dertaken.

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Registry No. 6β-Bromotestosterone acetate, 1458-93-1.

Preparation of a 6α-Substituted Optically Pure Steroid with Thiophene as the A Ring via Asymmetric Induction. A Circular Dichroism Study†

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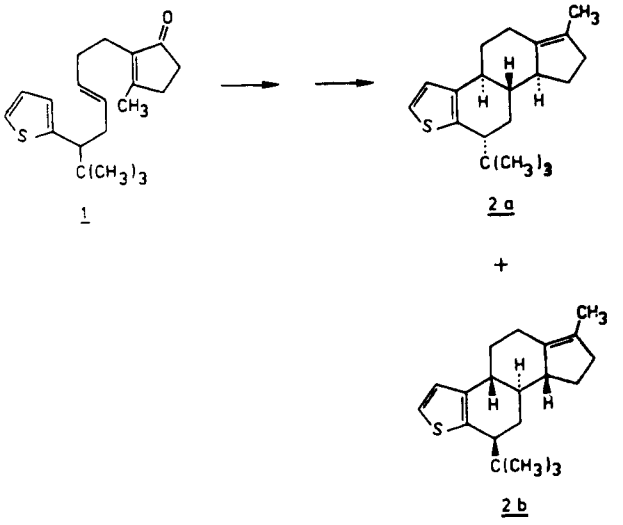
A number of asymmetrically induced cyclization reactions are described, furnishing specifically substituted steroid-like systems with thiophene as the A ring. Ring closure of achiral compounds gives two enantiomeric trans-anti-fused products, containing three chiral carbon atoms each. The presence of a nonepimerizable chirality in the cyclization precursor favors 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 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 in 97% yield to a 6α-substituted steroid. A 100% asymmetrically induced ring closure in favor of the 6α-substituted products is brought about by a *t*-Bu group. Aforementioned 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 atoms. This gives rise to a model description of the ring closure in terms of "precoiling". The ring closure of the optically pure *tert*-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.

Cyclization of chiral olefins offers an excellent method for the preparation of substituted optically active steroids 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 favors to a certain amount the formation of one of the two products. Recently, the cyclization of racemic **1** has been described (see Scheme I).[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 (vide infra). In order to obtain additional information about the absolute configuration of the steroid, the absolute configuration of **1** was determined.

Scheme I. Cyclization of a *pro*-C-6 *tert*-Butyl-Substituted Steroid Precursor Proceeding with 100% Asymmetric Induction (2a)



Results and Discussion

Resolution and Absolute Configuration of the *pro*-C-6 *tert*-Butyl-Substituted Precursor. 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 into two diastereomers which can then be separated by virtue of differences in physical properties. The usual separation methods may vary from pure classical methods such as differences in boiling points and differences in solubilities of a crystalline mixture to chromatographic adsorptions and gas chromatographic retention times. Resolutions were performed on the acids **3**–**5** (see Scheme II). Acid **3** is a precursor of **1** and has the advantage that racemizations are precluded during the en-

† This work was abstracted from the Ph.D. dissertation of A.A.M., Eindhoven University of Technology, The Netherlands.

(1) (a) Macco, A. A.; de Brouwer, R. J.; Buck, H. M. *J. Org. Chem.* 1977, *42*, 3196. (b) Macco, A. A.; de Brouwer, R. J.; Nossin, M. M. P.; Godefroi, E. F.; Buck, H. M. *Ibid.* 1978, *43*, 1591.

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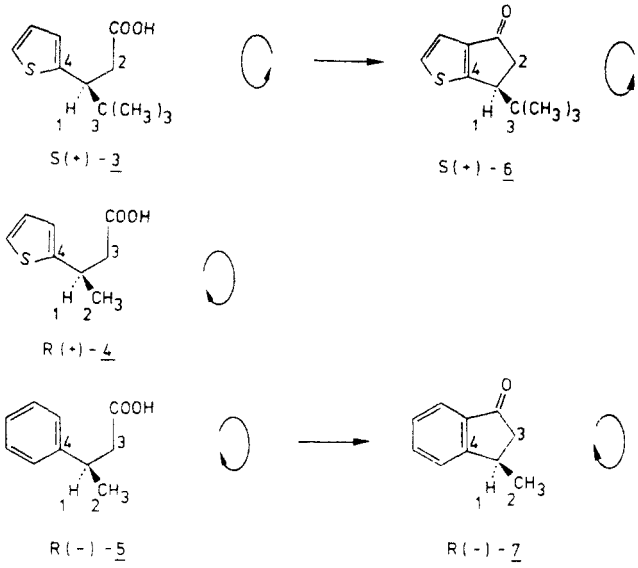
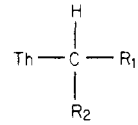
Scheme II. Cahn-Ingold-Prelog Notations for the Acids 3-5 and the Ketones 6 and 7



