TOTALLY SYNTHETIC STEROID HETEROCYCLES.† PART X. SYNTHESIS OF RACEMIC A-NOR-3,16-DITHIA- AND 2-METHYL-A-NOR-3-OXA-16-THIA-D-HOMO-1,5(10),8,14-ESTRATETRAEN-17a-OLS*

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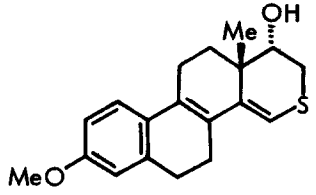
ABSTRACT

As a part of synthetic modifications directed toward biologically active 16-thia-D-homoestrogens, synthesis of the title steroids via the Torgov-Wendler route is described.

INTRODUCTION

Several of the 16-thia-D-homoestrogens (1) synthesized earlier in our laboratory were found to have interesting biological properties. Above all, 3-methoxy-16-thia-D-homo-1,3,5(10),8,14-estrapentaen-17aα-ol (I) was shown by primary bioassays in rodents to be an orally potent estrogen with a high antifertility to estrogenicity ratio compared with the well-known mestranol (d-3-methoxy-17α-ethinyl-1,3,5(10)-estratrien-17β-ol) (2). Additional evaluation revealed that the thiasteroid lowered serum cholesterol levels. These findings prompted us to further synthesize the A-heteroaromatic analogues. We now report the synthesis of racemic A-nor-3,16-dithia- and 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),8,14-estratetraen-17a-ols (VII) and (VIII).

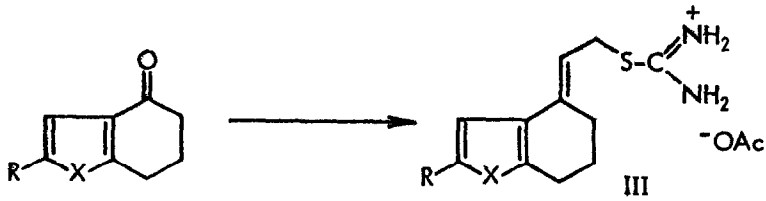


I

Following the Torgov-Wendler route (3), the known isothiuronium acetates IIIa and IIIb were chosen as starting materials which were prepared essentially according to previously described procedures (4,5,6).

Condensation of the salt IIIa with 2-methyl-5-thiacyclohexane-1,3-dione (IV) was smoothly carried out by stirring the mixture in 50% ethanol at room temperature affording 8,14-seco-A-nor-3,16-dithia-D-homo-1,5(10),9(11)-estratriene-14,17a-dione (Va) as a nicely crystalline solid in 70% yield. A similar coupling reaction of the salt IIIb was achieved by treating it with the dione IV in 80% ethanol at 45°C to give 2-methyl-8,14-seco-A-nor-3-oxa-16-thia-D-homo-1,5(10),9(11)-estratriene-14,17a-dione (Vb) in 66% yield. The structures of the seco-steroids Va and Vb were evident from the characteristic carbonyl bands in their IR spectra and the signals associated with the 13-methyl and 11-olefinic protons in their NMR spectra.

Cyclodehydration of the seco-dione Va was effected by brief treatment with p-toluenesulfonic acid in boiling benzene furnishing the expected A-nor-3,16-dithia-D-homo-1,5(10),8,14-estratetraen-17a-one (VIa) in 92% yield. The spectral data clearly confirmed the cyclized structure. Subsequent reduction with sodium borohydride in ethanol-tetrahydrofuran (5:2) yielded both epimers of the desired A-nor-3,16-dithia-D-homo-1,5(10),8,14-estratetraen-17a-ol, VIIa (60%) and VIIIa (26%), which were separable by preparative TLC (7). However, these alcohols were frequently contaminated with minor amounts of the dehydro isomers Xa and XIa, presumably originating from the oxidative aromatization of ring B during the above

