 14

To a solution of 331 mg (1.2 mmol) of unsaturated alcohol 12 in 10 mL of dichloromethane at -59 °C, 1.2 equiv of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product extracted with

dichloromethane. Chromatography yielded 154 mg of product (50%). Anal. Calcd for $C_{17}H_{22}S$: C, 79.07; H, 8.53. Found: C, 79.42; H, 8.85. NMR (CCl_4) δ 1.00-3.00 (m,14,aliphatic H), 1.22 (d,3,$CHCH_3$), 1.60 (s,3,$C=CCH_3$), 6.60-6.90 (AB,2,ThH), 6.70 (s,2,ThH).

References and Notes

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Chapter IV

The influence of a pro-C-7 substituent on the ring closure[1]

IV.1 *Introduction*

In Chapter II the chiral influence of pro-C-6 substituted polyalkenes on the cyclization process is described. Very high stereospecificities were attained, due to small 1,3-interactions between the pro-C-6 substituent and the protons at pro-C-8 and pro-C-10 during the formation of the 6β substituted product. These steric hindrances are absent during the generation of a 6α substituted tetracycle.

It goes without saying that the character of the chiral influence on the cyclization process depends in the first place on the location of the substituent. Cyclization of a pro-C-7 methylated alkene is less obvious, as model studies show. Both the 7α and the 7β substituted tetracycles feel during their formation mutually different interactions. They are visualized in figure 4.1 in structures A and B, respectively. In A two 1,3-interactions between the methyl group and the protons at pro-C-10 and pro-C-14 occur. An appreciable steric hindrance in B between the methyl group and the pro-D ring has to be overcome before the product is formed. In order to gain more insight in the influence of each of the above mentioned interactions, the cyclization of pro-C-7 substituted alkene 10a (see figure 4.5) was studied. Moreover, the influence of an additional second chiral center at pro-C-6, with its distinct influence on the cyclization *via* 1,3-interactions, was studied on cyclizing the *threo* and *erythro* alkenes 10b and 10c, respectively (see figure 4.5).

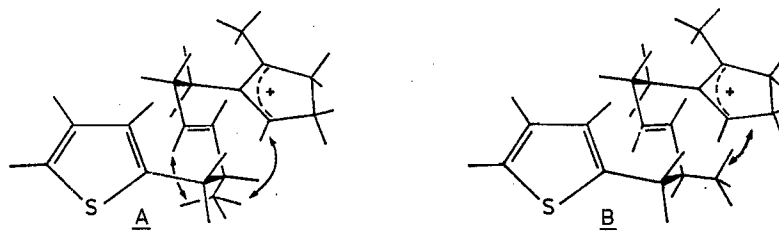


Figure 4.1 Interactions present on cyclizing the pro-C-7 methylated alkene

IV.2 *The preparation of pro-C-6 and/or pro-C-7 methyl substituted cyclization precursors*

The syntheses of the cyclization precursors 10a-c, substituted at pro-C-6 and/or pro-C-7, are given in figure 4.3. Compounds 1a and 1c were prepared on treating the corresponding thienyllithium (prepared from 2- or 3-bromothiophene and butyllithium) with N,N-dimethylformamide[2,3], whereas 1b was obtained by direct acetylation of thiophene under Friedel Crafts conditions[4]. The phosphono esters 2a,b were accessible *via* an Arbusov reaction by heating triethyl phosphite with α-bromoethyl acetate or propionate[5] (see figure 4.2). The

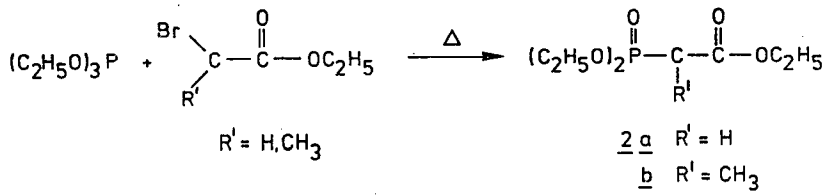


Figure 4.2 The preparation of the phosphono esters 2 *via* the Arbusov reaction

Wadsworth-Emmons condensation of 1a with phosphono ester 2a gave the unsaturated ester 3a. The isomeric esters 3b and 3c were obtained from 1b and 2b, and could be separated by spinning band distillation or even better by preparative gas chromatography (apiezon, 196 °C). The assignments of the Z- and E-configurations were established by comparing their ^{1}H-NMR chemical shift values with the corresponding phenyl analogues, reported by *Callagher* and *Webb*[6] (see Table IV.1).

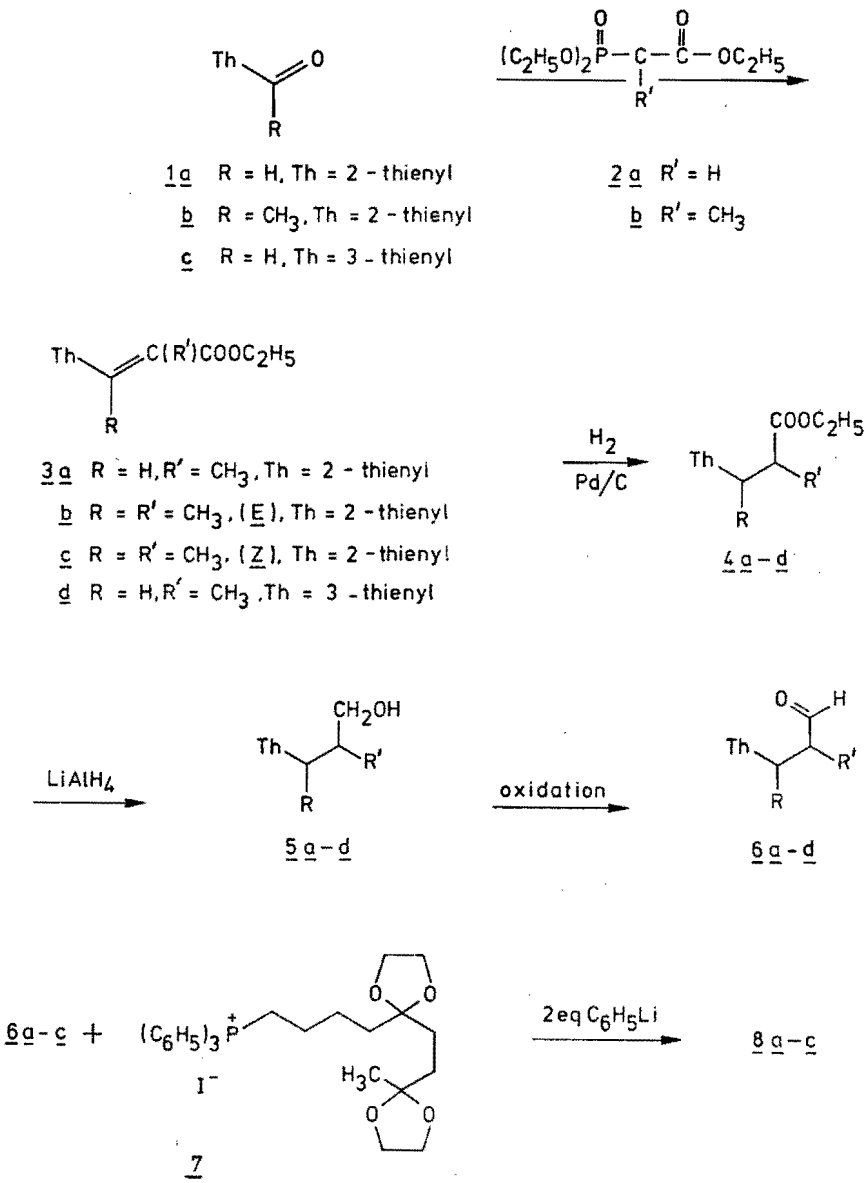


Figure 4.3 The syntheses of the pro-C-6 and or pro-C-7 methylated cyclization precursors

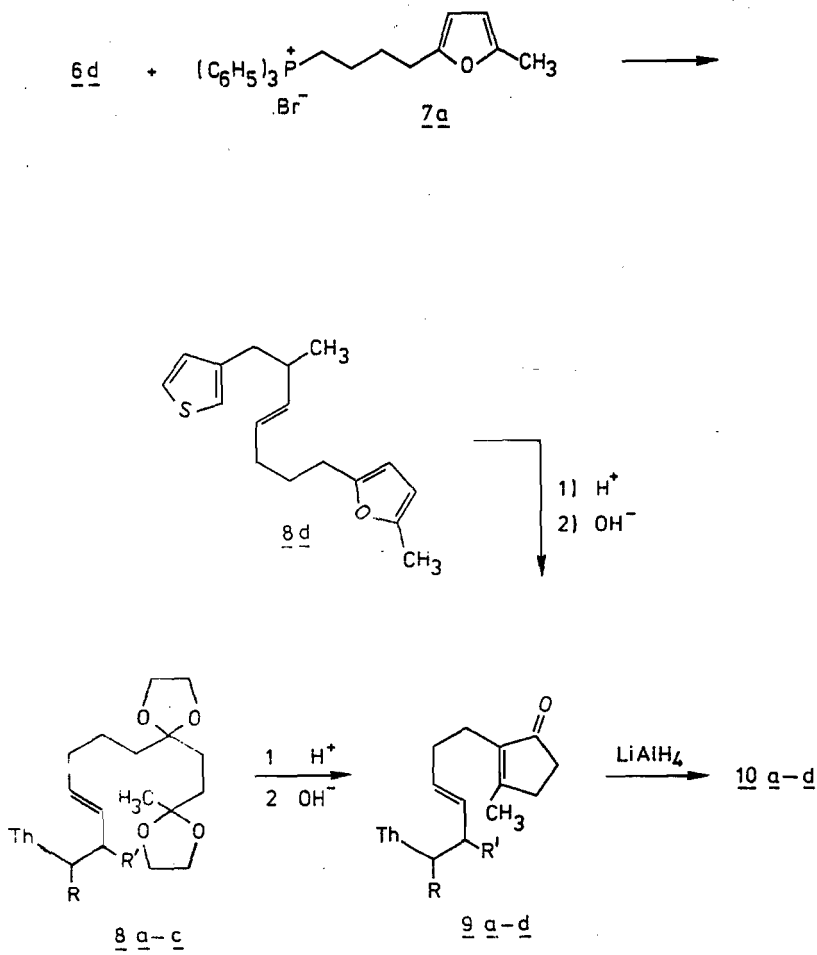


Figure 4.3 (continued)

Table IV.1 The ^1H NMR chemical shifts of 3b,c and their phenyl analogues

$$R(CH_3^a)C=C(CH_3^b)COOCH_2CH_3^c$$

	E-isomer			Z-isomer		
R	CH_3^a	CH_3^b	CH_3^c	CH_3^a	CH_3^b	CH_3^c
Phenyl	1.75	2.22	1.36	2.00	-	0.85
2-Thienyl	2.00	2.27	1.29	1.98	1.88	0.90

The different complexation behaviour of each isomer towards $Eu(fod)_3$ confirmed the assignments: the downfield shift of CH_3^a is much larger in the E-isomer than in the Z-isomer, whereas the shift of CH_3^b in each isomer is practically the same. Separate hydrogenation which is known to proceed *via syn*-addition of hydrogen gave the desired *threo* and *erythro* compounds 4b and 4c, respectively, as illustrated in figure 4.4. The reaction routes to 10a-c are analogous to the one described in Section 2.2. Thus, hydrogenation of 3a-c followed by reduction with $LiAlH_4$ and subsequent oxidation with pyridinium chlorochromate afforded 6a-c. On these aldehydes, a Wittig condensation under Schlosser conditions with phosphonium salt 7 was performed to yield the E-alkenes 8a-c. Acid treatment effected deketalization and subsequent cyclodehydration by base gave the unsaturated cyclopentenones 9a-c in good yields. The unsaturated alcohols 10a-c were formed on reduction with $LiAlH_4$ and were used immediately for the cyclization experiments. The cyclization results of 10a-c, as described in the next Section, necessitated the investigation of the ring closure of the pro-C-7 methyl substituted 3-thienyl analogue 10d. Its preparation deviates slightly

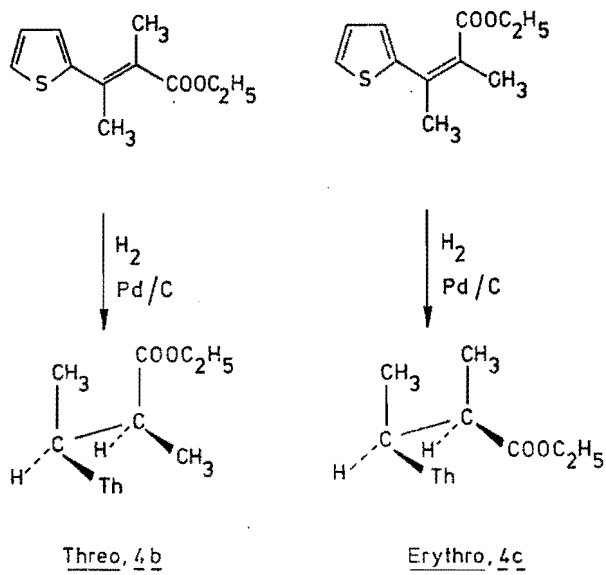


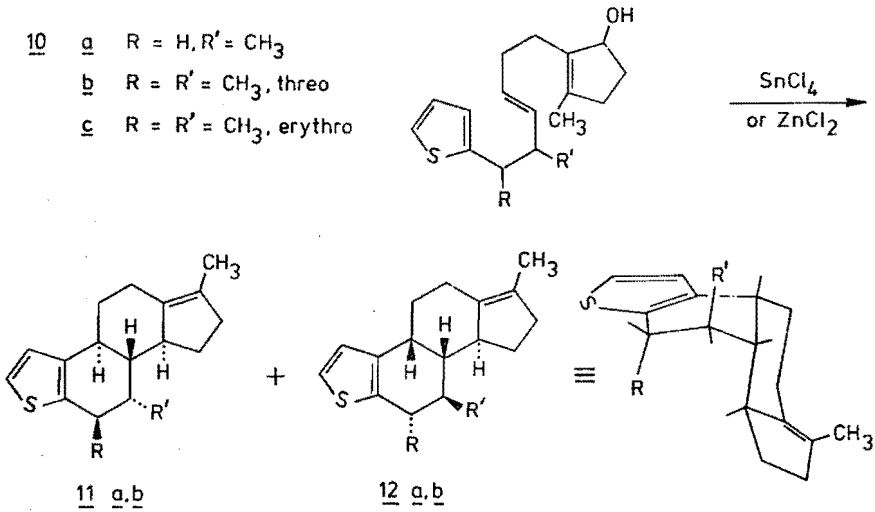
Figure 4.4 *Syn*-addition of hydrogen affording the *threo* and *erythro* esters

from the chiral cyclopentenols 10a-c. 3-Thiophenealdehyde was prepared by literature methods[3]. Its conversion to aldehyde 6d proceeded similarly to 6a-c. The Wittig-Schlosser condensation was performed with phosphonium salt 7a[7] affording 8d in good yields. Acid treatment of 8d gave the corresponding diketone (ring opening of the furanyl ring) and subsequent intramolecular cyclodehydration yielded cyclopentenone 9d in excellent yield. Although the total synthesis of 10d is shortened with two steps, the amount of Z-isomer in 9d amounted to 20%. The use of ther precursors, on the contrary, resulted in a 97% E-alkene formation[8]. Reduction of 9d with $LiAlH_4$ afforded cyclopentenol 10d.