suing reaction conditions. The resolution of 4 and 5 was necessary for determining the absolute configuration of 3 (vide infra). The resolution of acid 5 is described in the literature.[2] Following the most generally applied method,[3] 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 combination for resolution by fractional crystallization when chloroform was used as solvent for the salt of 3 and a dioxane–diisopropyl ether mixture for the salt of 4. Initially, nine crystallizations were necessary to obtain some optically pure material. However, once optically pure seed crystals were on hand, the number of crystallizations could be markedly reduced (three or four), using 0.5 equiv of base and allowing the solutions to cool very slowly. Crystallizations were repeated until no further increase in the specific rotation ($[\alpha]^T_\lambda$) of the acids was observed. A maximum specific rotation, obtained on fractional crystallization, is not necessarily a criterion for enantiomeric purity.[4] 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 on consideration of the analogous behavior 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 1-menthyl ester,[5] some side reactions like polymerization of the thiophene moiety took place, thus diminishing the accuracy when the gas chromatographic method was applied. 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 chiral shift reagents[6] or chiral solvents[7] are used. 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.

Table I. Chiral 2-Thienyl Derivatives with Known Configurations (Th = 2-Thienyl)



R_1	R_2	confign	ref
$CH_2C_6H_5$	COOH	(*R*)-(+)	9
CH_3	$CH_2C_6H_5$	(*S*)-(+)	9
COOH	OCH_3	(*R*)-(+)	10
$CH_2C_6H_5$	CH_2OH	(*R*)-(+)	10, 11
CH_2COOH	COOH	(*S*)-(−)	12

The notation used to describe the absolute configurations of the chiral compounds is the Cahn–Ingold–Prelog notation.[8] 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 Scheme II for a number of substances.

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 I all chiral 2-thienyl derivatives are listed with chemically derived absolute configurations and resemble 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)[13] 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).

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[14] has found a wide applicability. A number of general rules have been deduced empirically or semiempirically 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.[15] However, direct

(2) Prelog, V.; Scherrer, H. *Helv. Chim. Acta* **1959**, *42*, 2227.
(3) (a) Secor, R. M. *Chem. Rev.* **1963**, *63*, 297. (b) Russ, D. R.; Vermeulen, T. *Ind. Eng. Chem.* **1968**, *60*, 8. (c) Westley, J. W.; Halpern, B.; Karger, E. L. *Anal. Chem.* **1968**, *40*, 2046. (d) Wilen, S. H.; Collet, A.; Jaques, J. *Tetrahedron* **1977**, *33*, 2725.
(4) Horeau, A. *Tetrahedron Lett.* **1961**, 3132.
(5) (a) Vilt, S. V.; Saporowakaya, M. B.; Gulohava, I. P.; Belikov, V. E. *Tetrahedron Lett.* **1965**, 2575. (b) Hirota, K.; Koizumi, H.; Hironaka, Y.; Izumi, Y. *Bull. Soc. Chim. Jpn.* **1976**, *49*, 289.
(6) (a) Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1970**, *92*, 6979. (b) Goering, H. L.; Eikenberry, J. N. *Ibid.* **1971**, *93*, 5913.
(7) (a) Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1937. (b) *Ibid.* **1966**, *88*, 4294. (c) Pirkle, W. H.; Blare, S. D. *Ibid.* **1967**, *89*, 5485. (d) *Ibid.* **1968**, *90*, 6250. (e) *Ibid.* **1969**, *91*, 5150.
(8) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.
(9) Petterson, K. *Ark. Kemi* **1956**, *8*, 387.
(10) Raznikiewicz, T. *Ark. Kemi* **1962**, *18*, 467.
(11) Watson, M. B.; Youngson, G. W. *J. Chem. Soc.* **1968**, 258.
(12) Albers, H.; Albers, E. *Z. Naturforsch. B* **1954**, *9*, 122.
(13) Freudenberg, K.; Brauns, F.; Siegel, H. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 193.
(14) Velluz, L.; Legrand, M.; Grosjean, M. "Optical Circular Dichroism"; Verlag Chemie: Weinheim/Bergstr., Germany, Academic Press, New York, 1965.

