Notes

Asymmetric Induction in the Synthesis of Thiophene-Containing Steroidlike Molecules via Olefinic Cyclization. 2.[1] Evidence for Precoiling As Model Description for the Cyclization

Anton A. Macco,* Rud J. de Brouwer, Peter M. M. Nossin, Erik F. Godefroi, and Henk M. Buck

Department of Organic Chemistry, Eindhoven University of Technology, The Netherlands

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Recently, we demonstrated the occurrence of asymmetric induction in the preparation of thiophene-containing steroids via olefinic cyclization.[1] With the chiral center at *pro*-C-5 far from the reaction initiator, a 97 and 100% asymmetric induction in favor of the α isomer was realized on cyclizing **1b** and **1c** respectively (Scheme I). These high stereospecificities were ascribed to nonbonded interactions between R and the hydrogen atoms at *pro*-C-7 and *pro*-C-9 that bring about the initial stereospecific C–D ring closure.

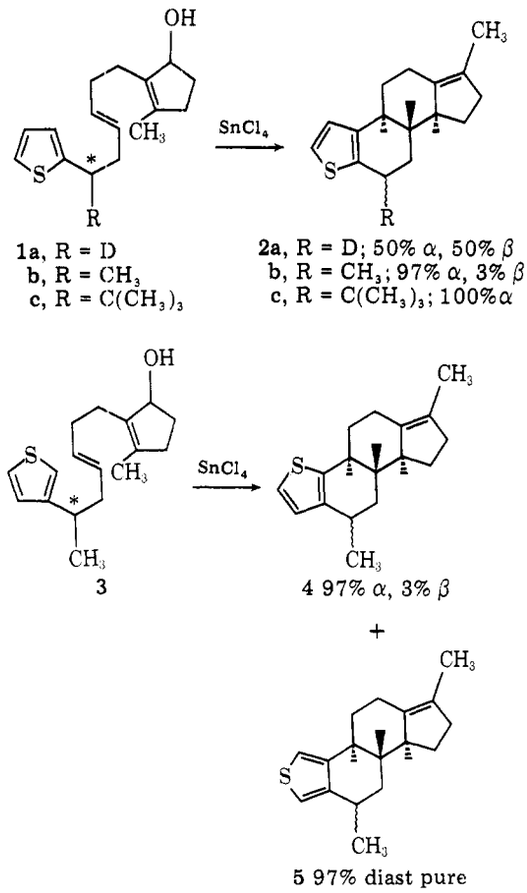
To gain further insight into such cyclization processes, we examined the reaction of deuterio derivative **1a** as well as the 3-substituted thiophene derivative **3.** From racemic **1a,** both the 5α as the 5β enantiomeric pairs of diastereomers were formed in equal amounts. Cyclization of racemic **3** gave compounds **4** and **5** each being 97% diastereomerically pure.

The starting materials **1a** and **3** were prepared according to Scheme II. 2-Thiophenecarboxylic acid, on esterification and reduction with $LiAlD_4$, gave 2-thienyldideuteriomethanol (**6a**). Oxidation with pyridinium chlorochromate[2] afforded aldehyde **7a.** 3-Thienyllithium reacted with acetaldehyde to afford 1-(3-thienyl)ethanol (**6b**) which, on oxidation with lead tetraacetate, furnished ketone **7b.** Wittig condensation of **11a,b** with phosphonium salt **12**[3] under Schlosser conditions[4] afforded *E* alkenes, a geometric prerequisite for cyclization.[5] The structures were confirmed with ^{13}C NMR by a method developed by de Haan and van de Ven.[6]

Upon cyclization of **1a,** both enantiomeric pairs of diastereomers **2a** were formed in equal amounts (±5%); in ^1H NMR (360 MHz) the integrals of the signals from the C-5–αH and C-5–βH at δ 2.74 and 2.84 ppm respectively were of equal magnitude.