IV.3 *The cyclization results*

The cyclizations of 10a-c were first performed at -97° C with $SnCl_4$ (in methylene chloride) as Lewis acid. A total yield of 50% was attained for 10a, but the *threo* and *erythro* precursors, 10b and 10c, respectively, failed to yield any product. The experiments were therefore repeated at higher temperatures using a milder Lewis acid ($ZnCl_2$ in nitroethane at -23° C). This time the cyclization of 10a-c amounted to 34% each. The inseparable steroid mixtures, obtained on aqueous work-up, were purified chromatographically and their compositions determined by GC-MS. The product distributions are listed in figure 4.5. Precursor 10c yielded two additional compounds, each 5%, whose structures could not be elucidated due to their small amounts. The structure determinations of 11 and 12 are based on the ^{13}C-NMR measurements. The peaks of each compound were selected by means of their relative magnitudes. One set of peaks of each mixture was found in the same general areas as those for the C-6 substituted[9] and several other unsubstituted ring systems[10]. Structure 11 was assigned to these compounds. The 7α substituent causes a downfield shift of C-1 of 0.37 ppm, comparable to 0.54 ppm in 7α-methyloestrone methyl ether. In the other set of peaks of each mixture an appreciable downfield shift of C-1 (+2 to +3 ppm) was observed, which can only be caused by the loss of a gauche 1,4- and/or the gain of a 1,5-interaction between C-1 and C-11 or C-12, respectively, in the *cis*-BC ring fused tetracycles 12. To substantiate these attributions, a number of oestrone derivatives were examined by ^{13}C-NMR[7]. The results showed that a 7β-methyl group in 7β-methyl oestrone methyl ether causes an upfield shift of C-1 of -2.61 ppm and -1.33 ppm at C-11. Substantially, a *cis*-BC ring fusion causes a downfield shift of 1.03 ppm at C-1 (see Appendix).

The structures arising from the cyclization of *erythro* 10c could not be elucidated as they polymerized rapidly as was evident from MS. The cyclization of 10d at -23 °C (with



Compound	Products	
	Reaction temp. -97 °C	Reaction temp. -23 °C
10a	90% 11a, 10% 12a	84% 11a, 16% 12a
10b	-	40% 11b, 50% 12b
10c	-	- [a]

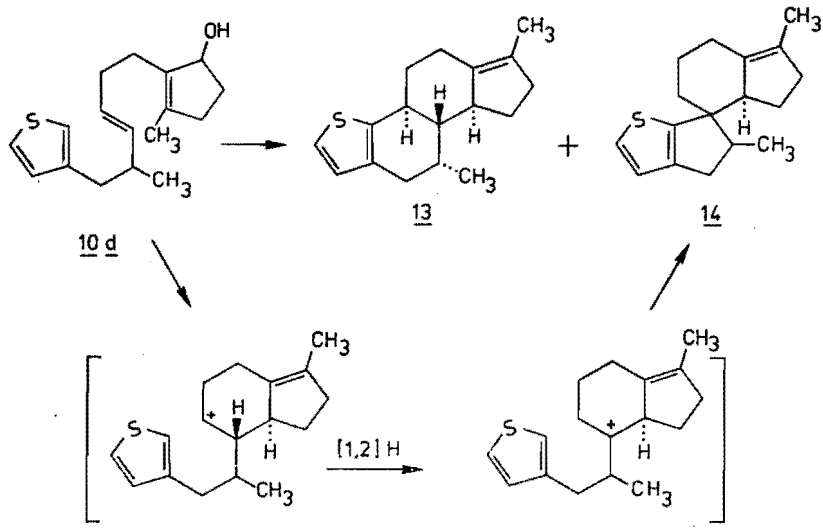


Figure 4.5 The cyclization results. [a]No structure determination was possible

$ZnCl_2$ as Lewis acid) afforded two products in a total yield of 35%. The main product (77%) could be ascribed to the 7α-substituted tetracycle 13 on basis of the ^{13}C NMR data. The structure of the by-product could not be elucidated for certain. However, most relevantly, the ^{13}C NMR data pointed out that its structure was *not* a *trans-anti* or *cis-anti* fused tetracycle. The assignment of the structure of 14 is principally based on its mass fragmentation pattern.

IV.4 *Discussion*

A decreased asymmetric induction on cyclizing 10a at higher temperature (see figure 4.5) agrees with the temperature dependence of asymmetric inductions. The degree of induction depends on the difference in transition state energy of each diastereomer which in turn is temperature dependent. The preferential formation of a 7α-substituted tetracycle indicates that the interaction of the methyl group with the pro-D-ring is more unfavourable than the 1,3-interactions.

The high amount of *cis*-fused 12b formed upon the ring closure of *threo* 10b once more emphasizes the influence of the additional 1,3-interactions that would be present on generating 11b. That the *threo* and *erythro* precursors did not cyclize at low temperatures (-97 °C) might be due to a high torsional strain, present in the pro-C-6,7 bond.

The formation of the *cis*-fused tetracycles on cyclizing E-alkenes involves an abnormal reaction sequence. Literature examination revealed only little about the formation of *cis*-fused rings upon cyclization reactions. Generally, unsubstituted E-alkenes always give *trans*-fused rings, while Z-isomers *can* provide *cis*-fused rings. Some examples of the latter are listed in figure 4.6. Formolysis of Z-sulphonate ester 15[11,12] gives the *cis* monocyclic alcohol 16 and the *cis*-2-decalols 17. *Johnson*[13] and *Goldsmith*[14] reported the cyclization of a Z-dienic acetal 18 to a mixture of the *cis*-decalones 19 and 20, obtained after a degradation and oxidation sequence. Equation (3)[15] of figure 4.6 seems to contradict

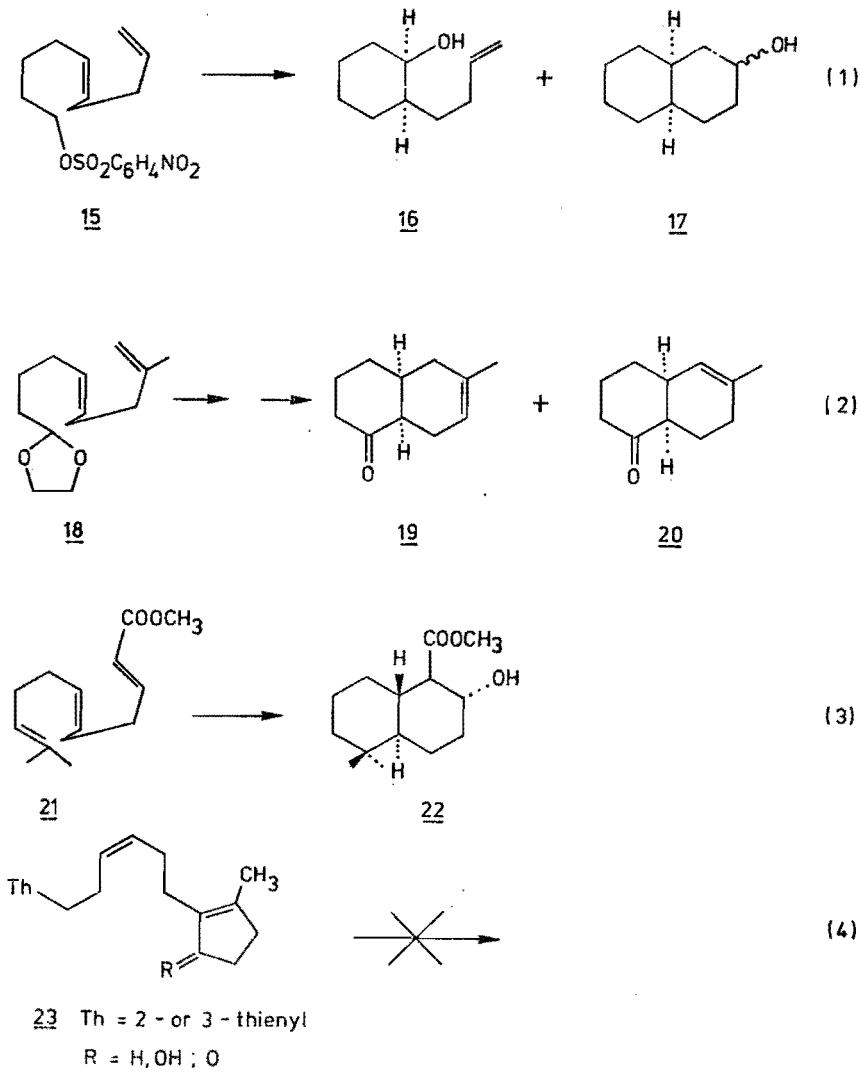


Figure 4.6 The ring closure of some *cis*-alkenes

the first two equations. However, as *Stork*[16] proved with the cyclization of the closely related farnesic acid, one can assume that the conversion 21 to 22 proceeds in two steps *via* de- and reprotonation. *The closely related "achiral" system 23, prepared by Corvers*[10], *yielded no cyclic products at all under a great variety of circumstances.* The *cis*-fused tetracycles as described above thus must be generated from the E-alkenes. Recently, *Groen* and *Zeelen*[17] published the asymmetrically induced cyclization of the pro-C-7 methyl substituted anisole analogue 24, as is illustrated in figure 4.7. The formation of *trans*-fused 25 proceeded with 100% induction, and 26 with 87.5% in favour of the 7α-isomer. The structures were unambiguously established by comparison with derivatives of authentic natural products. No *cis*-fused tetracycle has been detected. The essential difference between the thienyl and anisole derivatives is the sulphur atom in thiophene. The *cis*-fused systems thus must be formed *via* the intermediacy of sulphonium ion 27 (illustrated for the precursor of *threo* 12b).

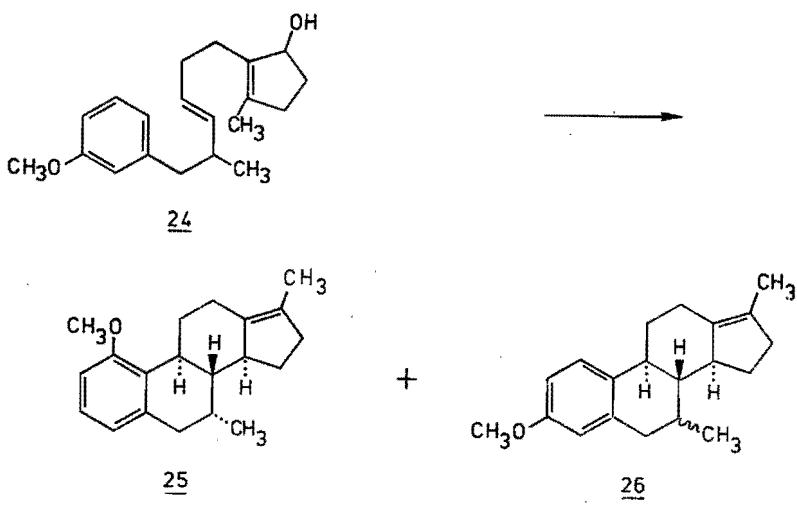
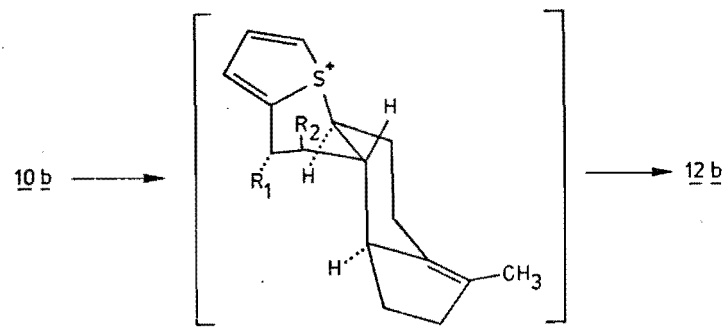


Figure 4.7 The cyclization of the pro-C-7 substituted anisole analogue

The ring closure of *i.e.* 10b to 12b can be rationalized as follows. The normal chair conformation of the pro-B ring before cyclization is hindered by the interaction between the pro-C-7β methyl group and the cyclopentenyl carbenium ion.