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

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 the influence of an acid. These ketones have the advantage of possessing, apart from the aromatic absorptions, additional α,β-unsaturated carbonyl absorptions. As proposed by several authors,[16] such systems may be considered as cyclopentenones, to which an octant rule as deduced for ketones is applicable. The sign of $\Delta\epsilon$ 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 $\Delta\epsilon$ (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 into 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[17] 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 comparison of the signs of $\Delta\epsilon$ 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 Figures 1 and 2.

In 1967 Brienne et al.[15] reported a study on the CD properties of some substituted indanones. They found (*S*)-(+)-3-ethylindanone (**9**), prepared from (*R*)-(−)-α-phenylbutyric acid via (*S*)-(+)-**8**, to exhibit a positive CD effect around 330 nm. Comparison 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 2 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 $\Delta\epsilon$ around 330 nm. This also holds for the thiophene absorptions around 230 nm of the acids **3** and **4** as shown in Figure 1.

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

Preparation of the 6α-*tert*-Butyl-Substituted Optically Pure Steroid via Asymmetric Induction. 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. The dependence of the stereospecificity of the cyclization of racemic **10** on the size of the *pro*-C-6 substituent (R) has been described.[1]

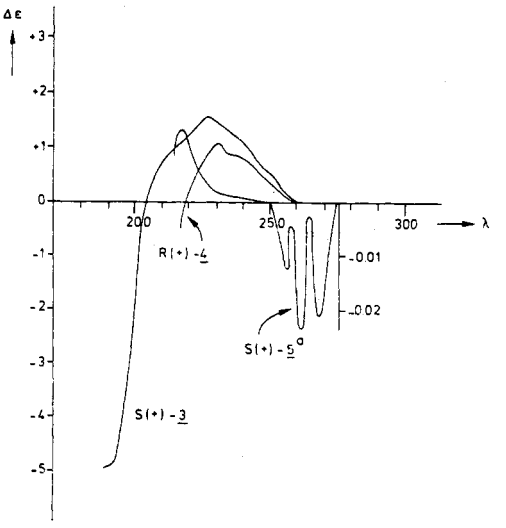


Figure 1. CD spectra of (*S*)-(+)-**3**, (*R*)-(+)-**4**, and (*S*)-(+)-**5**[a]. The spectrum for **5**[a] was not corrected for optical purity.

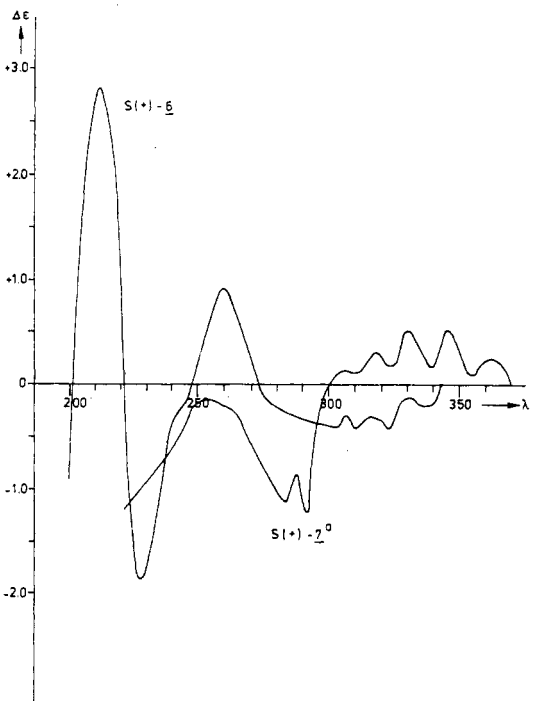
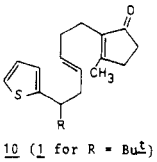


Figure 2. CD spectra of (*S*)-(+)-**6** and (*S*)-(+)-**7**[a]. Spectrum for **7**[a] was not corrected for optical purity.

Even a relatively small methyl group readily afforded 97% of an α-substituted steroid, while a 100% stereospecificity was attained on cyclizing the *pro*-C-6 *t*-Bu-substituted racemic mixture (see **10**). Conversion of enantiomerically



10 (**1** for R = Bu^t)

pure **1** thus has to lead to an optically pure steroid. This biomimetic polyene cyclization is now described in full extent. Also included is a study about the CD properties of the obtained steroid and its precursors.