Cyclization of the 3-substituted thiophene **3** afforded a mixture of tetracyclic products. ^{13}C NMR data revealed that approximately 70% consisted of a product in which ring closure has occurred at the 2 position of thiophene (**4**). The α configuration of the 5-methyl substituent in **4** was determined by the δ values of C-7 and C-8.[1] In the remaining 30% ring closure has taken place at the 4 position of thiophene to form compound **5** (see Table I). Also a singlet at 6.70 ppm in the ^1H-NMR spectrum for the two aromatic protons corroborates this structure. The TLC pure material could be separated partially by analytical HPLC, which showed both **4** and **5** to be 97% diastereomerically pure. The diastereomers in the mixture could be assigned by mass spectroscopy; the products show a two by two corresponding specific mass fragmentation.

Scheme I[a]



[a] The enantiomers are not drawn.

Scheme II

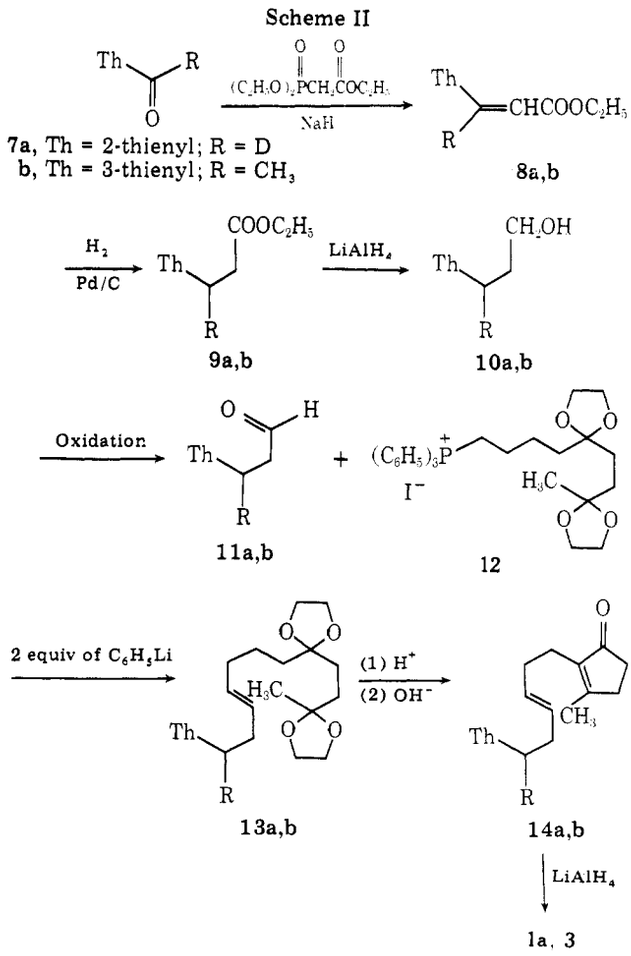


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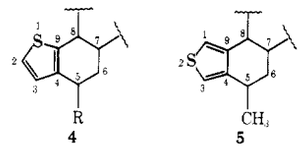
Table I[a]



4 5

Compd	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
4, R = H[b]	65166-17-8		122.63	128.16	135.25	26.78	28.89	42.52	50.42	141.16
4, R = CH_3	65121-19-9		122.73	126.73	141.16	32.28	38.91	42.83	50.68	140.63
5	65121-20-2	119.20		118.40	142.97	33.22	39.10	43.27	49.98	144.38

[a] Values in parts per million downfield from Me_4Si. [b] The values of this compound are obtained from ref 7.

The absolute configuration of the 5-methyl substituent in **5** could not be determined. The similarities of asymmetric induction with the different substrates suggest that the 5-methyl group in **5** also occupies the α position (for 97%). The different cyclization experiments show the diastereomeric purity to be the same (97%) regardless of the cyclization occurring at the 2, 3, or 4 position of thiophene.