27

Figure 4.8 The sulphonium ion leading to the BC-*cis* fused tetracycles

This sterical hindrance is lowered when the pro-B-ring adopts a pro-boat conformation. Normal ring closure to C-3 of thiophene then is interfered with a considerable 1,4-interaction between the C-3 proton of thiophene and the pro-C-7β substituent. This interaction is absent on forming the *trans-anti* fused sulphonium ion 27. The following [1,3] alkyl shift is necessarily accompanied by inversion of pro-C-9. A final proton elimination (at C-3 of thiophene) results in *cis*-fused 12b. The *pseudo*-boat conformation of the B-ring is confirmed by the ^{1}H NMR studies on a related system: *Groen*[8] found the B-ring of 7β-substituted oestrone to adopt a *pseudo*-boat conformation.

As a proof for the existence of an intermediate sulphonium ion the ring closure of the 3-thienyl derivative 10d was studied. In this case the formation of an intermediate sulphonium ion is sterically impossible. As described in the previous Section the cyclization of 10d did indeed *not* lead

to a *cis*-BC ring-fused system. The bicyclic carbenium ion is formed, followed by a [1,2] H shift to the more stable tertiary carbenium ion and ring closure.

IV.5 *Experimental*

► E+Z 2-Methyl-3-(2-thienyl)but-2-enoic acid ethyl ester (3b,c) To a solution of 3 g (100 mmol) of sodium hydride (80% in paraffin) in 100 mL of benzene (under a nitrogen atmosphere) was added 23.8 g (100 mmol) of triethyl-α-phosphonopropionate at a temperature below 20 °C. After the solution was stirred for 1 h, 12.6 g (100 mmol) of ketone 1b was added and refluxed for 16 h. The mixture was poured into water and the products extracted into ether. After the combined ether layers were dried with $MgSO_4$ the solvent was stripped off. Distillation gave 16.8 g of 3b,c (80%; Z/E≈2/3). The Z and E isomers were separated by PGC (apiezon, 196 °C), bp 78 °C (0.02 mm). NMR (CCl_4) Z isomer (3c): δ 1.01 (t,3,CH_2CH_3), 2.00 (s,3,ThCCH$_3$), 2.10 (s,3,C(CH_3)CO_2) , 3.95 (q,2,CH_2), 6.85-7.21 (m,3,ThH); E isomer (3b): δ 1.30 (t,3,CH_2CH_3), 2.02 (s,3,ThCCH$_3$), 2.28 (s,3,C(CH_3)CO_2), 4.22 (q,2,CH_2), 6.90-7.32 (m,3,ThH).

► 2-Methyl-3-(2-thienyl)prop-2-enoic acid ethyl ester (3a) Analogous to 3b,c. Only the E isomer was obtained, yield 77%, bp 130-132 °C (6 mm); NMR (CCl_4) δ 1.34 (t,3,CH_2CH_3), 2.10 (s,3,CCH_3), 4.15 (q,2,CH_2), 6.85-7.40 (m,3,ThH), 7.70 (s,1,CH).

► 2-Methyl-3-(3-thienyl)prop-2-enoic acid ethyl ester (3d) Analogous to 3b,c. Yield 70%, bp 156-160 °C (18 mm); NMR (CCl_4) δ 1.23 (t,3,CH_2CH_3), 2.10 (m,3,CCH_3), 4.12 (q,2,CH_2), 7.00-7.50 (m,4,ThH and CH).

► *Threo* 2-methyl-3-(2-thienyl)butanoic acid ethyl ester (4b) A mixture of 5 g of 3b (23.8 mmol) was hydrogenated in 30 mL of ethanol with 1.5 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 3.53 g (70%) of 4b: 66-68 °C (0.02 mm); NMR (CCl_4) δ 1.10

(d,3,$C(CH_3)CO_2$), 1.10 (t,3,CH_2CH_3) 1.29 (d,3,$ThCCH_3$), 2.39-2.83 (m,1,$CHCO_2$), 3.18-3.63 (m,1,ThCH), 4.00 (q,2,CH_2), 6.70-7.09 (m,3,ThH).

► *Erythro* 2-methyl-3-(2-thienyl)butanoic acid ethyl ester (4c)
Prepared as for 4b, bp 70-72 °C (0.025 mm), yield 73%; NMR (CCl_4) δ 0.96 (d,3,$C(CH_3)CO_2$), 1.16 (t,3,CH_2CH_3), 1.28 (d,3, $ThCCH_3$), 2.22-2.75 (m,1,$CHCO_2$), 3.06-3.58 (m,1,ThCH), 4.11 (q,2,CH_2CH_3), 6.71-7.15 (m,3,ThH).

► 2-Methyl-3-(2-thienyl)propanoic acid ethyl ester (4a)
Prepared as for 4b, bp 106 °C (8 mm); NMR (CCl_4) δ 1.15 (d,3, $CHCH_3CO_2$), 2.20 (t,3,CH_2CH_3), 2.40-3.40 (m,3,$C\underline{H}CH_3$ and $C\underline{H}_2CH$), 4.00 (q,2,CH_2CH_3), 6.60-7.10 (m,3,ThH).

► 2-Methyl-3-(3-thienyl)propanoic acid ethyl ester (4d)
Prepared as for 4b. NMR (CCl_4) δ 0.87-1.47 (d and t,6,$2CH_3$), 2.50-3.07 (m,2,CH_2), 3.78-4.33 (m,3,OCH_2 and CH), 6.67-7.33 (m,3,ThH).

► *Threo* 2-methyl-3-(2-thienyl)butanol (5b)
A solution of 4.2 g (20 mmol) of 4b in 10 mL of ether was added dropwise to a suspension of 20 mmol (0.76 g) of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing 1 N sodium was added. Filtering, drying and distillation yielded 3.1 g (90%) of 5b: bp 122 °C (15 mm); NMR (CCl_4) δ 0.88 (d,3,$CC\underline{H}_3CH_2OH$), 1.23 (d,3, $ThCCH_3$), 1.53-2.07 (m,1,$C\underline{H}CH_2OH$), 2.85-3.65 (m,4,$ThC\underline{H}$,$C\underline{H}_2OH$), 6.57-7.13 (m,3,ThH).

► *Erythro* 2-methyl-3-(2-thienyl)butanol (5c)
Analogous to 5b, bp 122 °C (7.5 mm), yield 95%; NMR (CCl_4) δ 0.82 (d,3,$CC\underline{H}_3CH_2OH$), 1.33 (d,3,$ThCHCH_3$), 1.61-2.00 (m,1, $C\underline{H}CH_2OH$), 2.99-3.48 (m,4,$ThC\underline{H}$,$C\underline{H}_2O\underline{H}$), 6.67-7.08 (m,3,ThH).

► 2-Methyl-3-(2-thienyl)propanol (5a)
Analogous to 5b, yield 85%, bp 122-124 °C (14 mm); NMR (CCl_4) δ 0.90 (d,3,CH_3), 1.60-2.10 (m,1,$CHCH_3$), 2.30-3.20 (m,2, CH_2CH), 3.36 (d,2,CH_2OH), 3.95 (s,1,OH), 6.55-7.05 (m,3,ThH).

► 2-Methyl-3-(3-thienyl)propanol (5d)
Analogous to 5b (83%), bp 66-68 °C (0.01 mm); NMR (CCl_4) δ 0.90 (d,3,CH_3), 1.53-2.90 (m,3,CH_2CHCH_2OH), 3.37 (d,2,CH_2OH), 3.85 (s,1,OH), 6.67-7.23 (m,3,ThH).

► *Threo* 2-methyl-3-(2-thienyl)butanal (6b)
A solution of 6.4 mmol (1 g) of 5b in 6 mL of dichloromethane was rapidly added to a suspension of 9.6 mmol (2.1 g) of pyridinium chlorochromate in 12 mL of dichloromethane at room temperature. A fivefold excess of ether was added when no alcohol could be monitored by TLC. Thereafter the concentrated solution was filtered over Florisil. Distillation afforded 0.9 g of aldehyde 6b (85%).

► *Erythro* 2-methyl-3-(2-thienyl)butanal (6c)
Prepared as for 6b (87%); NMR (CCl_4) δ 0.96 (d,3,CCH_3CHO), 1.35 (d,3,$ThCCH_3$), 2.22-2.69 (m,1,$CHCHO$), 3.17-3.75 (m,1, ThCH), 6.72-7.09 (m,3,ThH), 9.58 (d,1,CHO).

► 2-Methyl-3-(2-thienyl)propanal (6a)
Prepared as for 6b (90%), bp 102 °C (18 mm); NMR (CCl_4) δ 1.04 (d,3,CH_3), 2.30-3.40 (m,3,CH and CH_2), 6.60-7.10 (m,3, ThH), 9.50 (d,1,CHO).

► 2-Methyl-3-(3-thienyl)propanal (6d)
Prepared as for 6b (50%), bp 48-50 °C (0.05 mm); NMR (CCl_4) δ 1.03 (d,3,CH_3), 1.90-3.20 (m,3,CH_2CH), 6.57-7.20 (m,3,ThH), 9.37 (d,1,CHO).

► *Threo* 2,5-Bis(ethylenedioxy)-11-methyl-12-(2-thienyl)-(E)-tridec-9-ene (8b)

Phenyllithium (16 mL, 2 N solution) was added to 32 mmol (20.23 g) of phosphonium salt 7 in 75 mL of tetrahydrofuran (THF) at 0 °C under a nitrogen atmosphere. At -70 °C 32 mmol of 6b in 5 mL of THF was added, followed by a second equivalent phenyllithium. The mixture was maintained between -30 and -50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 6.2 g (49%) of product 8b; NMR (CCl_4) δ 0.92 (d,3,CCH_3C=C), 1.35 (d,3,ThCCH_3), 1.20 (s,3,diox CH_3), 1.56 (s,4,$O_2CCH_2CH_2CO_2$), 5.00-5.35 (m,2,CH=CH), 1.10-3.20 (m,8,aliphatic H), 3.77 (s,8,4OCH_2), 6.52-7.02 (m,3,ThH).

► *Erythro* 2,5-Bis(ethylenedioxy)-11-methyl-12-(2-thienyl)-(E)-tridec-9-ene (8c)

Analogous to 8b (50%); NMR (CCl_4) δ 0.88 (d,3,$C(CH_3)C$=C), 1.45 (d,3,ThCCH_3), 1.22 (s,3,diox CH_3), 1.58 (s,4,$O_2CH_2CH_2CO_2$), 5.06-5.37 (m,2,CH=CH), 1.10-3.20 (m,8,aliphatic H), 3.77 (s,8,4OCH_2), 6.52-7.02 (m,3,ThH).

► 2,5-Bis(ethylenedioxy)-11-methyl-12-(2-thienyl)-(E)-dodec-9-ene (8a)

Analogous to 8b (40%); NMR (CCl_4) δ 0.99 (d,3,$CHCH_3$), 1.20 (s,3,diox CH_3), 1.30-2.80 (m,13, aliphatic H), 3.77 (s,8, 4OCH_2), 5.05-5.40 (m,2,CH=CH),6.50-7.00 (m,3,ThH).

► 1-(3-Thienyl)-7-(5-methyl-2-furyl)-(E)-hept-3-ene (8d)

Analogous to 8b, using phosphonium salt 7a in stead of 7. Yield: 53%. NMR (CCl_4) δ 0.96 (d,3,$CHCH_3$), 1.28 (s,3,furyl-CH_3), 1.40-2.63 (m,8,4CH_2), 5.10-5.33 (m,2,CH=CH), 5.65 (s,2, furyl H), 6.60-7.13 (m,3,ThH). The ^{13}C NMR data pointed out this compound to be contaminated with 20% Z-isomer.

► *Threo* 2-[5-methyl-6-(2-thienyl)-(E)-hept-3-enyl]-3-methyl cyclopent-2-enone (9b)

A mixture of 7.5 mmol (2.96 g) of diketal 8b, 30 mL of 0.5 N

HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere during 1.5 h, whereupon the solution was rendered alkaline with 1 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane yielded 1.95 g (90%) of pure product 9b; NMR (CCl_4) δ 0.92 (d,3,CCH_3C=C), 1.20 (d,3,ThCCH_3), 1.95 (s,3, cyclopent CH_3), 5.05-5.33 (m,2,CH=CH), 6.50-7.00 (m,3,ThH).

► *Erythro* 2-[5-methyl-6-(2-thienyl)-(E)-hept-3-enyl]-3-methylcyclopent-2-enone (9c)

Prepared as for 9b (90%); NMR (CCl_4) δ 0.82 (d,3,CCH_3C=C), 1.18 (d,3,ThCCH_3), 1.95 (s,3,cyclopent CH_3), 5.03-5.33 (m,2, CH=CH), 6.50-7.00 (m,3,ThH).

► 2-[5-Methyl-6-(2-thienyl)-(E)-hex-3-enyl]-3-methylcyclopent-2-enone (9a)

Prepared as for 9b (70%); NMR (CCl_4) δ 0.95 (d,3,$CHCH_3$), 1.90 (s,3,diox CH_3), 1.95-2.80 (m,11,aliphatic H), 5.05-5.30 (m,2, CH=CH), 6.50-7.00 (m,3,ThH).