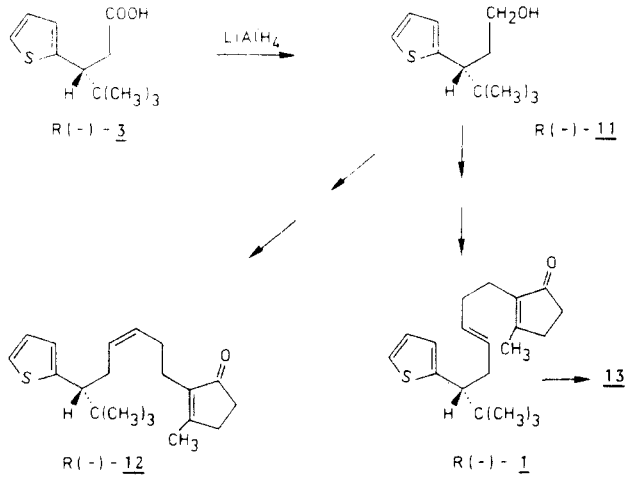
Synthesis of the Optically Pure Cyclization Precursor. In Scheme III a shortened synthesis of the cyclization precursor **13** is given. The route corresponds to the one described earlier. An advantage of this reaction scheme is the possibility of resolving the antipodes at an

(15) Brienne, M. J.; Quannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613.

(16) (a) Adachi, A.; Naemura, K.; Nakazaki, M. *Tetrahedron Lett.* **1968**, 5467. (b) Hugel, G.; Lods, L.; Mellor, J. M.; Curisson, G. *Bull. Soc. Chim. Fr.* **1965**, 2854. (c) Hanna, R.; Curisson, G. *Ibid.* **1967**, 219.

(17) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternack, T. *Helv. Chim. Acta* **1970**, *53*, 739.

Scheme III. Preparation of the Optically Pure Cyclization Precursor 13



early stage. During the reactions on **3** no racemization can occur, as the chiral center is located sufficiently far from the acid function. The conversion of (*R*)-(−)-**3** or (*S*)-(+)-**3** will each lead to a steroid with known absolute configuration, since it appeared from ^{13}C NMR measurements that the C-6 substituent and the proton at C-8 will occupy *both* positions or either the α or the β position in the trans–anti-fused tetracycles.[1] The two enantiomers of **3** were each converted into the steroid. Since essentially the same results were obtained, only one isomer (starting from (*R*)-(−)-**3**) will be described. Thus, reduction of (*R*)-(−)-**3** with $LiAlH_4$ gave the alcohol (*R*)-(−)-**11**, which was oxidized to the aldehyde with pyridinium chlorochromate. A Wittig condensation reaction under Schlosser conditions followed by deketalization and cyclodehydration gave the (*R*)-(−)-(*E*)-cyclopentenone **1**.[1] For additional information about the CD properties of **1**, the *Z* isomer **12** was also prepared via the normal Wittig reaction. It appeared, however, that **12** was contaminated with 25% of **1**.

Wittig reactions are most suited for the unambiguous synthesis of substituted alkenes.[18] Reaction of an aldehyde or ketone with an *unstabilized* phosphorane gives initially a betaine (see Scheme IV), 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 modifiction[19] of Wittig reactions with unstabilized phosphoranes 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,[19] the kind of base,[20] 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 II). Optimal reaction conditions for the preparation of the chiral (*E*)-alkenes by the Wittig–

Scheme IV. Wittig Reaction of an Unstabilized Phosphorane with and without the use of Schlosser Conditions

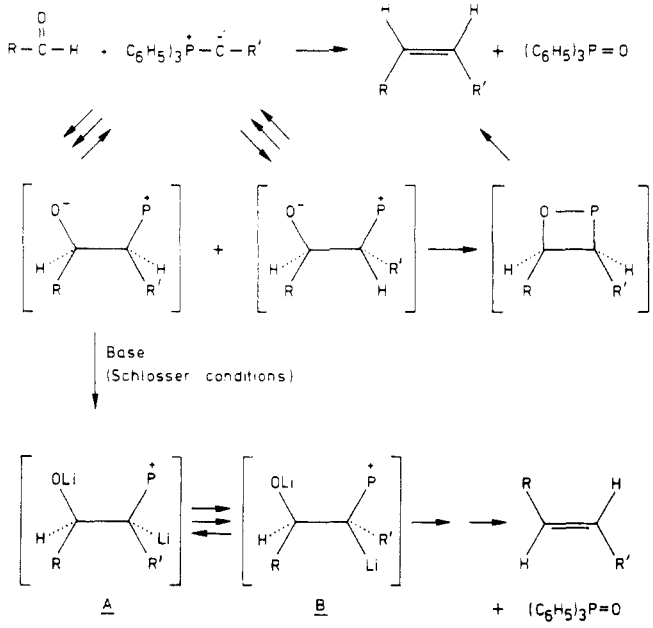
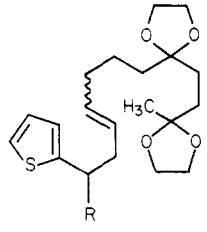