To the best of our knowledge the formation of **5** represents an unusual mode of cyclization in the thiophene series. The only known electrophilic cyclizations of achiral 3-substituted thiophene analogues take place at the 2 position exclusively.[5] Moreover, the 4 position of 3-alkylthiophenes is the least reactive one toward substitution reactions. In our opinion the isomer formation finds its cause in a considerably retarded or stopped conformer exchange A ⇌ B (Scheme III) at the low reaction temperature (−95 °C) due to a steric interaction between the methyl substituent at *pro*-C-5 and the hydrogen atoms at *pro*-C-3 and *pro*-C-9.

The cyclizations proceed concertedly, as already has been confirmed by Johnson for phenyl analogues,[11] via a distinct productlike transition state. Cyclization of **1a–c** demonstrates how slight steric variation of substituents can effectively influence the 1,3-diaxial interactions which ultimately govern the asymmetric induced stereospecific C–D ring closure. The cyclization of **3** to the least reactive 4 position of thiophene implies that the reaction is initiated from a fixed conformer. *All these results confirm strongly our earlier proposal to describe the stereochemical course of the reaction by precoiling of the initial formed allylic cation.*[1]

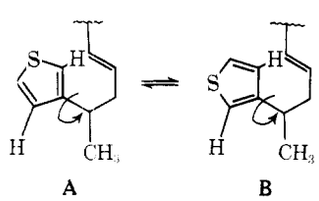
Experimental Section

The ^1H NMR data were obtained on a Varian EM-360 spectrometer using Me_4Si as internal standard (δ 0.00). The ^{13}C 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 analyses were carried out by Mr. G. J. Bezemer. 3-Bromothiophene was prepared according to the literature.[8]

2-Thienyldideuteriomethanol (6a). 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 °C. After 2 h of refluxing 1 N NaOH was added. Filtering and extracting with ether followed by distillation yielded 6 g of **6a** (100%): bp 96–98 °C (12 mm); NMR (CCl_4) δ 4.53 (s, 1, OH), 6.69–7.18 (m, 3, ThH).

2'-Thienyl-1-deuteriocarbaldehyde (7a). A solution of 4 g (35 mmol) of **6a** in 25 mL of dichloromethane was rapidly added to a suspension of 11.4 g (53 mmol) of pyridinium chlorochromate[9] in 50 mL of dichloromethane at room temperature. After 3 h of stirring no alcohol could be monitored. A fivefold excess of ether was added and the solution was filtered over Florisil. Distillation afforded 3.7 g of aldehyde **7a** (94%): bp 67–68°C (13 mm); NMR (CCl_4) δ 7.00–7.67 (m, 3, ThH).

Scheme III



A B

1-(3-Thienyl)ethanol (6b). To a solution of 20 g (122 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 being stirred for 4 h at −78 °C, the mixture was poured into water and the product was extracted into ether. The combined ether layers were dried with $MgSO_4$ and concentrated. The alcohol **6b** was immediately oxidized to 3-acetylthiophene (**7b**): 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 (7b). To a solution of 4.8 g (38 mmol) of **6b** in 100 mL of pyridine 20 g (130 mmol) 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 was extracted into benzene. Chromatography yielded 4.6 g of **7b** (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-(2-Thienyl)-3-deuterioprop-2-enoic Acid Ethyl Ester (8a). To a solution of 3 g (0.1 mol) of sodium hydride (80% in paraffin) in 100 mL of dimethoxyethane (under a nitrogen atmosphere) was added 21.2 g (0.1 mol) of triethyl phosphonoacetate at a temperature below 20 °C. After the solution was stirred for 1 h 11.3 g (0.1 mol) of aldehyde **7a** was added and refluxed for 16 h. The mixture was poured into water and the product was extracted into ether. After the combined ether layers were dried with $MgSO_4$, the solvent was stripped off. Distillation gave 14.5 g of **8a** (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-(3-Thienyl)but-2-enoic Acid Ethyl Ester (8b) was prepared as for **8a** with benzene as solvent. The product 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-(2-Thienyl)-3-deuteriopropanoic Acid Ethyl Ester (9a). A mixture of 10 g of **8a** (54.6 mmol) was hydrogenated 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-(3-Thienyl)butanoic Acid Ethyl Ester (9b) was prepared analogous to **9a:** yield 89%; bp 125 °C (18 mm); NMR (CCl_4) δ 1.15 (t, 3, CH_2CH_3), 1.27 (d, 3, CH_3), 2.35–2.55 (AA'B, 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-(2-Thienyl)-3-deuteriopropanol (10a). A solution of 3.7 g (0.02 mol) of **9a** in 10 mL of ether was added dropwise to a suspension of 0.02 mol (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 **10a:** 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-(3-Thienyl)butanol (10b) was prepared as for **10a:** yield 90%; 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-(2-Thienyl)-3-deuteriopropanal (11a). This compound was prepared analogous to **7a:** yield 95%; bp 60 °C (0.8 mm).