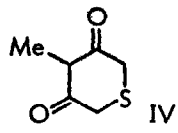


II

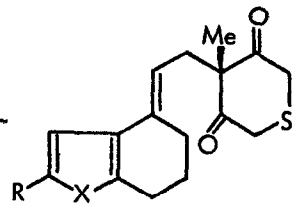
a: X = S, R = H

b: X = O, R = Me

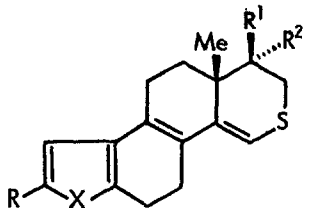
III



IV



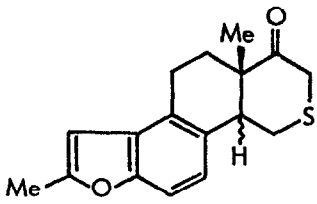
V



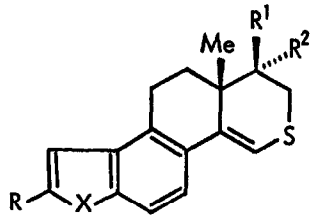
VI, R^1, R^2 = O

VII, R^1 = H, R^2 = OH

VIII, R^1 = OH, R^2 = H



XII



IX, R^1, R^2 = O

X, R^1 = H, R^2 = OH

XI, R^1 = OH, R^2 = H

mentioned acid-catalyzed cyclodehydration. The presence of the benzothiophene moiety in the latter compounds was supported by UV, NMR, and MS data.

Such oxidative aromatization was observed to occur more readily in the case of the furanosteroid Vb, which was more acid labile than the thiophene analogue. When the seco-dione Vb was treated with p-toluenesulfonic acid in chloroform under mild conditions, a mixture of three compounds was obtained then carefully separated by chromatography. The products were identified as 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),8,14-estratetraen-17a-one (VIb) (51%), 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),6,8,14-estrapentaen-17a-one (IXb) (6.5%), and 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),6,8-14ξ-estratetraen-17a-one (XII) (13%) based on their spectra. There are a number of precedents for the latter type of aromatization caused by an acid-catalyzed double-bond isomerization (8).

The fact that the furanotetraene VIb tends to undergo facile oxidation even on the surface of an acid adsorbent such as silica gel was found in the further transformation. Thus, an almost pure sample of the tetraenone VIb was reduced with sodium borohydride in ethanol-tetrahydrofuran (10:1) and the crude product was subjected to preparative TLC on silica gel. As expected, two epimeric 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),8,14-estratetraen-17a-ols, VIIb and VIIIb, were isolated in 41 and 19% yield, respectively (7). In addition, the dehydro epimers Xb (7%) and XIb (3%) were obtained as by-products.

The orientation for the hydroxy groups in all the epimeric

alcohols obtained in this work was easily determined by IR on the basis of the intramolecular hydrogen bonding (OH···S).

EXPERIMENTAL

M.p.s were determined on a calibrated Kofler hot-stage apparatus. IR spectra were recorded on a JASCO-DS-403G spectrophotometer and UV spectra on a Hitachi EPS-3T spectrophotometer. NMR spectra were taken on a Varian A-60 instrument using tetramethylsilane as internal standard. MS spectra were recorded using a Hitachi RMU-6 mass spectrometer (70 eV). Preparative TLC was carried out on 20 x 20 x 0.2 cm glass plates precoated with Kieselgel F-254 (type 60, Merck). Alumina used for column chromatography refers to activity grade I, manufactured by M. Woelm, Eschwege, Germany, and made up to activity grade II by the addition of 3% water prior to use.

Starting materials:

According to literature procedures (4,5,6), 4,5,6,7-tetrahydrothianaphthenylideneethylisothiuronium acetate (IIIa), mp 131-134°C, and 2-methyl-4,5,6,7-tetrahydrobenzofuranylideneethylisothiuronium acetate (IIIb), mp 122-124°C, were prepared from commercially available 4-oxo-4,5,6,7-tetrahydrothianaphthene (IIa) and readily accessible 2-methyl-4-oxo-4,5,6,7-tetrahydrocoumarone (IIb) in 76 and 81% overall yields, respectively.