Table II. Influence of Reaction Conditions on the *Z*/*E* Ratio



R	base	isomerization time, h	reaction temp, °C	*Z*/*E* ratio
H	butyllithium	*a*	−78	>90:10
H	butyllithium	*a*	−78	50:50
H	phenyllithium	0.1	−78	<10:90
CH_3	phenyllithium	5	−78	<5:95
CH_3	phenyllithium	1	−30	<5:95
$C(CH_3)_3$	phenyllithium	5	−78	50:50
$C(CH_3)_3$	phenyllithium	1	−30	<5:95
$C(CH_3)_3$	butyllithium	*a*	0	75:25

[a] These reactions were performed under normal Wittig conditions.

Schlosser reaction were found by using phenyllithium as the base. An isomerization time of ca. 0.5–1 h at −30 °C was required after the betaine adduct is formed at −78 °C.

CD Data of the Cyclization Precursors. 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,[21] some studies are reported about a thiophene-containing tripticene,[22] a heterohelicene,[23] and substituted bithienyls.[23a]

The CD spectrum of acid (*S*)-(+)-**3** is given in Figure 1. The spectra of the alcohol (*R*)-(−)-**11** and the (*Z*)- and (*E*)-cyclopentenones (*R*)-(−)-**12** and (*R*)-(−)-**1**, respectively,

(18) For a review see: Reucroft, J.; Sammes, P. G. *Q. Rev., Chem. Soc.* **1971**, *25*, 135.
(19) (a) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126. (b) *Justus Liebigs Ann. Chem.* **1967**, *708*, 1. (c) Schlosser, M.; Christmann, K. F.; Pascala, A. *Chem. Ber.* **1970**, *103*, 2814.
(20) Corvers, A. Thesis Eindhoven University of Technology, The Netherlands, 1977.
(21) Verbit, L. *Tetrahedron Lett.* **1967**, 2169.
(22) de Wit, J.; Wijnberg, H. *Tetrahedron* **1972**, *28*, 4617.
(23) (a) Hakansson, R.; Wiklund, E. *Acta Chem. Scand.* **1971**, *25*, 2509. (b) Wijnberg, H.; Groen, M. B. *J. Am. Chem. Soc.* **1968**, *90*, 5339. (c) Groen, M. B.; Wijnberg, H. *Ibid.* **1971**, *93*, 2968.

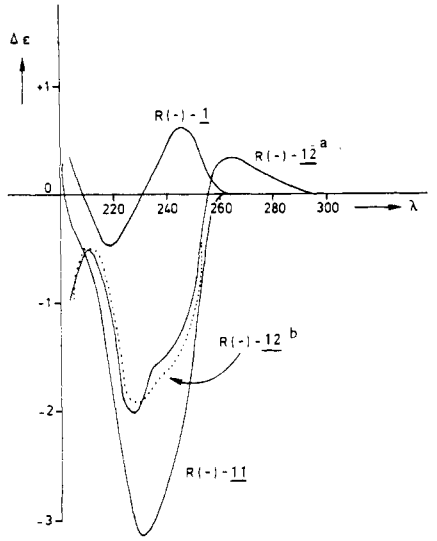
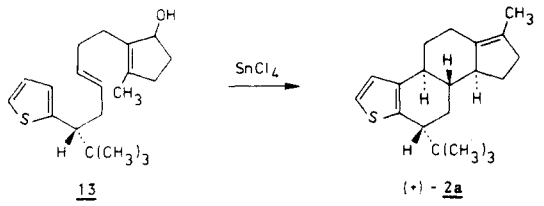


Figure 3. CD spectra of (*R*)-(−)-**1**, (*R*)-(−)-**11**, (*R*)-(−)-**12** (mixture of 75% *Z* and 25% *E* isomer), and (*R*)-(−)-**12** (corrected for 100% *Z* isomer).