3-(3-Thienyl)butanal (11b) was also prepared analogous to **7a:** yield 90%; bp 112 °C (16 mm).

2,5-Bis(ethylenedioxy)-12-(2-thienyl)-12-deuterio-(*E*)-dodec-9-ene (13a). To 20.23 g (32 mmol) of phosphonium salt **12**[3] in 75 mL of tetrahydrofuran (THF) was added 16 mL of phenyllithium (2 N solution) at 0 °C under a nitrogen atmosphere. At −70 °C 5.0 g (32 mmol) of **11a** in 5 mL of THF was added, followed by a second equivalent of C_6H_5Li. 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 **13a:** NMR (CCl_4) δ 1.23 (s, 3, diox CH_3), 1.65 (s, 4, $O_2CCH_2CH_2CO_2$), 3.79 (s, 8, 4 OCH_2), 5.20–5.50 (m, 2, C**H**=C**H**), 6.61–7.04 (m, 3, ThH).

2,5-Bis(ethylenedioxy)-12-(3-thienyl)-(*E*)-tridec-9-ene (13b) was prepared as for **13a:** yield 42%; NMR (CCl_4) δ 1.22 (d, 3, $CHCH_3$), 1.23 (s, 3, diox CH_3), 1.62 (s, 4, $O_2CCH_2CH_2CO_2$), 2.48–3.17 (m, 1, $CHCH_3$), 3.88 (s, 8, 4 OCH_2), 5.20–5.40 (m, 2, C**H**=C**H**), 6.77–7.28 (m, 3, ThH).

2-[6-(2-Thienyl)-6-deuterio-(*E*)-hex-3-enyl]-3-methylcyclopent-2-enone (14a). A mixture of 2.75 g (7.5 mmol) of diketal **13a,** 30 mL of 0.5 N HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere of 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 **14a:** NMR (CCl_4) δ 1.30–2.52 (m, 13, aliphatic H), 2.52–3.04 (m, 1, CHD), 5.20–5.47 (m, 2, C**H**=C**H**), 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-(3-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enone (14b) was prepared as for **14a:** yield 80%; 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**H**=C**H**), 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-(2-Thienyl)-6-deuterio-(*E*)-hex-3-enyl]-3-methylcyclopent-2-enol (1a). 2-[6-(3-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enol (3). At −30 °C 2 mmol of $LiAlH_4$ was added in small portions to a solution of 2.0 mmol of ketone **14a** or **14b.** 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 cyclization experiments.

5-Methyl-11-deuterio-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]tridec-4-ene (2a). To a solution of 500 mg of unsaturated alcohol **1a** in 10 mL of dichloromethane at −95 °C, 1.2 equiv of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product was extracted with dichloromethane. Chromatography yielded 230 mg of product (50%): 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). Anal. Calcd for $C_{16}H_{19}DS$: C, 78.31; H, 8.62. Found: C, 78.47; H, 8.67.