► 2-[5-Methyl-6-(3-thienyl)-(E)-hex-3-enyl]-3-methylcyclopent-2-enone (9d)

A mixture of 375 mg of 8d, 3 mL of acetic acid, 1.5 mL of water, and 10 µL of 4 N of sulphuric acid was refluxed for 5 h. TLC pointed out that the conversion was not complete. The mixture was poured into ice-water and the product extracted into ether. Chromatographic purification afforded 163 mg of diketone (40%). This was dissolved in 7.3 mL of ethanol/2N of KOH (2:1) and refluxed for 2 h. Extraction with pentane after evaporation of the ethanol gave 108 mg of GC pure 9d (72%). NMR (CCl_4) δ 0.83-1.03 (d,3,$CHCH_3$), 1.25 (s,3,cyclopent CH_3), 1.92-2.60 (m,11,aliphatic H), 5.10-5.33 (m,2,CH=CH), 6.67-7.17 (m,3,ThH).

► *Threo and erythro* 2-[5-methyl-6-(2-thienyl)-(E)-hept-3-enyl]-3-methylcyclopent-2-enol (10b) and (10c)

► 2-[5-Methyl-6-(2-thienyl)-(E)-hex-3-enyl]-3-methylcyclopent-2-enol (10a)

► 2-[5-Methyl-6-(3-thienyl)-(E)-hex-3-enyl]-3-methylcyclopent-2-enol (10d)

At -30 °C a mol equiv. of $LiAlH_4$ was added in small portions to a solution of the unsaturated ketone in ether. After 1 h 1N of sodium hydroxide was added. The mixture was filtered, dried, and concentrated at low temperature. Due to their susceptibility for dehydration, the cyclopentenols were used immediately for the cyclization experiments.

► The cyclization of 10a,b, and 10c at -97 °C

To a solution of 100 mg of unsaturated alcohol 10 in 5 mL of dichloromethane, 1.2 equivalents of freshly distilled $SnCl_4$ were added. After 1 h the solution was poured into saturated ammonium chloride and the product extracted into dichloromethane. Chromatographic purification gave 50% pure product from 10a, while 10b,c failed to react.

► The cyclization of 10a-d at -23 °C

To a suspension of $ZnCl_2$ in nitroethane at -23 °C 0.25 equivalent of unsaturated alcohol 10 was added. After 1 h the mixture was poured into saturated ammonium chloride. Extraction with pentane and chromatographic purification gave the tetracyclic products in 34% yield.

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Chapter V

Resolution and absolute configuration of the pro-C-6 t-butyl substituted precursor

V.1 *Introduction*

Cyclization of chiral olefins offers an excellent method for the preparation of substituted optically active steroids,

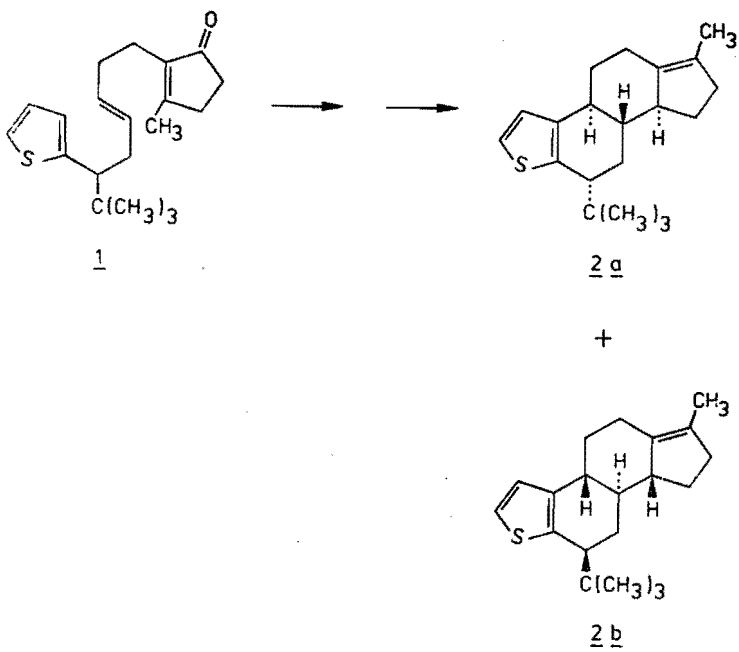


Figure 5.1 The ring closure of a racemic alkene proceeding with 100% asymmetric induction

provided that a high degree of asymmetric induction is operative. A pro-C-6 substituted optically pure substrate can afford in principle the 6α,9α and the 6α,9β *trans-anti* fused tetracycles or their mirror images, depending on the configuration of the substrate used. The asymmetric induction on the stereochemical outcome of the cyclization favours to a certain amount the formation of one of the two products. In Chapter II the cyclization of racemic 1 is described (see figure 5.1). Only one racemate, 2a and 2b, was formed, demonstrating the ring closure to proceed with 100% asymmetric induction. The cyclization of optically pure 1 thus leads to an optically pure 6α-substituted steroid. This ring closure is described in Chapter VI. In order to obtain additional information about the absolute configuration of the steroid, the absolute configuration of 1 was determined.

V.2 *The resolution of the optical isomers*

The method most generally used for separating enantiomers entails the separation of diastereomeric forms. To this effect, the racemic pair is derivatized in two diastereomers which can then be separated by virtue of differences in physical properties. The usual separation methods may vary from pure classical as differences in boiling points, differences in solubilities of a crystalline mixture, to chromatographic adsorptions and gas chromatographic retention times. Resolutions were performed on the acids 3, 4 and 5 (see figure 5.2). Acid 3 is a precursor of 1 and has the advantage that racemizations are precluded during the ensuing reaction conditions. The resolution of 4 and 5 was necessary for determinating the absolute configuration of 3 (see Section V.3). The resolution of acid 5 is described in the literature[1]. Following the most generally applied method[2], the racemic acids 3 and 4 were each converted into a pair of diastereomeric ammonium salts with optically pure amines like phenylethylamine, dehydroabietylamine, cinchonine, quinine, and brucine. From these possibilities the phenylethylammonium salts appeared to offer the best com-

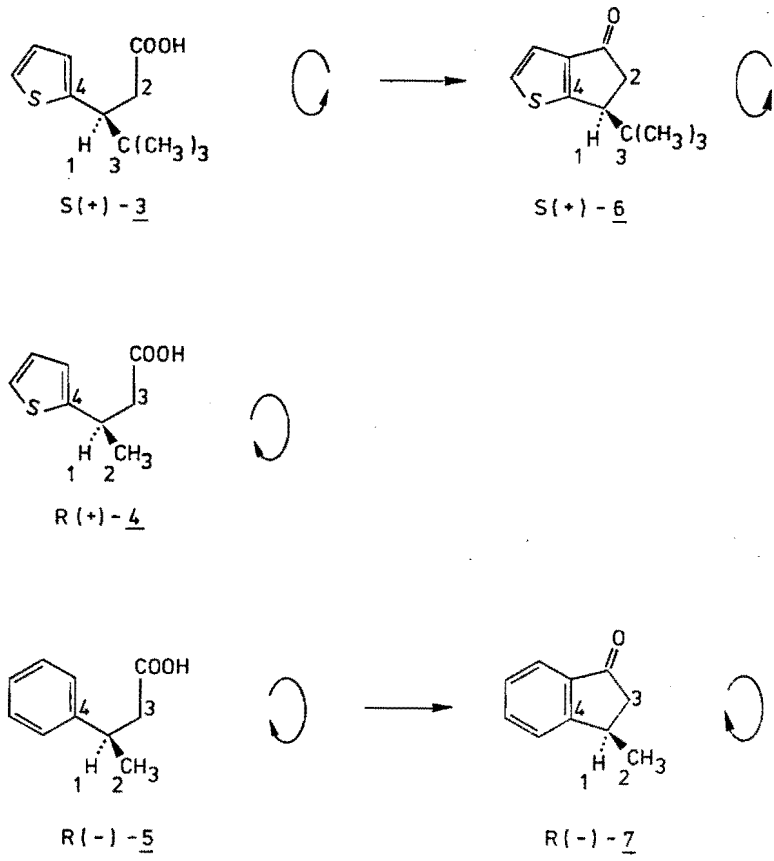


Figure 5.2 The Cahn-Ingold-Prelog notation for the substances used

bination for resolution by fractional crystallization when chloroform was used as solvent for the salt of 3 and a dioxan-diisopropylether mixture for the salt of 4. Initially, nine crystallizations were necessary to obtain some optically pure material. However, once having optically pure seed crystals on hand, the number of crystallizations could be markedly reduced (3-4), using half an equivalent of base and allowing the

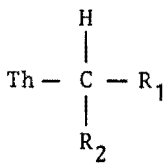
solutions to cool very slowly. Crystallizations were repeated till no further increase in the specific rotation ($[\alpha]_{\lambda}^{T}$) of the acids was observed. A maximum specific rotation, obtained on fractional crystallization, is not necessarily a criterion for enantiomeric purity[3]. Sometimes a eutectic composition is reached, from which no further enrichment is possible. Although this was not to be expected with the thienyl derivatives 3 and 4 considering the analogous behaviour of the phenyl analogue, some mutually different methods were investigated from which enantiomeric excesses can be determined. One method consists of the occurrence of differences in gas chromatographic retention times of diastereomers, obtained by a reaction of an (enriched) mixture with an optically pure compound. However, on conversion of acid 3 into its l-menthyl ester[4], some side reactions like polymerization of the thiophene moiety took place, thus diminishing the accuracy when applying the gas chromatographic method. During any derivation the same amount of each isomer must be converted. If side reactions do occur one also has to ascertain that these proceed equally with each isomer. Another method consists of the recognition of enantiomers by NMR when using chiral shift reagentia[5] or chiral solvents[6]. No differences in chemical shifts ($\Delta\delta$) could be observed on applying these techniques on the chiral acids 3 and 4 or their derivatives (alcohols and aldehydes). The effects will probably be too small in view of the long distance of the chiral center with respect to the functionality.

The notation used to describe the absolute configurations of the chiral compounds is the Cahn-Ingold-Prelog notation[7]. It must be noted, however, that at times compounds with the same chirality but with different substituents at the chiral carbon atom, are described with opposite R,S-nomenclature. This is illustrated in figure 5.2 for a number of substances, described in this Chapter.

V.3 *Determination of absolute configuration*

There exists a number of methods for determining absolute configurations. The simplest and most obvious chemical method is to convert the substance of unknown configuration into a compound with known configuration. These reactions can affect the center of asymmetry. In Table V.1 all chiral 2-thienyl derivatives are listed with chemically derived absolute configurations and resembling most closely the acid 3. Conversion of 3 into one of the compounds listed would entail a number of steps. The "rule of shift" (also called "verschiebungssatz" of Freudenberg)[12] could not be applied due to the lack of information about the influence of the specific rotation on derivatives of 3. The absolute configuration of 3 was therefore established by circular dichroism (CD).

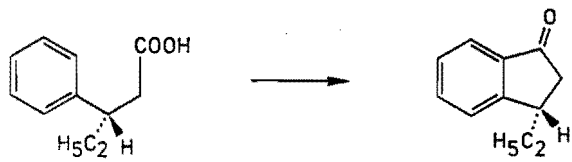
Table V.1 Chiral 2-thienyl derivatives with known configurations (Th=2-thienyl)



R_1	R_2	Configuration	Lit.
$CH_2C_6H_5$	COOH	R(+)	8
CH_3	$CH_2C_6H_5$	S(+)	8
COOH	OCH_3	R(+)	9
$CH_2C_6H_5$	CH_2OH	R(+)	9,10
CH_2COOH	COOH	S(-)	11

Circular dichroism as a method for the determination of (absolute) configurations and conformations has proven to be a reliable and relatively fast method. This relatively young method[13] has found a wide applicability. A number of general rules has been deduced empirically or semi-empirically for a variety of UV-absorbing chromophores. These rules allow unknown configurations to be determined and the signs of Cotton effects to be predicted. CD data of compounds most closely resembling 3, are available from the ethyl-substituted phenyl analogue and its indanone derivative, 8 and 9, respectively[16].

However, direct comparison of the thienyl with the phenyl absorptions is not feasible. Therefore, the acids 3 and 5 were converted into the bicyclic ketones 6 and 7, respectively, under influence of an acid (see Experimental). These



S(+) - 8 S(+) - 9

ketones have the advantage to possess, apart from the aromatic, additional α,β-unsaturated carbonyl absorptions. As proposed by several authors[14], such systems may be considered as cyclopentenones, to which an octant rule as deduced for ketones is applicable. The sign of Δε is determined by the most stable ring conformation which in turn is determined by the substituent at the chiral carbon atom. This rule, in a simplified form for indanones, then states that the opposite sign of Δε (around 330 nm) is determined by the dihedral angle between the carbonyl group and benzene. It is easily applicable to systems, in which the cyclopentenone part is forced in a certain conformation. Because the ring deformation in a cyclopentenone derivative can only be very small, the analysis of the most stable ring conformation is very difficult. The ^{1}H-NMR studies on 4-substituted cyclopentenones already showed[15] that the ring assumes a coplanar conformation, irrespective of the bulkiness of the substituent. The only reliable method to determine the absolute configuration of 3 by CD thus consisted of comparing the signs of Δε around 330 nm ($n \rightarrow \pi^*$ transition of the carbonyl group, also called R band) with the same CD absorptions of the phenyl analogues,

whose configurations already were established chemically. The CD spectra of the compounds 3-7 are given in figure 5.3 and 5.4.