Scheme V. Acid-Catalyzed Ring Closure of Optically Pure 13 into (+)-2a



13 (+)-2a

are given in Figure 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, except for one absorption in (*R*)-(−)-**1**, which is inversed. This must be caused by a difference in conformational freedom between **1** and **12**.

Ring Closure of the Optically Pure Substrate. Yield Improvement of the Cyclization. The cyclization of optically pure **13** → **2a** was performed exactly as on the racemates. Whereas the yields on C-6-substituted racemic steroids were always 50% as a maximum, the conversion **13** → **2a** proceeded reproducibly in 80% yield[32] (see Scheme V). 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 (*R*)- and (*S*)-coniine was already reported in 1895 by Ladenburg.[24] More recently, Young[25] observed local optical activity in a racemic liquid crystal. These and several other differences in physical measurements could only be explained if nonbonded interactions between the chiral molecules were taken into account.[26] 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. Wijnberg[27] recognized for the first time the consequences of the different interactions on the *chemical reactivity* between chiral molecules. He postulated the following 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 is demonstrated, the carbenium ion derived from **13** assumes a precoiled conformation before ring closure.[1a] *This conformation might fit better in an optically pure solution than in a racemic one, resulting in an increased reaction rate in favor of the rates of the side reactions.*

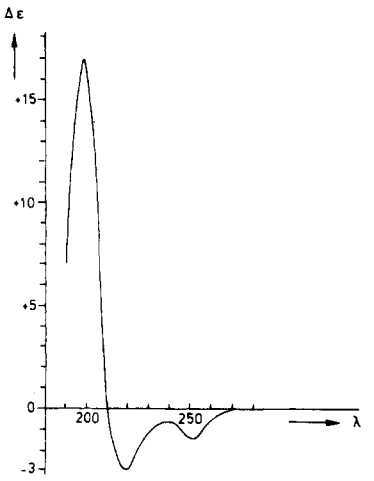
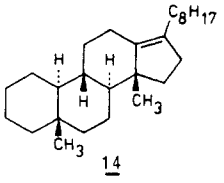
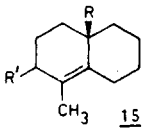


Figure 4. CD spectrum (+)-**2a** obtained after ring closure of (−)-**13**.

Confirmation of the Absolute Configuration. The CD spectrum of steroid **2a**, as given in Figure 4, shows three maxima at 198 nm (Δε = +16.96), 217 (−3.04), and 252 (−1.46). The first two absorption maxima can be ascribed to the ethylene chromophore. Recently, Hudec and Kirk[28] 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 **2a**, there are two absorption maxima between 215–225 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 Δε thus are determined to a large extent by the absolute configuration of C-14. Suitable compounds for the comparison of the CD data are the cholestenes **14**, which in turn appear to



14



15

have characteristics similar to those of $\Delta^{1(9)}$-octaline **15** (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 as λ_0, while in **15** (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 **15** (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 **2a** shows this to agree with the α-axial absolute configuration of the proton at C-14. *The absolute con-*

(24) (a) Ladenburg, A. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 163. (b) Mauser, H. *Chem. Ber.* **1957**, *90*, 301.
(25) Young, W. R.; Aviram, A.; Cox, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 3976.
(26) Horeau, A.; Guetté, J. P. *Tetrahedron* **1974**, *30*, 1923.
(27) Wijnberg, H.; Ferings, B. *Tetrahedron* **1976**, *32*, 2831.
(28) Hudec, J.; Kirk, D. N. *Tetrahedron* **1976**, *32*, 2475.

figuration 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.[1a] The absorption of thiophene at 252 nm could not be related to the absolute configurations in **2a**, because no CD studies have yet been made on related compounds.

Experimental Section

The ^1H NMR data were obtained on a Varian EM 360A spectrometer with Me_4Si as an 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. Bezemer and Dr. W. Leunissen; the GC/MS spectra were recorded by Dr. P. Leclercq, J. Bakker, Ir. A. de Jong, and G. Scherpenzeel. The optical rotations were measured on a Bendix NPL automatic polarimeter, Model 143C. The CD spectra were recorded by Dr. L. Bastiaansen on a Jobin Yvon Dichrograph Mark III-S. The UV spectra were obtained from a Perkin-Elmer double beam grating spectrophotometer, Model 124; the wavelengths are given in parentheses.