8,14-Seco-A-nor-3,16-dithia-D-homo-1,5(10),9(11)-estratriene-14,17a-dione (Va):

A mixture of the isothiuronium salt IIIa (2.98 g, 10 mmol) and 2-methyl-5-thiacyclohexane-1,3-dione (IV) (1.44 g, 10 mmol) was vigorously stirred in aqueous 50% ethanol (220 ml). A clear solution was observed within 5 min followed by precipitation of product after an additional 10 min. The mixture was stirred at room temperature for 3 hr, chilled, and filtered to give the dione Va (2.16 g, 70.4%), mp 97-99°C. Recrystallization from dichloromethane-ether afforded an analytical sample, mp 98-99.5°C; UV (EtOH) λ_{max} 230 and 257 nm (ε 5600 and 5700); IR ($CHCl_3$) ν_{max} 1728 and 1696 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.38 (s, 3 H, 13-Me), 3.39, 3.48 (ABq, 4 H, J = 15 Hz, SCH_2CO), 5.57 (bt, 3 H, J = 7.5 Hz, 11-H), and 6.99, 7.06 (ABq, 2 H, J = 5.5 Hz, 1- and 2-H). Anal. Calcd. for $C_{16}H_{18}O_2S_2$: C, 62.71; H, 5.92; S, 20.93. Found: C, 62.94; H, 6.04; S, 20.65%.

2-Methyl-8,14-seco-A-nor-3-oxa-16-thia-D-homo-1,5(10),9(11)-estratriene-14,17a-dione (Vb):

A stirred mixture of the isothiuronium acetate IIIb (2.96 g, 10 mmol) and 2-methyl-5-thiacyclohexane-1,3-dione (IV) (1.44 g, 10 mmol) in aqueous 80% ethanol (70 ml) was warmed at 45°C for 3 hr. After cooling, the formed precipitate was filtered to furnish the dione Vb (2.0 g, 65.8%), mp 131-134°C. Recrystallization from ether gave an authentic specimen, mp 136.5-137°C;

UV (EtOH) λ_{max} 240 (sh) and 260 (sh) nm (ε 11200 and 8900); IR ($CHCl_3$) ν_{max} 1726 and 1694 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.36 (s, 3 H, 13-Me), 2.23 (bs, 3 H, 2-Me), 3.35, 3.48 (ABq, 4 H, J = 14 Hz, SCH_2CO), 5.18 (t, 1 H, J = 7.5 Hz, 11-H), and 5.98 (d, 1 H, J = 1 Hz, 1-H). Anal. Calcd. for $C_{17}H_{20}O_3S$: C, 67.07; H, 6.62; S, 10.53. Found: C, 67.26; H, 6.78; S, 10.49%.

A-Nor-3,16-dithia-D-homo-1,5(10),8,14-estratetraen-17a-one (VIa):

A solution of the seco-dione Va (2.3 g, 7.5 mmol) in dry benzene (38 ml) containing p-toluenesulfonic acid (0.23 g) was heated at reflux under nitrogen for 0.5 hr. The cooled solution was poured into cold aqueous sodium bicarbonate solution. The aqueous layer was extracted with ether-dichloromethane (3:1). The organic layers were combined, washed with aqueous saline, and dried (Na_2SO_4). The solvent was evaporated to leave a crystalline residue which afforded, on trituration with ether, the tetraenone VIa, (1.99 g, 92.0%), mp 123-125°C. The analytical specimen was obtained by recrystallization from dichloromethane-ether, mp 127-128.5°C; UV (EtOH) λ_{max} 245, 268, 335, and 350 nm (ε 11200, 8000, 20100, and 14300); IR ($CHCl_3$) ν_{max} 1706 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.38 (s, 3 H, 13-Me), 3.35, 3.48 (ABq, 4 H, J = 13 Hz, SCH_2CO), 6.33 (bs, 1 H, 15-H), and 6.98, 7.06 (ABq, 2 H, J = 5 Hz, 1- and 2-H). Anal. Calcd. for $C_{16}H_{16}OS_2$: C, 66.63; H, 5.59; S, 22.24. Found: C, 66.49; H, 5.53; S, 22.02%.