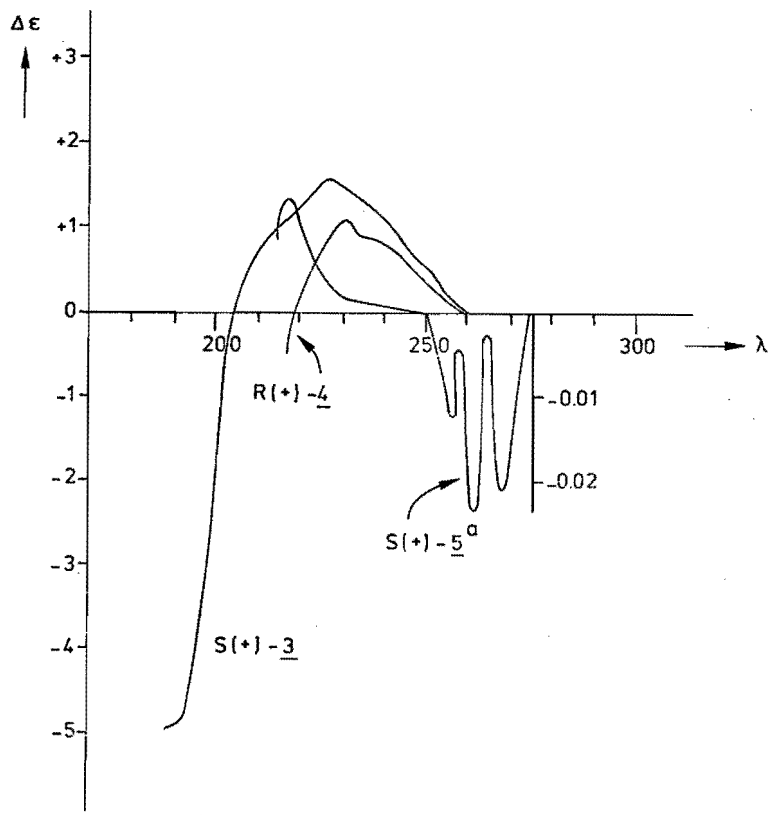


Figure 5.3 The CD spectra of the acids. [a]Not corrected for optical purity

In 1967 *Brienne et al.*[16] reported a study on the CD properties of some substituted indanones. They found S(+)-3-ethyl-indanone 9, prepared from R(-)-α-phenylbutyric acid *via* S(+)-8, to exhibit a positive CD effect around 330 nm. Com-

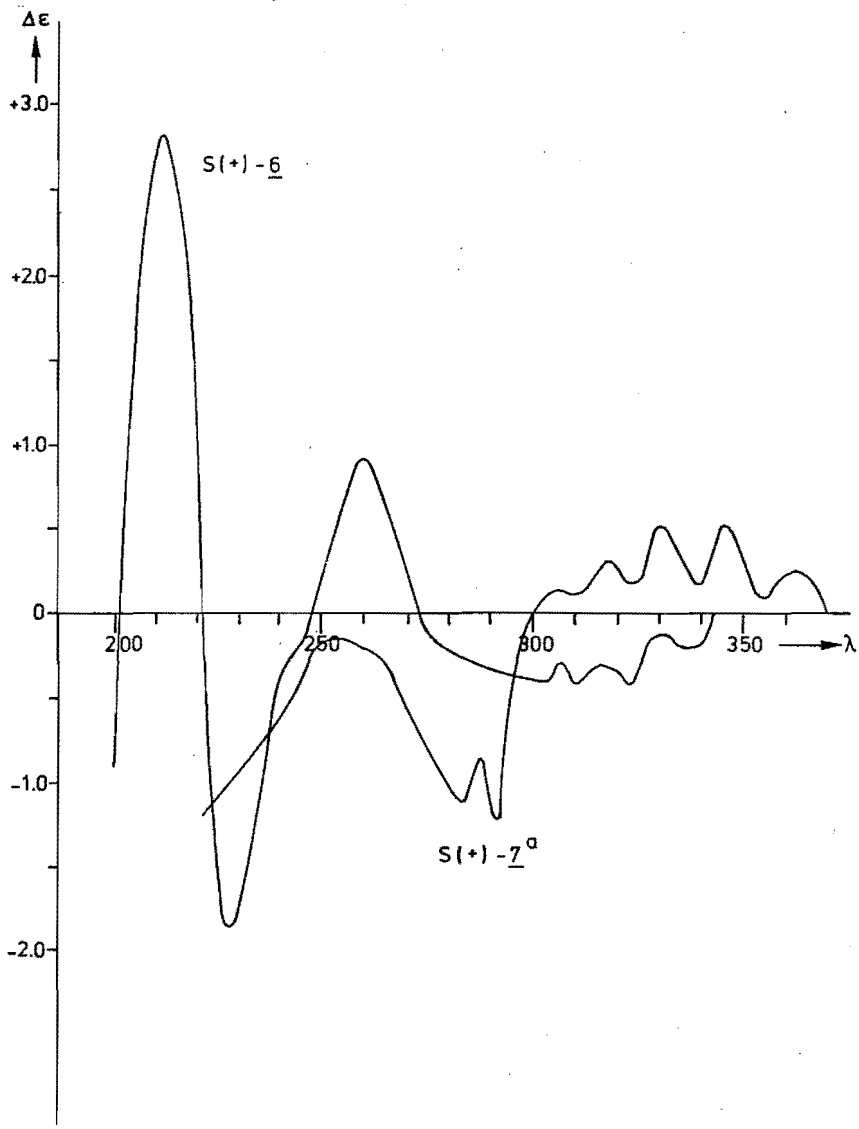


Figure 5.4 The CD spectra of the α,β-unsaturated ketones.
[a]Not corrected for optical purity

parison with the CD spectrum of (+)-6 shows, that this substance must have an S configuration. Since this compound was prepared from the (+)-acid 3, the latter must also possess the S-configuration. In figure 5.4 the CD spectrum of methyl substituted ketone S(+)-7 is included to demonstrate, as expected, that the kind of alkyl substituent does not affect the sign of $\Delta\varepsilon$ around 330 nm. This also holds for the thiophene absorptions around 230 nm of the acids 3 and 4 as shown in figure 5.3.

In conclusion, there is no doubt that the optically pure acids, used for the steroid synthesis as described in Chapter VI, exist in an S(+)- or an R(-)-configuration.

V.4 *Experimental*

The optical rotations were measured on a Bendix NPL automatic polarimeter 143 C. The CD spectra were recorded by Drs. L.A.M. Bastiaansen on a Jobin Yvon Dichrograph Mark III-S. The UV spectra were obtained from a Perkin-Elmer Doublebeam grating spectrophotometer model 124.

The preparations of the ethyl esters of 3 and 4 are described in Chapter II. Acid 5 was prepared and resolved according to the methods described in the literature[17,1].

► S(+)-3-(2-thienyl)-4,4-dimethylpent-2-enoic acid (3)
A mixture of 3 g (12.5 mmol) of the ethyl ester of 3 (see Chapter II), 50 mL of 0.5 N of sodium hydroxide and 20 mL of ethanol was refluxed for 2 hours. After evaporation of the ethanol, the solution was acidified with concentrated hydrochloric acid. Extraction with ether afforded 2.4 g (88%) of 3, mp 89.5-90.5 °C; NMR (CCl_4) δ 0.90 (s,9,$C(CH_3)_3$), 2.55-2.78 (m,2,CH_2), 3.10-3.35 (m,1,CH), 6.67-7.17 (m,3,ThH), 9.45 (s,1,COOH); El. Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60. Found: C, 62.45; H, 7.70.
Resolution was effected by fractional crystallization of the (+)-phenylethylammonium salt in chloroform. They were repeated until no further increase of specific rotation was

observed. $[\alpha]_D^{22}$= +8.8, $[\alpha]_{546}^{22}$= +17.6 ($CHCl_3$, c= 0.0114 g/mL). UV: log ε = 5.80 (235 nm). CD (c= $2.77.10^{-4}$ mol/L in hexane): Δε= +1.56 (227 nm).

► R(+)-3-(2-thienyl)butanoic acid (4)
Prepared analogous to 3. Yield: 90%. The resolution was performed on the (+)-phenylethylammonium salt by repeated fractional crystallization until a maximum value of the specific rotation was reached. As solvent for the crystallizations a mixture of dioxan-diisopropyl ether was used. NMR: (CCl_4) δ 1.36 (d,3,CH_3), 2.18-3.00 (m,2,CH_2), 3.17-3.86 (m,1,CH), 6.62-7.12 (m,3,ThH), 9.60 (s,1,COOH). UV: log ε= 4.0 (220 nm), 3.7 (232 nm). CD (c= 1.75. 10^{-4} mol/L in hexane): Δε= +1.03 (230 nm).

► S(+)-β-phenylbutyric acid (5)
UV (c= 3.8. 10^{-4} mol/L in hexane): log ε= 3.6 (214 nm), 1.9 (247 nm), 2.1 (252 nm), 2.2 (258 nm), 2.1 (264 nm), 2.0 (267 nm). CD (c= 3.8. 10^{-4} mol/L in hexane): Δε= +1.26 (217 nm), -0.013 (256 nm), -0.024 (261.5 nm), -0.022 (268 nm).

► S(+)-6-t-Butyl-5,6-dihydrocyclopenta[b]thiophene-4-one (6)[18]
A solution of 1.8 g (8.5 mmol) of S(+)-3 in 10 mL of chlorobenzene was slowly added to 30 g of preheated polyphosphoric acid (130-135 °C). After 15 minutes the solution was poured into an ice-salt mixture, from which the product was extracted with ether. After washing the ether solution successively with a 10% solution of sodium bicarbonate and water 1.5 g (92%) of NMR pure 6 was obtained. Chromatography with dichloromethane as eluens afforded analytically pure 6; NMR δ 1.00 (s,9,$C(CH_3)_3$), 2.63-2.83 (2d,2,CH_2), 3.06-3.37 (m,1, CH), 6.90-7.27 (AB,2,ThH). Anal. Calcd for $C_{17}H_{19}N_4O_4S$ (2,4-dinitrophenylhydrazone, mp 187-190 °C (d)): C, 54.53; H, 4.84; N, 14.97. Found: C, 54.27; H, 4.96; N, 14.83. UV (c= $1.36.10^{-4}$ mol/L in hexane): log ε= 4.2 (220 nm), 3.9 (240 nm). CD (c= 1.36. 10^{-4} mol/L in pentane): Δε= +2.82 (213 nm), -1.75 (228

nm), +0.90 (260 nm), -0.41 (300 nm), -0.45 (310 nm), -0.43 (323 nm), -0.21 (338 nm).

► S(+)-3-methylindan-1-one (7)[19]
A mixture of 9.0 g (0.055 mol) of (+)-β-phenylbutyric acid was heated with 20 g (0.168 mol) of freshly distilled thionyl chloride at 80 °C for 3 hours. The excess reagent was removed in vacuum; dry benzene was added and the evaporation process repeated. The acid chloride was dissolved in 30 mL of dry benzene and slowly added to 20 g of anhydrous aluminium trichloride in 70 mL of dry benzene. The resulting mixture was refluxed for 1.5 hour, cooled and poured onto ice and concentrated hydrochloric acid. After extraction and distillation 6.5 g (81%) of (+)-3-methylindan-1-one (7) was isolated: bp 112-113.5 °C (9 mm). UV (c= 2.10^{-4} mol/L in hexane): log ε= 4.0 (220 nm), 4.0 (238 nm), 4.0 (245 nm), 3.4 (274 nm), 3.5 (282 nm), 3.5 (291 nm). CD (c= 2.10^{-4} mol/L in hexane): Δε= -1.14 (283 nm), -1.23 (291 nm), +0.13 (306 nm), +0.33 (317 nm), +0.51 (331 nm), +0.53 (346 nm), +0.24 (363 nm).

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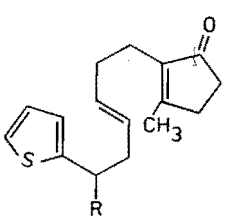
Chapter VI

The preparation of a 6α-substituted optically pure steroid via asymmetric induction. A CD study

VI.1 *Introduction*

Pharmacological activity of chiral compounds is frequently limited to but one enantiomer. The synthesis of optically pure steroids *via* asymmetrically induced polyolefinic cyclizations offers attractive perspectives, especially when a high degree of induction is attainable. In Chapter II the dependence of the stereospecificity of the cyclization of racemic 1 on the size of the pro-C-6 substituent (R) is described. Even a relatively small methyl group ($R=CH_3$) readily afforded for 97% an α-substituted steroid, while a 100% stereospecificity was attained on cyclizing the pro-C-6 *t*-butyl substituted racemic 1 ($R=C(CH_3)_3$).



1

Conversion of enantiomerically pure 1 ($R=C(CH_3)_3$) thus has to lead to an optically pure steroid (see also Section V.1). This biomimetic polyene cyclization is described in this Chapter. Also included is a study about the CD properties of the obtained steroid and its precursors (see figure 6.1).

VI.2 *The synthesis of the optically pure cyclization precursor*

In figure 6.1 a shortened synthesis of the cyclization precursor 6 is given. The route corresponds to the one in Chapter II. An advantage of this reaction scheme is the possibility of resolving the antipodes at an early stage. Separation of the enantiomers of 2 and the determination of their absolute configuration is described in the previous Chapter.