(*S*)-(+)-3-(2-Thienyl)-4,4-dimethylpentan-2-oic Acid (3). A mixture of 3 g (12.5 mmol) of the ethyl ester of **3** (see ref 1), 50 mL of 0.5 N of sodium hydroxide and 20 mL of ethanol was refluxed for 2 h. 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). 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. This was repeated until no further increase of specific rotation was observed: $[\alpha]^{22}_D$ +8.8, $[\alpha]^{22}_{546}$ +17.6 (l = 0.100 06 dm, c = 0.0114 g/mL, $CHCl_3$); UV ($c = 2.77 \times 10^{-4}$ mol/L in hexane) log ϵ 5.80 (235 nm); CD ($c = 2.77 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ +1.56 (227 nm). This fractional crystallization also led to the isolation of (*R*)-(−)-**3**.

(*R*)-(+)-3-(2-Thienyl)butanoic Acid (4). This was prepared analogously 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 dioxane–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 ($c = 1.75 \times 10^{-4}$ mol/L in hexane) log ϵ 4.0 (220 nm), 3.7 (232); CD ($c = 1.75 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ +1.03 (230 nm).

(*S*)-(+)-β-Phenylbutyric Acid (5). This compound was prepared and resolved according to the methods described in the literature:[2,29] UV ($c = 3.8 \times 10^{-4}$ mol/L in hexane) log ϵ 3.6 (214 nm), 1.9 (247), 2.1 (252), 2.2 (258), 2.1 (264), 2.0 (267); CD ($c = 3.8 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ +1.26 (217 nm), −0.013 (256), −0.024 (261.5), −0.022 (268).

(*S*)-(+)-6-*tert*-Butyl-5,6-dihydrocyclopenta[*b*]thiophen-4-one (6).[30] 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 min the solution was poured into an ice–salt mixture, from which the product was extracted with ether. After the ether solution was washed successively with a 10% solution of sodium bicarbonate and water, 1.5 g (92%) of NMR-pure **6** was obtained. Chromatography with dichloromethane as eluent afforded analytically pure **6**: NMR δ 1.00 (s, 9, $C(CH_3)_3$), 2.63–2.83 (2 d, 2, CH_2), 3.06–3.37 (m, 1, CH), 6.90–7.27 (AB, 2, ThH); UV ($c = 1.36 \times 10^{-4}$ mol/L in hexane) log ϵ 4.2 (220 nm), 3.9 (240); CD ($c = 1.36 \times 10^{-4}$ mol/L in pentane) $\Delta\epsilon$ 2.82 (213 nm), −1.75 (228), +0.90 (260), −0.41 (300), −0.45 (310), −0.43 (323), −0.21 (338). Anal. Calcd for $C_{17}H_{18}N_4O_4S$ (2,4-dinitrophenylhydrazone, mp 187–190 °C dec): C, 54.53; H, 4.84; N, 14.97. Found: C, 54.27; H, 4.96; N, 14.83.

(*S*)-(+)-3-Methylindan-1-one (7).[31] A mixture of 9.0 g (0.055 mol) of (*S*)-(+)-**5** was heated with 20 g (0.168 mol) of freshly distilled thionyl chloride at 80 °C for 3 h. The excess reagent was removed in vacuo, dry benzene was added, and the evaporation process was repeated. The acid chloride was dissolved in 30 mL of dry benzene and slowly added to 20 g of anhydrous aluminum trichloride in 70 mL of dry benzene. The resulting mixture was refluxed for 1.5 h, cooled, and poured onto ice and concentrated hydrochloric acid. After extraction and distillation, 6.5 g (81%) of (*S*)-(+)-**7** was isolated: bp 112–113.5 °C (9 mm); UV ($c = 2 \times 10^{-4}$ mol/L in hexane) log ϵ 4.0 (220 nm), 4.0 (238), 4.0 (245), 3.4 (274), 3.5 (282), 3.5 (291); CD ($c = 2 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ −1.14 (283 nm), −1.23 (291), +0.13 (306), +0.33 (317), +0.51 (331), +0.53 (346), +0.24 (363).

(*R*)-(−)-2-[7,7-Dimethyl-6-(2-thienyl)-(*E*)-oct-3-enyl]-3-methylcyclopent-2-enone (1). The preparation was analogous to the racemic compound as described in ref 1 via the alcohol (*R*)-(−)-3-(2-thienyl)-4,4-dimethylpentanol (**11**):[1] yield 32% (based on alcohol); $[\alpha]^{21}_D$ −0.6, $[\alpha]^{21}_{534}$ −1.7 (l = 0.100 06 dm, c = 0.0105 g/mL, dichloromethane); UV ($c = 1.35 \times 10^{-4}$ mol/L in hexane) log ϵ 3.77 (211 nm), 3.56 (235); CD ($c = 1.35 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ −0.47 (217 nm), +0.62 (244).