A-Nor-3,16-dithia-D-homo-1,5(10),8,14-estratetraen-17a-ols (VIIa) and (VIIIa):

Sodium borohydride (0.084 g, 2.2 mmol) was added to a stirred solution of the pentaenone VIa (1.27 g, 4.4 mmol) in ethanol (88 ml) and tetrahydrofuran (35 ml). Stirring was continued for 0.5 hr at room temperature. The mixture was quenched with water, neutralized with cold 20% HCl, concentrated in vacuo, and extracted with ether-dichloromethane (3:1). The extract was washed with aq. saline, dried, and evaporated. The residue was purified by preparative TLC (20:1 benzene-ethyl acetate) to furnish the 17aα-ol VIIa (0.77 g, 60.3%) and the 17aβ-ol VIIIa (0.33 g, 25.8%) as crystalline solids. The major alcohol was recrystallized from dichloromethane-ether to give an analytical sample, mp 127-128°C; UV (EtOH) λ_{max} 257.5, 265 (sh), and 333 nm (ε 11500, 10900, and 21300); IR (dilute CCl_4) ν_{max} 3552 cm^{-1} (bonded OH); NMR ($CDCl_3$) δ 1.02 (s, 3 H, 13-Me), 6.07 (bs, 1 H, 15-H), and 6.97, 7.03 (ABq, 2 H, J = 5.5 Hz, 1- and 2-H), MS m/e 290 (M^+). Anal. Calcd. for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25; S, 22.08. Found: C, 65.98; H, 6.23; S, 22.03%. The acetate had mp 116-118°C (ether-pentane); NMR ($CDCl_3$) δ 1.08 (s, 3 H, 13-Me), 2.08 (s, 3 H, OAc), 4.95 (bt, 1 H, J = 3 Hz, 17a-H), and 6.11 (bs, 1 H, 15-H).

The minor alcohol afforded, on recrystallization from ether-pentane, an analytical specimen, mp 94-99°C; UV (EtOH) λ_{max} 257, 265 (sh), and 334 nm (ε 10400, 9700, and 18900); IR (dilute CCl_4) ν_{max} 3630 cm^{-1} (free OH); NMR ($CDCl_3$) δ 1.04 (s, 3 H, 13-Me), 5.98 (bs, 1 H, 15-H), and 6.97, 7.03 (ABq, 2 H, J = 5.5 Hz, 1- and

2-H); MS m/e 290 (M^+). Anal. Found: C, 66.04; H, 6.21; S, 21.97%. The acetate had mp 115-117°C (ether-pentane); NMR ($CDCl_3$) δ 1.11 (s, 3 H, 13-Me), 2.09 (s, 3 H, OAc), 5.03 (q, 1 H, J = 5 and 10.5 Hz, 17a-H), and 5.97 (bs, 1 H, 15-H).

A-Nor-3,16-dithia-D-homo-1,5(10),6,8,14-estrapentaen-17a-ols (Xa) and (XIa):

A crude material of VIa (530 mg) was successively reduced with sodium borohydride (35 mg) in ethanol (37 ml) and tetrahydrofuran (15 ml) and worked up as described above. The crude product was similarly subjected to preparative TLC to give two fractions, either of which was still contaminated with another component. The major fraction (165 mg) was purified again by preparative TLC (2:1 cyclohexane-ether with double development), affording the 17aα-pentaenol Xa (20 mg) together with the 17aα-tetraenol VIIa (123 mg). The pure material of Xa was obtained by recrystallization from benzene-ether, mp 156-158°C; UV (EtOH) λ_{max} 229, 264, and 297 nm (ε 15600, 26100, and 22300); IR ($CHCl_3$) ν_{max} 1582 and 1546 cm^{-1} (aromatic); IR (dilute CCl_4) ν_{max} 3536 cm^{-1} (bonded OH); NMR ($CDCl_3$) δ 1.05 (s, 3 H, 13-Me), 6.55 (bs, 1 H, 15-H), 7.38 (s, 2 H, 1- and 2-H), and 7.41, 7.64 (ABq, 2 H, J = 9 Hz, 6- and 7-H); MS m/e 288 (M^+). Anal. Calcd. for $C_{16}H_{16}OS_2$: C, 66.63; H, 5.59; S, 22.24. Found: C, 66.47; H, 5.55; S, 22.09%.