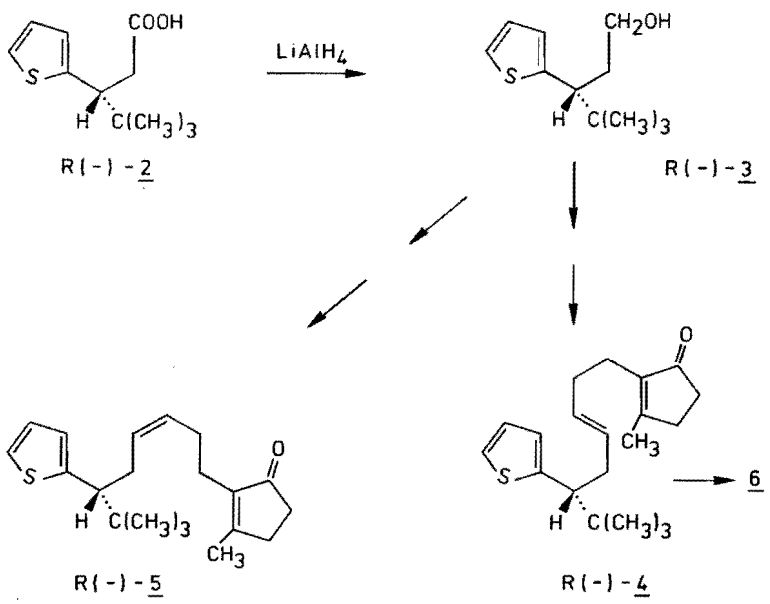


Figure 6.1 The preparation of the optically pure alkenes

During the reactions on 2 no racemization can occur, as the chiral center is located sufficiently far from the acid function. The conversion of R(-)-2 or S(+)-2 will each lead to a steroid with known absolute configuration, since it appeared

from ^{13}C NMR measurements (see Chapter II), that the C-6 substituent and the proton at C-8 will occupy *both* or the α- or the β-position in the *trans-anti* fused tetracycles. The two enantiomers of 2 were each converted into the steroid. Since essentially the same results were obtained, only one isomer (starting from R(-)-2) will be described. Thus reduction of R(-)-2 with $LiAlH_4$ gave the alcohol R(-)-3, which was oxidized to the aldehyde with pyridinium chlorochromate. A Wittig condensation reaction under Schlosser conditions (see Chapter II) followed by deketalization and cyclodehydration gave the R(-)-E-cyclopentenone 4. To obtain additional information about the CD properties of 4, the Z-isomer 5 was also prepared *via* the normal Wittig reaction. It appeared however, that 5 was contaminated with 25% of 4.

Wittig reactions are most suited for the unambiguous synthesis of substituted alkenes[1]. Reaction of an aldehyde or ketone with an *unstabilized* phosphorane gives initially a betaine (see figure 6.2), followed by a fast elimination of phosphine oxide and formation of predominantly Z-alkene. This differs from Wittig reactions involving *stabilized* phosphoranes. These more thermodynamically controlled reactions afford mainly E-alkenes. The Schlosser modification[2] of Wittig reactions with unstabilized phosphoranes, as described in the previous Chapters II-IV, involves treatment of the betaine-lithium adduct with an additional equivalent of base. It is assumed that the adduct is converted into the anion A, establishing a fast equilibrium between A and B, with B dominating due to minimized sterical interactions between R and R'. Protonation and elimination yield predominantly E-alkenes. The polarity of the solvent, the presence of lithium salts[2], the kind of base[3], temperature and isomerization time appear to have a distinct influence on the product distribution. Also the presence and size of the substituents in the chiral substrates showed a pronounced influence on the Z/E-ratio of the diketals formed (see Table VI.1). Optimal reaction conditions for the preparation of

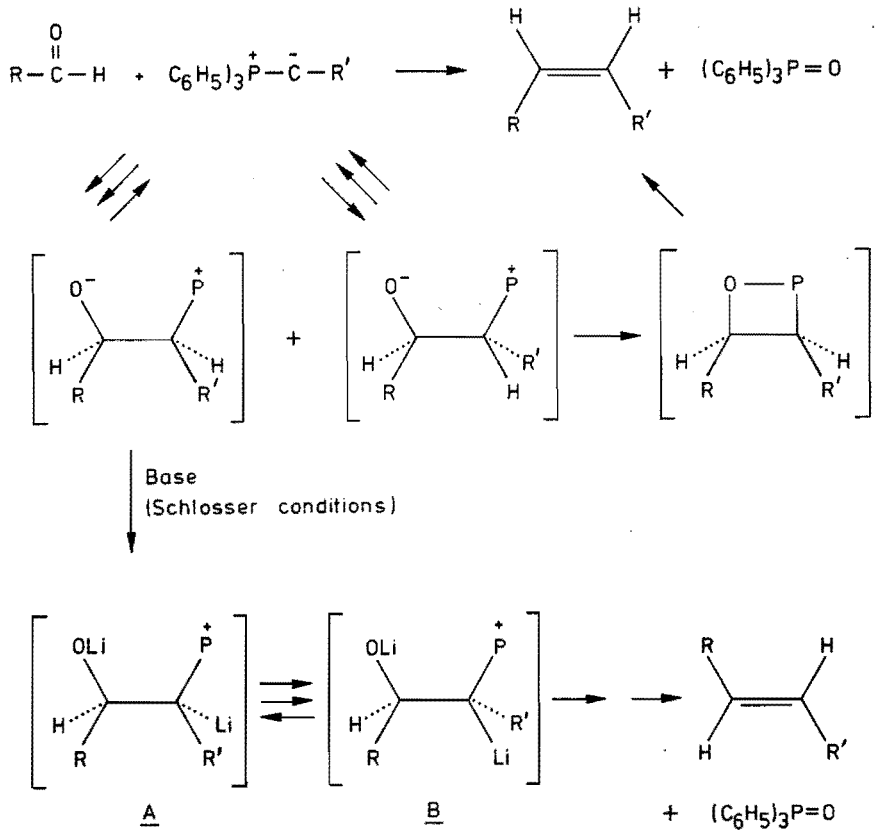
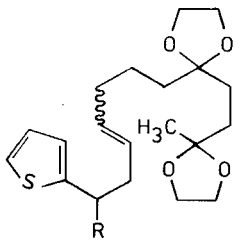


Figure 6.2 The Wittig reaction of an unstabilized phosphorane with and without the use of Schlosser conditions

the chiral E-alkenes by the Wittig-Schlosser reaction were found, using phenyllithium as base. An isomerization time of *ca* ½-1 h at -30 °C was required after the betaine adduct is formed at -78 °C.

Table VI.1 The influence of reaction conditions on the Z/E ratio



R	Base	Isomerization time (hours)	Reaction temperature	Z/E ratio
H	butyllithium	--[a]	-78 °C	>90:10
H	butyllithium	--[a]	-78 °C	50:50
H	phenyllithium	0.1	-78 °C	<10:90
CH_3	phenyllithium	5	-78 °C	< 5:95
CH_3	phenyllithium	1	-30 °C	< 5:95
$C(CH_3)_3$	phenyllithium	5	-78 °C	50:50
$C(CH_3)_3$	phenyllithium	1	-30 °C	< 5:95
$C(CH_3)_3$	butyllithium	--[a]	0 °C	75:25

[a]These reactions were performed under normal Wittig conditions

VI.3 *The CD data of the cyclization precursors*

Only little is known about the CD characteristics of thiophene derivatives. They add a further complication of the lone pair and, possibly, of 3d orbitals to the already complex situation of the aromatic hydrocarbons. Besides the characteristics of a simple 2-thienyl derivative[4], some studies are reported about a thiophene-containing triptycene[5], heterohelicene[6] and substituted bithienyls[6a].

The CD spectrum of acid S(+)-2 is given in Chapter V (figure 5.3). The spectra of the alcohol R(-)-3 and the Z-

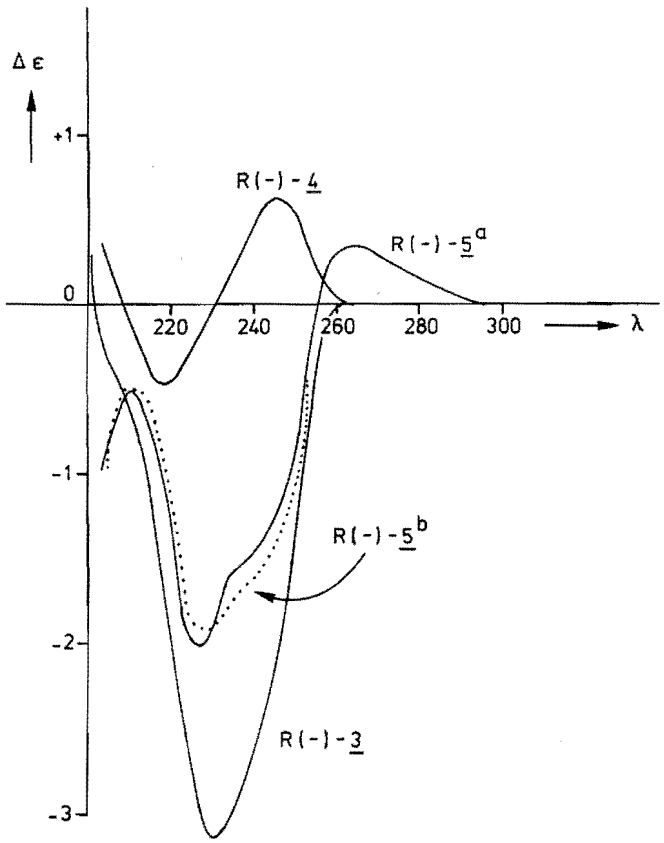


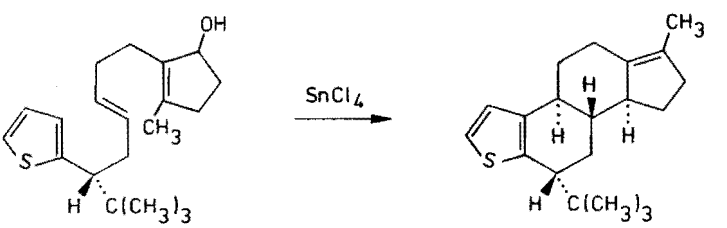
Figure 6.3 CD spectra of some precursors. [a]As a mixture of 75% Z- and 25% E-isomer. [b]Corrected for 100% Z-isomer

and E-cyclopentenones, R(-)-5 and R(-)-4, respectively, are given in figure 6.3. The shape of the curves shows them to consist of at least two absorptions. The signs of the Cotton effects are all the same, besides one absorption in R(-)-4, which sign is inversed. This must be caused by a difference in conformational freedom between 4 and 5.

VI.4 *The ring closure of the optically pure substrate*

VI.4.1 *Yield improvement of the cyclization*

The cyclization of optically pure 6 → 7 was performed exactly as on the racemates. Whereas the yields on C-6 substituted racemic steroids were always 50% at the top, the conversion 6 → 7 proceeded reproducably in 80% yield. The yield increment can be explained as follows. It has long been recognized that there are differences in physical properties between racemic solutions and solutions enriched with an antipode. A change in temperature observed on mixing



6 (+) - 7

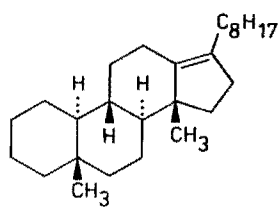
Figure 6.4 The ring closure

R- and S-coniine was already reported in 1895 by *Ladenburg*[7]. More recently, *Young*[8] observed local optical activity in a racemic liquid crystal. These, and several other differences in physical measurements could only be explained if non-bonded interactions between the chiral molecules were taken into account[9]. In a solution containing equal amounts of R- and S-isomers a chiral molecule sustains the presence of the R- and S-isomer. In an enantiomeric-free solution the molecule is always solvated by the same chirality. *Wynberg*[10] recognized for the first time the consequences of the different

interactions on the chemical reactivity between chiral molecules. He postulated the general principle: "When a chiral substance undergoes a reaction, the reaction rate will depend *-inter alia-* upon the enantiomeric excess in the starting material". This statement may well be applied to the above mentioned cyclization. As deduced in Chapter II, the carbenium ion derived from 6 assumes a precoiled conformation before ring closure. *This conformation might fit better in an optically pure solution than in a racemic one, resulting in an increased reaction rate in favour of the rates of the side reactions.*

VI.4.2 *A confirmation of the absolute configuration*

The CD-spectrum of steroid 7, as given in figure 6.5 shows three maxima: at 198 nm ($\Delta\varepsilon$=+16.96), 217 nm ($\Delta\varepsilon$=-3.04) and at 252 nm ($\Delta\varepsilon$=-1.46). The first two absorption maxima can be ascribed to the ethylene chromophore. Recently, *Hudec* and *Kirk*[11] analyzed empirically over 200 alkenes in order to determine the main features of the relationship between the molecular structure and chiroptical properties. For tetrasubstituted ethylenes, like the one in 7, there are two absorption maxima between 215-225 nm and 195-210 nm (assigned as λ_0 and λ_1, respectively). In general, asymmetric induction induced by a group in a chromophore decreases rapidly with distance. The signs of $\Delta\varepsilon$ thus are determined in large extent by the absolute configuration of C-14. Suitable compounds for the comparison of the CD data are the cholestenes 8, which in turn appear to have similar characteristics as $\Delta^{1(9)}$-octa-



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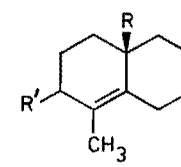

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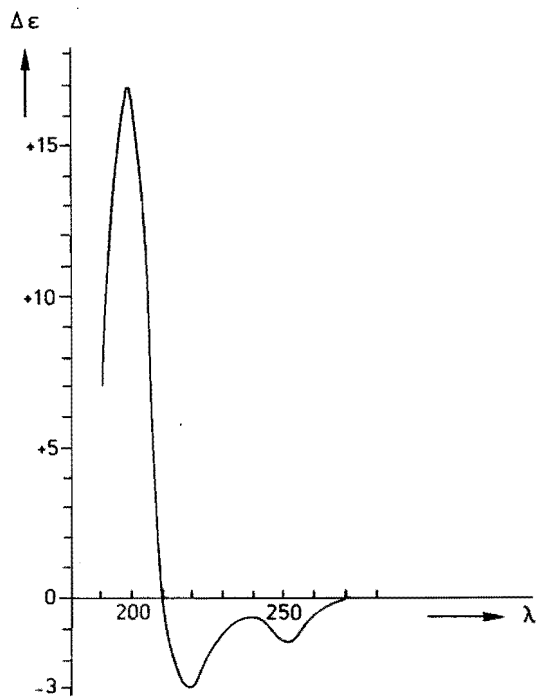

Figure 6.5 The CD spectrum of (+)-7, obtained after ring closure of (-)-6

line 9 ($R=CH_3$). The difference in ring size is only expressed in the amplitude of Δε. The signs of the Cotton effects are identical for the same absolute configuration. These compounds show negative Cotton effects at λ_0, while in 9 ($R=CH_3$) an additional positive effect at λ_1 has been detected. The presence of the allylic methyl group appears to have a dominating effect on the sign of the Cotton effects. Without these substituents, opposite Cotton effects have been observed, as in 9 (R=H) and in cholest-4-enes and cholest-5-enes as compared

to their 19-nor analogues. Comparison of these data with the CD-spectrum of 7 shows this to agree with the α-axialic absolute configuration of the proton at C-14. *The absolute configuration of C-14, obtained by CD measurements agrees with the conclusions made by ^{13}C NMR measurements and the knowledge of the C-6 absolute configuration.* The absorption of thiophene at 252 nm could not be related to the absolute configurations in 7, because no CD studies have yet been made on related compounds.