The cyclization of **3** was analogous to **1a:** yield 50%; NMR (CCl_4) δ 1.00–3.00 (m, 14, aliphatic H), 1.22 (d, 3, $CHCH_3$), 1.60 (s, 3, $C{=}CH_3$), 6.60–6.90 (AB, 2, ThH), 6.70 (s, 2, ThH). Anal. Calcd. for $C_{17}H_{22}S$: C, 79.07; H, 8.53. Found: C, 79.42; H, 8.85.

Acknowledgment. The authors are indebted to Dr. P. A. Leclercq and Dr. J. W. de Haan from the Department of Instrumental Analysis for recording and interpretation of the mass and ^{13}C NMR spectra, respectively. This investigation has been supported by the Netherlands Foundation for Chemical Research with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

Registry No.—**1a,** 65121-21-3; **2a** α-isomer, 65121-22-4; **2a** β-isomer, 65166-18-9; **3,** 65121-23-5; **6a,** 42006-95-1; **6b,** 14861-60-0; **7a,** 42007-08-9; **7b,** 1468-83-3; **8a,** 65121-24-6; (*E*)-**8b,** 65121-25-7; (*Z*)-**8b,** 65121-26-8; **9a,** 65121-27-9; **9b,** 65121-28-0; **10a,** 65121-29-1; **10b,** 65121-30-4; **11a,** 65121-31-5; **11b,** 65121-32-6; **12,** 33548-59-3; **13,** 65121-33-7; **13b,** 65121-34-8; **14a,** 65121-35-9; **14b,** 65121-36-0; 2-thiophenecarboxylic acid methyl ester, 5380-42-7; 3-bromothiophene, 872-31-1; acetaldehyde, 75-07-0; triethyl phosphonoacetate, 867-13-0.

References and Notes

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Methylation of Pyrimidines, the Corresponding Nucleosides, and Inosine with Trimethyloxosulfonium Hydroxide

Kiyoshi Yamauchi,* Kazue Nakamura, and Masayoshi Kinoshita

Department of Applied Chemistry, Osaka City University, Sumiyoshi-ku, Osaka, Japan

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The methylation of nucleic acid components is being actively pursued. The most interesting aspects of the problem have arisen from the discovery of various kinds of methylated ribonucleosides from RNA,[1-3] and from studies of the interaction of alkylating agents with nucleic acids and their components.[4-6]

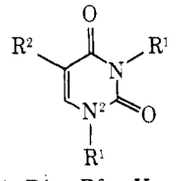
We wish to describe the methylation of pyrimidines (**1, 2,** and **5**), the corresponding nucleosides (**7, 10,** and **16**), and inosine (**13**), using trimethyloxosulfonium hydroxide (MOSH) as a new alkylating agent. Although the preparation of MOSH was reported about two decades ago,[7] its chemistry has been little studied. We prepared MOSH in methanol by a modified procedure, finding that this reagent is potentially very useful for methylation of a wide variety of compounds.

Results and Discussion

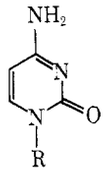
The general procedure consists of heating pyrimidines or nucleosides with MOSH at 40–140 °C in dimethylformamide (DMF). The reaction was followed by thin-layer chromatography and the products were isolated through a very simple workup of the reaction mixture. The results are summarized in Table I.

This method converted uracil (**1**), thymine (**2**), and cytosine (**5**) to the corresponding *N*-methylated derivatives in excellent yields.

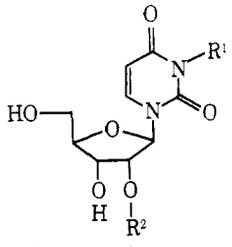
Similarly, uridine (**7**), thymidine (**10**), and inosine (**13**)



1, $R^1 = R^2 = H$
2, $R^1 = H$; $R^2 = Mo$
3, $R^1 = Me$; $R^2 = H$
4, $R^1 = R^2 = Me$



5, R = H
6, R = Me



7, $R^1 = R^2 = H$
8, $R^1 = Me$; $R^2 = H$
9, $R^1 = R^2 = Me$

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