The minor fraction (77 mg) was similarly purified by TLC, furnishing the 17aβ-pentaenol XIa (7 mg) and the 17aβ-tetraenol VIIIa (58 mg). The analytical sample of XIa was prepared by recrystallization from ether-pentane, mp 156-160°C; UV (EtOH) λ_{max} 229, 264, and 296 nm (ε 15300, 23900, and 20500); IR ($CHCl_3$) ν_{max} 1583 and 1547 cm^{-1} (aromatic); IR (dilute CCl_4) ν_{max} 3630 cm^{-1} (free OH); NMR ($CDCl_3$) δ 1.08 (s, 3 H, 13-Me), 6.46 (bs, 1 H, 15-H), 7.39 (s, 2 H, 1- and 2-H), and 7.40, 7.64 (ABq, 2 H, J = 8.5 Hz, 6- and 7-H); MS m/e 288 (M^+). Anal. Found: C, 66.52; H, 5.57; S, 22.20%.

2-Methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),8,14-estratetraen-17a-one (VIb), 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),6,8,14-estrapentaen-17a-one (IXb), and 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),6,8-14ξ-estratetraen-17a-one (XII):

A solution of the seco-dione Vb (2.08 g, 6.83 mmol) in chloroform (75 ml) containing p-toluenesulfonic acid (208 mg) was stirred at room temperature for 1 hr and then at 45-50°C for 5 hr under nitrogen. The mixture was concentrated and roughly chromatographed on neutral alumina (20 g) by eluting with petrolether-benzene. The eluates were collected according to their purities and further purified by preparative TLC (4:1 cyclohexane-ether). Following three compounds were isolated. The tetraenone VIb (1 g, 51.1%), mp 102-108°C, was recrystallized from ether-pentane to provide an analytical sample, mp 105-107°C; UV (EtOH) λ_{max} 233, 255 (sh), 333.5, and 345 (sh) nm; IR ($CHCl_3$) ν_{max} 1703 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.32 (s, 3 H, 13-Me), 2.28 (bs, 3 H, 2-Me), 3.27, 3.36 (ABq, 2 H, J = 14 Hz, SCH_2CO), 5.90 (bs, 1 H, 15-H),

and 6.18 (s, 1 H, 1-H). Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.29; H, 6.34; S, 11.20. Found: C, 71.10; H, 6.35; S, 11.07%.

The pentaenone IXb (0.126 g, 6.5%), mp 131-137°C, gave on recrystallization from dichloromethane-ether an analytical specimen, mp 135-138°C; UV (EtOH) λ_{max} 256, 263 (sh), and 289 nm (ε 28100, 23900, and 14400); IR ($CHCl_3$) ν_{max} 1710 (C=O), and 1596 cm-1 (aromatic); NMR ($CDCl_3$) δ 1.36 (s, 3 H, 13-Me), 2.45 (d, 3 H, J = 1 Hz, 2-Me), 3.32, 3.69 (ABq, 2 H, J = 12.5 Hz, SCH_2CO), 6.35 (bs, 1 H, 1-H), 6.56 (sb, 1 H, 15-H), and 7.22, 7.29 (ABq, 2 H, J = 9.5 Hz, 6- and 7-H); MS m/e 284 (M^+). Anal. Calcd. for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.66; H, 5.66; S, 11.20%.

The tetraenone XII (0.254 g, 13.0%), mp 125-127°C, provided on recrystallization from ether an analytical specimen, mp 127-128.5°C; UV (EtOH) λ_{max} 256, 263 (sh), 278, 283 (sh), and 289 nm (ε 15600, 11200, 6400, 4500, and 5900); IR ($CHCl_3$) ν_{max} 1700 (C=O), 1605 (sh), and 1595 cm-1 (aromatic); NMR ($CDCl_3$) δ 1.16 (s, 3 H, 13-Me), 2.46 (d, 3 H, J = 1 Hz, 2-Me), 2.95, 3.62 (ABq, 2 H, J = 13 Hz, SCH_2CO), 6.35 (bs, 1 H, 1-H), and 6.93, 7.22 (ABq, 2 H, J = 8.5 Hz, 6- and 7-H); MS m/e 286 (M^+). Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.29; H, 6.34; S, 11.20. Found: C, 71.04; H, 6.34; S, 10.97%.