VI.5 *Experimental*

The preparation, resolution and determination of absolute configuration of R(-)-2 is described in Chapter V.

► R(-)-3-(2-thienyl)-4,4-dimethylpentanol (3)
A solution of 1.38 g (6.5 mmol) of R(-)-acid 2 in 10 mL of dry ether was slowly added to a suspension of 50 mg (13 mmol) of $LiAlH_4$ in 40 mL of ether at 0° C. After 2 h of refluxing no acid was detected by TLC. Usual work-up yielded 1.03 g of 3: yield 83%; $[\alpha]_D^{21}$=-22.6, $[\alpha]_{534}^{21}$=-28.3 (l=0.10006 dm, c= 0.01135 g/mL in methanol). UV: log ε=3.40 (196 nm), 3.92 (235 nm); CD: Δε=+1.90 (197 nm), -3.22 (232 nm) ($c=2.9.10^{-4}$ mol/L in hexane).

► R(-)-2-[7,7-dimethyl-6-(2-thienyl)-(E)-oct-3-enyl]-3-methyl-cyclopent-2-enone (4)
The preparation was analogous to the racemic compound as described in Chapter II. Yield: 32%, based on alcohol; $[\alpha]_D^{21}$= -0.6, $[\alpha]_{534}^{21}$=-1.7 (l=0.10006 dm, c=0.0105 g/mL in dichloromethane). UV: log ε=3.77 (211 nm), 3.56 (235 nm); CD: Δε= -0.47 (217 nm), +0.62 (244 nm) ($c=1.35.10^{-4}$ mol/L in hexane).

► R(-)-2-[7,7-dimethyl-6-(2-thienyl)-(Z)-oct-3-enyl]-3-methyl-cyclopent-2-enone (5)

Analogous to 4 without the use of Schlosser conditions.

► 6R(+)-17-methyl-6*t*-butyl-3-thia-4-noroestra-1,5(10), 13(17)-triene (7)

The cyclization was performed at - 95 °C with $SnCl_4$ as Lewis acid. For the experimental procedure see Chapter II. Yield: 80%; $[\alpha]_D^{24}$=+20.7, $[\alpha]_{534}^{24}$=+22.5 (l=0.10006 dm, c=0.00217 g/mL in benzene); UV: log ε=3.84 (212 nm), 3.75 (238 nm); CD: Δε= +16.96 (198 nm), -3.04 (217 nm), -1.46 (252 nm) ($c=2.3.10^{-4}$ mol/L in hexane).

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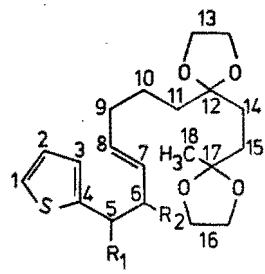
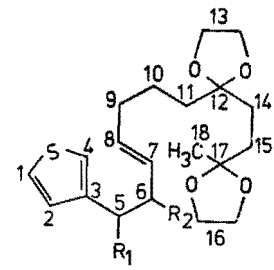
Appendix

Table I ^{13}C NMR chemical shifts of the diketals[a]



A

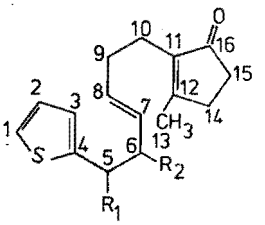


B

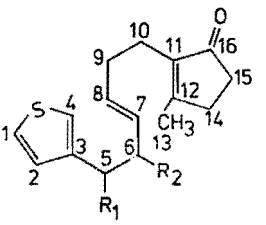
atom number	Compound A						Compound B	
	$R_1=R_2=H$[b]	$R_1=CH_3$ $R_2=H$	$R_1=t$-Bu $R_2=H$	$R_1=R_2=CH_3$ *threo*	$R_1=R_2=CH_3$ *erythro*	$R_1=H$ $R_2=CH_3$	$R_1=R_2=H$[b]	$R_1=CH_3$ $R_2=H$
1	123.87	123.56	123.69	123.38	123.47	124.00	126.07	125.98
2	127.57	127.40	126.91	127.04	127.04	127.35	129.16	127.70
3	125.15	123.56	126.51	124.22	124.53	125.94	143.19	148.79
4	145.48	152.48	147.20	150.86	149.94	144.07	121.04	119.76
5	30.97	36.61	53.99	48.08	41.35	38.60	31.32	36.35
6	35.64	43.41	34.85	45.57	44.38	39.75	34.49	42.22
7	130.08	129.16	130.31	131.14	134.63	136.12	130.71	129.47
8	132.29	135.35	132.20	135.16	131.06	130.17	131.83	132.87
9	33.70	33.75	33.61	33.74	33.79	33.70	33.75	33.70
10	24.79	24.97	24.92	24.66	24.92	24.61	24.83	24.91
11	32.41	32.47	32.42	32.33	32.38	32.33	32.47	32.38
12	112.22	112.53	112.44	112.22	112.22	112.26	112.22	112.22
13	65.37	65.68	65.35	65.37	65.37	65.37	65.42	65.37
14	34.24	34.28	34.28	34.27	34.31	34.28	34.49	34.32
15	37.67	37.72	37.45	37.58	37.58	37.58	37.72	37.58
16	65.68	65.95	65.82	65.64	65.64	65.64	65.73	65.64
17	110.55	110.90	110.77	110.59	110.55	110.59	110.54	110.59
18	24.79	24.70	24.61	24.88	24.92	24.92	24.83	24.66
R_1	---	23.34	36.26[c] 29.90	20.03	20.12	---	---	22.14
R_2	---	---	---	21.61	18.31	21.17	---	---

[a]Deviation of the conventional numbering as given in the heading of the Table was preferred in order to obtain comparable data; [b]These data were obtained from: A. Corvers, Thesis, Eindhoven University of Technology, March 1977; [c]The first number refers to the quaternary carbon atom, the second one to the primary carbon atom.

Table II ^{13}C NMR chemical shifts of the cyclopentenones[a]



A

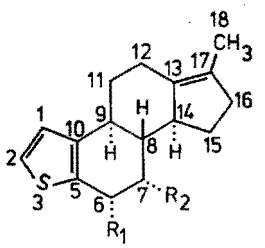


B

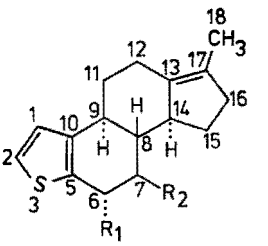
	Compound A					Compound B		
Atom number	$R_1=R_2=H$[b]	$R_1=CH_3$ $R_2=H$	$R_1=t$-Bu $R_2=H$	$R_1=R_2=CH_3$ *erythro*	$R_1=H$ $R_2=CH_3$	$R_1=R_2=H$[b]	$R_1=CH_3$ $R_2=H$	$R_1=H$ $R_2=CH_3$
1	123.88	123.34	123.64	123.34	124.01	126.01	126.01	125.58
2	127.58	127.22	126.98	127.10	127.40	129.10	127.77	128.98
3	125.16	123.34	126.43	124.25	126.01	143.06	148.88	140.93
4	145.36	151.91	147.18	150.76	143.97	120.97	119.70	121.70
5	30.88	36.40	53.87	42.10	38.46	31.12	36.22	
6	35.55	43.38	35.25	45.56	39.55	34.34	42.16	
7	130.26	129.28	130.38	135.53	136.38	130.86	129.77	126.93
8	131.71	132.80	131.47	130.56	129.53	131.10	132.32	129.41
9	32.15	32.15	32.09	32.21	32.15	32.15	32.15	32.88
10	24.08	24.21	24.08	24.27	24.15	24.09	24.21	24.21
11	140.21	140.81	140.75	140.81	140.63	140.20	140.51	141.66
12	169.93	168.48	170.90	168.54	169.14	170.05	169.39	167.93
13	17.78	18.08	18.26	18.08	18.02	17.78	17.96	18.02
14	32.15	32.34	32.46	32.24	32.27	32.15	32.28	32.28
15	34.94	34.76	34.76	34.76	34.88	34.94	34.88	34.64
16	208.09	207.24	209.67	207.30	207.73	208.15	207.79	207.06
R_1	---	23.30	36.28[c] 29.12	20.12	---	---	21.96	---
R_2	---	---	---	18.31	20.93	---	---	21.11

For footnotes, see under Table I.

Table III ^{13}C NMR chemical shifts of the heterocyclic steroids



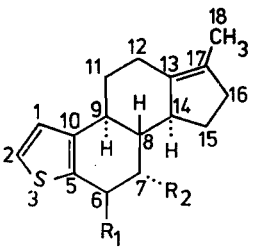
A



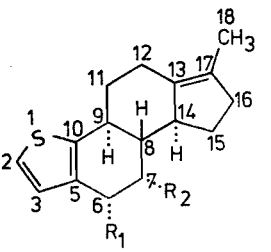
B

	Compound A				Compound B[c]	
Atom number	$R_1=R_2=H$[a]	$R_1=CH_3$ $R_2=H$	$R_1=t$-Bu $R_2=H$	$R_1=H$ $R_2=CH_3$	$R_1=H$ $R_2=CH_3$	$R_1=R_2=CH_3$
1	126.03	125.94	125.83	126.03	128.63	128.45
2	122.72	122.85	123.04	122.76	122.98	123.12
3	---	---	---	---	---	---
5	136.04	143.00	138.93	134.81	133.79	139.48
6	26.29	33.22	48.72	34.27		
7	29.29	39.22	33.45	29.73		
8	42.48	42.70	42.35	52.62		
9	49.76	50.33	50.05	49.18		
10	139.61	139.26	142.81	138.20	139.88	139.39
11	32.55	32.65	32.76	32.91		
12	28.94	28.85	28.94	28.54		
13	136.70	136.75	136.75	136.79	136.61	136.66
14	52.71	52.67	53.02	36.83		
15	26.78	26.78	26.57	26.64		
16	38.29	38.24	38.34	38.16		
17	129.56	129.60	129.65	129.29	129.51	129.56
18	14.69	14.64	14.62	14.64		
R_1	---	24.44	35.67[b] 29.06	---		---
R_2	---	---	---	13.76	---	---

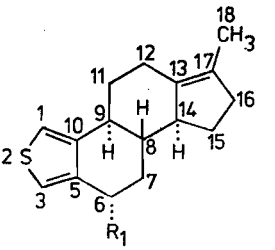
Table III (continued)



C



D

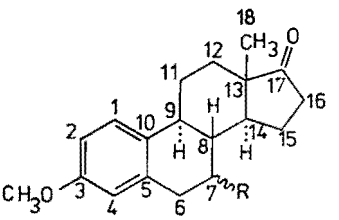


E

Atom number	Compound C[c] $R_1=R_2=CH_3$	Compound D $R_1=H$[a] $R_2=H$	Compound D $R_1=CH_3$ $R_2=H$	Compound D $R_1=H$ $R_2=CH_3$	Compound E $R_1=CH_3$
1	125.67	---	---	---	119.20
2	123.12	122.63	122.72	122.99	--
3	---	128.14	126.73	128.60	118.40
5	137.54	135.25	141.16		142.97
6		26.78	32.28	32.91	33.22
7		28.89	38.91	29.20	39.10
8		45.52	42.83	53.33	43.27
9		50.42	50.68	49.10	49.98
10	141.47	141.16	140.63		144.38
11		34.32	34.45	34.94	30.70
12		28.89	28.76	28.45	
13	136.79	136.48	136.53	136.63	136.67
14		52.71	52.63	36.79	52.93
15		26.68	26.64	26.51	
16		38.20	38.24	38.11	
17	129.29	129.73	129.78	129.26	129.47
18		14.60	14.60	14.65	
R_1		---	22.76	---	
R_2		---	---	13.94	---

[a]These data were obtained from: A. Corvers, Thesis, Eindhoven University of Technology, March 1977; [b]The first number refers to the quaternary carbon atom, the second one to the primary carbon atom; [c]The aliphatic parts of these compounds were not assigned.