(*R*)-(−)-2-[7,7-Dimethyl-6-(2-thienyl)-(*Z*)-oct-3-enyl]-3-methylcyclopent-2-enone (12). The synthesis was analogous to that for **1** without the use of Schlosser conditions.

(*R*)-(−)-3-(2-Thienyl)-4,4-dimethylpentanol (11). A solution of 1.38 g (6.5 mmol) of (*R*)-(−)-**3** 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 the mixture was refluxed for 2 h, no acid was detected by TLC. The usual workup yielded 1.03 g of the alcohol: yield 83%; $[\alpha]^{21}_D$ −22.6, $[\alpha]^{21}_{534}$ −28.3 (l = 0.100 06 dm, c = 0.011 35 g/mL, methanol); UV ($c = 2.9 \times 10^{-4}$ mol/L in hexane) log ϵ 3.40 (196 nm), 3.92 (235); CD ($c = 2.9 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ +1.90 (197 nm), −3.22 (232).

(6*R*)-(+)-17-Methyl-6-*tert*-butyl-3-thia-4-noroestra-1,5(10),13(17)-triene (2a). The cyclization was performed at −95 °C with $SnCl_4$ as a Lewis acid. For the experimental procedure, see ref 1a,b: yield 80%; $[\alpha]^{24}_D$ +20.7, $[\alpha]^{24}_{534}$ +22.5 (l = 0.100 06 dm, c = 0.002 17 g/mL in benzene); UV ($c = 2.3 \times 10^{-4}$ mol/L in hexane) log ϵ 3.84 (212 nm), 3.75 (238); CD ($c = 2.3 \times 10^{-4}$ mol/L in hexane) $\Delta\epsilon$ +16.96 (198 nm), −3.04 (217), −1.46 (252).

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Registry No. (*R*)-(−)-(*E*)-**1**, 77340-69-3; (6*R*)-(+)-**2a**, 77340-70-6; (±)-**3**, 77270-47-4; (±)-**3** ethyl ester, 62815-74-1; (*R*)-(−)-**3**, 77340-71-7; (*S*)-(+)-**3**, 77340-72-8; (*S*)-(+)-**3** (+)-phenylethylammonium salt, 77340-73-9; (±)-**4**, 77270-48-5; (*R*)-(+)-**4**, 77340-74-0; (*R*)-(+)-**4** (+)-phenylethylammonium salt, 77340-75-1; (*S*)-(+)-**5**, 772-15-6; (*S*)-(+)-**6**, 77270-49-6; (*S*)-(+)-**6** dinitrophenylhydrazone, 77270-50-9; (*S*)-(+)-**7**, 935-77-3; (*R*)-(−)-**11**, 77340-76-2; (*R*)-(−)-(*Z*)-**12**, 77340-77-3; **13**, 62815-67-2; (*Z*)-12-(2-thienyl)-9-dodecene-2,5-dione bis(ethylene ketal), 62429-59-8; (*E*)-12-(2-thienyl)-9-dodecene-2,5-dione bis(ethylene ketal), 77270-51-0; (*Z*)-12-(2-thienyl)-9-tridecene-2,5-dione bis(ethylene ketal), 77270-52-1; (*E*)-12-(2-thienyl)-9-tridecene-2,5-dione bis(ethylene ketal), 77270-53-2; (*Z*)-13,13-dimethyl-12-(2-thienyl)-9-tetradecene-2,5-dione bis(ethylene ketal), 77270-54-3; (*E*)-13,13-dimethyl-12-(2-thienyl)-9-tetradecene-2,5-dione bis(ethylene ketal), 77270-55-4.

(29) "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 762.

(30) Sam, J.; Thompson, A. C. *J. Pharmaceut. Sci.* **1963**, *52*, 898.

(31) Weidler, A. M.; Bergson, G. *Acta Chem. Scand.* **1964**, *18*, 1484.

(32) The dramatic increase in yield on ring closure of **13** leading to enantio- and diastereomerically free (+)-**2a** opens an interesting strategy for the preparation of estrogen-like steroids via Johnson's procedure. For effectuation of this route an easily removal group at *pro*-C-6 in **13** (instead of *t*-Bu), which also introduces complete asymmetric induction, must be involved.