2-Methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),8,14-estratetraen-17a-ols (VIIb) and (VIIIb) and 2-methyl-A-nor-3-oxa-16-thia-D-homo-1,5(10),6,8,14-estrapentaen-17a-ols (Xb) and (XIb):

Sodium borohydride (0.093 g, 2.5 mmol) was added to a stirred solution of the tetraenone VIb (1.4 g, 4.9 mmol) in ethanol (100 ml) and tetrahydrofuran (10 ml). Stirring was continued at room temperature for 0.5 hr under nitrogen. The mixture was worked up as described in the reduction of VIa. Preparative TLC of the crude product (4:1 cyclohexane-ether) separated the 17aα-tetraenol VIIb (0.573 g, 40.6%), the 17aβ-tetraenol VIIIb (0.268 g, 19.0%), the 17aα-pentaenol Xb (0.103 g, 7.3%), and the 17aβ-pentaenol XIb (0.038 g, 2.7%) as crystalline solids. Recrystallization from dichloromethane-ether provided the analytically pure samples. The pure VIIb had mp 127-130°C; UV (EtOH) λ_{max} 253, 328, 341 (sh) nm (ε 14000, 21100, and 15400); IR (dilute CCl_4) ν_{max} 3548 cm-1 (bonded OH); NMR ($CDCl_3$) 1.01 (s, 3 H, 13-Me), 2.28 (bs, 3 H, 2-Me), 5.91 (bs, 1 H, 15-H), and 5.94 (d, 1 H, J = 1 Hz, 1-H); MS m/e 288 (M^+). Anal. Calcd. for $C_{17}H_{20}O_2S$: C, 70.79; H, 6.99; S, 11.12. Found: C, 70.72; H, 6.94; S, 10.97%.

The pure VIIIb had mp 154-157°C; UV (EtOH) λ_{max} 253, 328, and 342 (sh) nm (ε 12500, 19900, and 14300); IR (dilute CCl_4) ν_{max} 3630 cm-1 (free OH); NMR ($CDCl_3$) δ 1.03 (s, 3 H, 13-Me), 2.27 (bs, 3 H, 2-Me), 5.80 (bs, 1 H, 15-H), and 5.93 (bs, 1 H, 1-H); MS m/e 288 (M^+). Anal. Found: C, 70.62; H, 6.95; S, 11.02%.

The pure Xb had mp 159-161°C; UV (EtOH) λ_{max} 254, 262 (sh), and 291 nm (ε 31400, 26700, 19100); IR (dilute CCl_4) ν_{max} 3533 cm-1 (bonded OH); NMR ($CDCl_3$) δ 1.03 (s, 3 H, 13-Me), 2.43 (d, 3 H, J = 1 Hz, 2-Me), 6.33 (bs, 1 H, 1-H), 6.43 (bs, 1 H, 15-H), and 7.17, 7.26 (ABq, 2 H, J = 9.5 Hz, 6- and 7-H); MS m/e 286 (M^+). Anal. Calcd. for $C_{17}H_{18}O_2S$: C, 71.29; H, 6.34; S, 11.20. Found:

C, 71.18; H, 6.33; S, 11.07%.

The pure XIb had mp 196-200°C; UV (EtOH) λ_{max} 254, 262 (sh), and 288.5 nm (ε 29100, 23600, and 18100); IR (dilute CCl_4) ν_{max} 3631 cm^{-1} (free OH); NMR ($CDCl_3$) δ 1.06 (s, 3 H, 13-Me), 2.44 (d, 3 H, J = 1 Hz, 2-Me), 6.34 (bs, 2 H, 1- and 15-H), and 7.17 7.26 (ABq, 2 H, J = 9.5 Hz, 6- and 7-H); MS m/e 286 (M^+). Anal. Found: C, 71.04; H, 6.30; S, 10.96%.

NOTES AND REFERENCES

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*. All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only the one enantiomer is named and depicted.

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8. For an example, see Ananchenko, S. N., Limanov, V. Ye., Leonov, V. N., Rzheznikov, V. N., and Torgov, I. V., TETRAHEDRON, 18, 1355 (1962).