Table IV ^{13}C NMR chemical shifts of estrone derivatives



Atom number	R=H	R=α-CH_3	R=β-CH_3	9β[a] R=H	3-OH[b] 9β, R=H
1	126.86	127.40	124.25	127.89	127.89
2	112.11	112.36	111.27	112.54	113.87
3	158.53	158.59	158.71	158.22	155.37
4	114.42	115.03	114.54	114.54	115.94
5	138.14	136.75	139.42	138.87	138.93
6	30.27	38.22	37.01		
7	27.30	27.91	32.03		
8	39.25	47.93	42.47		
9	44.89	38.71	46.71		
10	132.80	131.71	135.11	130.26	129.16
11	26.63	27.24	25.30		
12	32.46	32.58	32.03		
13	48.23	48.29	48.96	48.05	48.11
14	51.02	41.80	51.87		
15	22.08	21.48	23.84	22.26	22.26
16	35.86	35.67	35.92	35.19	35.19
17	218.77	218.71	218.65	218.59	218.77
18	13.83	13.83	13.83	13.41	13.35
OCH_3	55.15	55.03	55.15	55.03	---
R	---	12.83	23.26	---	---

[a]Further signals at 42.71, 38.16, 34.58, 28.21, 26.45, 25.48, and 24.63 ppm; [b]Further signals at 42.65, 38.10, 34.64, 28.15, 26.33, 25.54, and 24.63 ppm. These signals could not be assigned unambiguously.

Summary

This thesis describes a number of asymmetrically induced cyclization reactions, furnishing specifically substituted steroid-like systems with thiophene as A-ring. *In vitro* ring closure of achiral compounds gives two enantiomeric *trans-anti* fused products, containing three chiral carbon atoms each. The presence of a non-epimerizable chirality in the cyclization precursor favours production of one ring-closed diastereomer over the other. A comparable example of an *in vivo* ring closure is found in the conversion of 2,3-epoxysqualene to various steroids.

A chiral center far removed from the cyclization initiator also influences the stereochemical outcome of such cyclizations. A deuterium atom at pro-C-6 (steroid numbering) causes no measurable asymmetrically induced ring closure because of the deuterium's comparable size to a hydrogen atom. A methyl group at pro-C-6, however, will cause ring closure to proceed for 97% to a 6α-substituted steroid. A 100% asymmetrically induced ring closure in favour of the 6α-substituted product is brought about by a *t*-butyl group. Afore-mentioned stereospecificities are believed to stem from 1,3-diaxial interactions between the substituent at the chiral carbon atom and the pro-C-8 and pro-C-10 hydrogen atom. This gave rise to a model description of the ring closure in terms of "precoiling".

The 1,3-diaxial interactions between the pro-C-6 substituent and the thiophene protons are demonstrated by ring closure of a 3-thienyl analogue. Here, interactions occur with the thienyl 2- and 4-protons. This causes ring closure to proceed not only to the most reactive 2-position, but also to the least susceptible 4-position of thiophene, both with 97% asymmetric induction. This reaction may well reflect the

strongly hindered rotation of the pro-C-5,6 bond in the allylic carbenium ion, caused by the above-mentioned additional 1,3-interaction.

On ring closing pro-C-7 methylated polyalkenes, the formation of 7α-substituted products is prevented by 1,3-interactions; production of a 7β analogue is impeded by a steric interference with the cyclopentenyl ring. This makes that the cyclization proceeds with a lower asymmetric induction: at -96 °C a 7α-substituted product is formed for 90% with for 10% production of a *cis*-BC ring-fused product. Raising the reaction temperature results, as expected, in a lower asymmetric induction: at -23 °C 84% of the 7α-substituted and 16% of the *cis*-fused products are formed. The amount of *cis*-fused compound increases under these conditions by the presence of an extra methyl group (*threo*) at pro-C-6 (by additional 1,3-interactions). The *threo* and *erythro* pro-C-5,6 dimethyl-substituted cyclopentenols do not cyclize at -96 °C. The formation of the *cis*-BC ring fused tetracycles may well proceed *via* an intermediate sulphonium ion, with the pro-B ring existing in a boat conformation. The *cis*-fusion arises after inversion of pro-C-9. Intermediacy of a sulphonium ion is sterically precluded on ring closing the 3-thienyl analogue. This reaction (- 23 °C) leads to a 7α-substituted *trans-anti*-fused tetracycle (77%) plus a previously unencountered spiro compound (23%). The latter is formed *via* a [1,2]H shift in the non-stabilized bicyclic carbenium ion.

The ring closure of the optically pure pro-C-6 *t*-butyl substituted alkene gives an optically pure steroid, since the reaction proceeds with 100% asymmetric induction. Hereby, a significant yield increase is observed (50% → 80%). The absolute configurations of the precursors and the cyclized products are determined by circular dichroism.

Samenvatting

In dit proefschrift wordt een aantal asymmetrisch geïnduceerde cyclisatiereacties beschreven, welke leiden tot specifiek gesubstitueerde steroidachtige verbindingen met thiofeen als A-ring. Bij de *in vitro* ringsluiting van de symmetrische verbindingen worden twee enantiomere *trans-anti* verknoopte producten gevormd, die beide drie chirale koolstofatomen bevatten. De aanwezigheid van een chiraal centrum in de cyclisatie-precursor kan de vorming van een bepaald diastereomer begunstigen. Een vergelijkbaar voorbeeld van een *in vivo* ringsluiting is de omzetting van 2,3-epoxysqualeen tot tal van steroiden.

Een chiraal centrum op grote afstand van de cyclisatie-initiator bepaalt ook het stereochemisch verloop van soortgelijke cyclisaties. Een deuterium atoom aan pro-C-6 (steroid nummering) veroorzaakt geen asymmetrische inductie bij de ringsluiting, omdat een waterstof- en een deuterium atoom van vergelijkbare grootte zijn. Echter, een methylgroep aan pro-C-6 initieert reeds een asymmetrische inductie voor 97% ten gunste van het 6α-gesubstitueerde steroid. Een volledig asymmetrisch geïnduceerde ringsluiting wordt gevonden bij substitutie van methyl door *t*-butyl. De hiervoor vermelde stereospecificiteiten worden veroorzaakt door 1,3-diaxiale interacties tussen de substituent aan het chirale koolstofatoom en de waterstofatomen aan pro-C-8 en pro-C-10. Dit leidt tot de veronderstelling, dat de ringsluitingsreacties plaatsvinden vanuit "precoiled" conformaties.

De 1,3-diaxiale interacties tussen de pro-C-6 substituent en de thiofeen protonen zijn aangetoond met de cyclisatiereactie van het 3-thienyl analogon. Hierbij vindt

de ringsluiting niet alleen plaats naar de meest reactieve 2-positie, maar ook naar de minst reactieve 4-positie van thiofeen, elk met 97% asymmetrische inductie. Deze reactie geeft de sterk gehinderde rotatie weer van de pro-C-5,6 binding in het allylisch carbenium ion, veroorzaakt door de reeds genoemde additionele 1,3-interacties.

Bij de cyclisatie van pro-C-7 gemethyleerde polyalkenes wordt de vorming van 7α-gesubstitueerde producten tegengewerkt door 1,3-interacties en de vorming van een 7β-gesubstitueerd analogon door een sterische interactie met de cyclopentenyl ring. Dit veroorzaakt een lagere asymmetrische inductie bij ringsluiting: bij -96 °C wordt voor 90% een 7α-gesubstitueerd product gevormd en voor 10% een *cis*-BC ring verknoopt product. Een verhoging van de reactietemperatuur resulteert, zoals is te verwachten, in een lagere asymmetrische inductie: bij -23 °C bedragen de percentages respectievelijk 84% en 16%. De hoeveelheid *cis*-verknoopte verbinding wordt onder deze omstandigheden verhoogd door de aanwezigheid van een extra methyl groep (*threo*) aan pro-C-6 (door additionele 1,3-interacties). De *threo* en *erythro* pro-C-6,7 dimethyl-gesubstitueerde cyclopentenolen cycliseren niet bij -96 °C. De vorming van de *cis*-BC verknoopte tetracycli kan verlopen *via* een intermediair sulfonium ion, met de B-ring in een bootconformatie. De *cis*-verknoping ontstaat door inversie van pro-C-9. Een intermediair sulfonium ion is sterisch gezien uitgesloten bij de ringsluiting van het 3-thienyl analogon. Deze reactie (-23 °C) leidt tot een 7α-gesubstitueerd *trans-anti* tetracycle en een spiroverbinding. De laatste verbinding wordt gevormd *via* een [1,2] H shift in het niet-gestabiliseerde bicyclisch carbenium ion.

De cyclisatie van een optisch zuiver pro-C-6 *t*-butyl gesubstitueerd alkeen leidt tot een optisch zuiver steroid, omdat deze reactie met 100% asymmetrische inductie plaatsvindt. Hierbij is tevens een belangrijke opbrengstverhoging geconstateerd (50% → 80%). De absolute configuraties van de uitgangsstoffen en de gecycliseerde verbindingen zijn bepaald met behulp van circulair dichroisme.

Curriculum vitae

De auteur van dit proefschrift werd geboren op 14 augustus 1951 te Zuilen. Na het behalen van het HBS-B diploma aan de Albert Schweitzer Scholengemeenschap te Geleen werd in september 1969 begonnen met de studie Scheikundige Technologie aan de Technische Hogeschool te Eindhoven. Het afstudeeronderzoek werd verricht bij de vakgroep Organische Chemie met dr. E.F. Godefroi als afstudeerdocent. Het doctoraalexamen werd op 8 januari 1975 afgelegd.

Op 1 mei 1975 trad hij in dienst van de Technische Hogeschool te Eindhoven bij de vakgroep Organische Chemie. Het in dit proefschrift beschreven onderzoek stond onder leiding van prof. dr. H.M. Buck.

Thans is hij als hoofd van het laboratorium werkzaam bij Volvo Car B.V. te Born.

Dankwoord

Aan het totstandkomen van dit proefschrift hebben velen een bijdrage geleverd, waarvoor ik zeer erkentelijk ben. Enkelen wil ik met name noemen. Tegenover ir. R.J. de Brouwer, ir. J.M.G. Driessen-Engels, ir. P.N.N. Nossin, ir. M.L.M. Pennings en ir. R.J.E.M. de Weerd zou ik mijn hartelijke dank willen uitspreken voor hun bijdragen op het gebied van de synthese. Voor de fysische metingen en, ten dele, de interpretaties ben ik dank verschuldigd aan: J.A. Bakker, drs. L.A.M. Bastiaansen, G.J. Bezemer, P.L.M. van den Bosch, H. Eding, dr. ir. J.W. de Haan, ir. A. de Jong, dr. ir. P.A. Leclercq, ir. W.J.J. Leunissen, G.J. Scherpenzeel en L.J.M. van de Ven.

C. Bijdevier, H. Eding en mevrouw P. Meyer-Timan dank ik zeer voor hun medewerking aan de totstandkoming van de uiteindelijke vormgeving van dit proefschrift.

Stellingen

1. Bij de bestudering van het stereochemisch gedrag van de C-6 methyl groep bij de *in vivo* ringsluiting van gemerkt 2,3-epoxysqualeen tot cycloartenol is een substraat gebruikt, waarvan de absolute configuratie van de epoxy ring niet éénduidig is vastgesteld.

   L.J. Altman, C. Yol Han, A. Bertolino, G. Handy, D. Laungani, W. Muller, S. Schwartz, D. Shanker, W.H. de Wolf en F. Yang, J. Am. Chem. Soc., 100, 3235 (1978).

2. De circulair dichroïtische eigenschappen van iso-γ-lupeen kunnen niet alleen worden verklaard door conformatieveranderingen van de zijketen.

   J. Hudec en D.N. Kirk, Tetrahedron, 32, 2475 (1976).

3. Dat bij de hydrolyse van 1,3-dibenzoyl-2-(1-benzoyl-2-benzimidazolyl)-benzimidazoline in verdund zwavelzuur een zout wordt gevormd, ligt meer voor de hand dan de vorming van een gesulfoneerd product.

   G. Scherowsky, Ann. Chem., 739, 45 (1970).

4. De volledige asymmetrische inductie, vastgesteld bij de vorming van 1-methoxy-7α-methylestra-1,3,5(10),13(17)tetraeen, is het gevolg van sterische interacties tussen de methoxy groep en de protonen aan pro-C-11.

   M.B. Groen en F.J. Zeelen, Recl. Trav. Chim. Pays-Bas, 97, 301 (1978).

5. De vorming van het rhodium complex uit 8-fenyl-1,7-dioxa-4-aza-8-fosfa^{V} [3.3.0] bicyclooctaan en $Rh(C_2H_4)Cl_2$ impliceert niet het bestaan van een driewaardig tautomeer.

D. Bondoux, I. Tkatchenko, D. Houalla, R. Wolf, C. Pradat, J. Riess en B.F. Mentzen, Chem. Commun., 1022 (1978).

6. Het door *Ramana et al.* voorgestelde mechanisme van de oxidatie van boranen tot ketonen met behulp van pyridinium chlorochromaat is aanvechtbaar.

V.V. Ramana Rao, D. Devaprabhakara en S. Chandrasekaran, J. Organometal. Chem., 162, C9 (1978).

7. Het is vanuit theoretisch standpunt gezien belangwekkend om homo-aromatische ionen nader te onderzoeken met behulp van magnetisch circulair dichroïsme.

J. Michl, J. Am. Chem. Soc., 100, 6812 (1978).

8. De afgeleide relatieve gevoeligheden van de ^{13}C chemical shifts van C_1 en C_4 in een *gauche* pentaanfragment vergeleken met eenzelfde *anti* fragment, berusten op een aanvechtbare interpretatie van cyclische modelsystemen.

G. Mann, E. Kleinpeter, H. Werner, Org. Magn. Res., 11, 561 (1978).

9. Door de taalstrijd in België wordt genealogisch onderzoek in Wallonië vaak hinderlijk tegengewerkt.

A.A. Macco

Eindhoven, 6 april 1979