(*R*)-2-phenylpropionic acid by using Jones Reagent[19] and converted to the acid halide with $SOCl_2$/DMF in ether. To a magnetically stirred solution of (*R*)-α-methylbenzylamine (0.48 g, 4.0 mmol) in toluene (20 mL) was added (*R*)-phenylpropionic acid chloride (0.3 g, 1.8 mmol). The reaction mixture was then shaken at room temperature for 1 h and washed with dilute HCl and successively with water. The organic layer was dried ($MgSO_4$) and evaporated to dryness, and the residue was crystallized from ethyl acetate/hexane to give desired product in 62% yield. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.50; H, 7.52; N, 5.58. Enantiomeric excess was estimated by GLC analysis of diastereomeric amides: *R,R* form 3.10 min, *R,S* form 3.40 min (lit.[2c] 3.14, 3.48).

The procedure above described has been used for determination of ee of 2-ethyl-1-hexanol (**6**).

Electrophoresis. Polyacrylamide discontinuous gel electrophoresis in nondenaturating conditions was performed according to the method developed by Ornstein[20] and by Davis.[21] The concentrations of acrylamide were 8% in the resolving gel and 4% in the stacking gel. The electrophoretic separations were run under constant current output (25 mA). The gels were stained with Coomassie blue G-250. Three lipase P samples were recovered by filtration from the reactions in benzene in the presence of acetic, propionic, and butyric anhydrides, respectively. The enzymes were then extracted from the solid support with an aqueous buffer at pH 7. No differences in the electrophoretic mobility were observed between the three protein samples and a freshly prepared aqueous solution of lipase P. Conversely, acetylation of lipase P with acetic anhydride in aqueous solution[18] was complete after 1 h at pH 7.

(19) Means, G. E.; Feeney, R. E. *Chemical Modification of Proteins*; Holden-Day: San Francisco, 1971.

(20) Ornstein, L. *Ann. N.Y. Acad. Sci.* **1964**, *121*, 321.
(21) Davis, B. J. *Ann. N.Y. Acad. Sci.* **1964**, *121*, 404.

Notes

A Simple Way to (3a*R*,4*S*,7a*S*)-(*Z*)-1-Ethylideneoctahydro-7a-methyl-1*H*-4-indenol, a Synthon for Total Synthesis of Vitamins D

Andrzej Robert Daniewski* and Jarosław Kiegiel

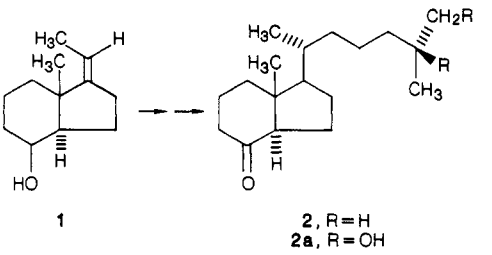
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

Received March 8, 1988

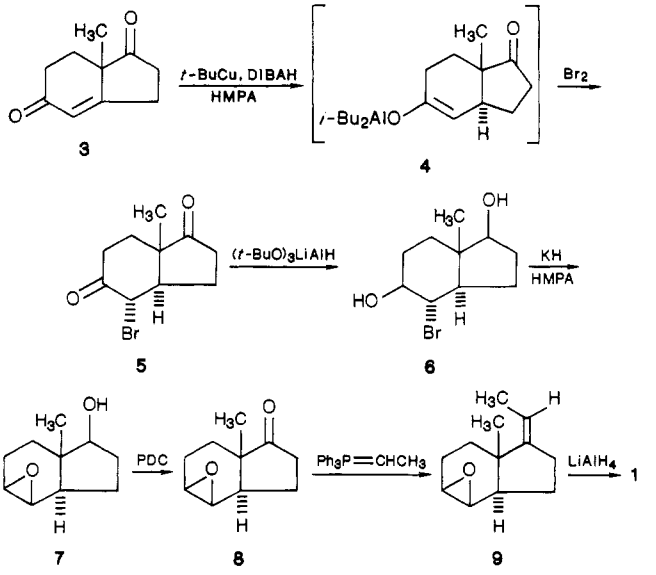
The discovery of hydroxylated metabolites[1] of vitamin D_3, which are more active than commonly used vitamin D_3, has induced interest in the synthesis of these compounds. Several reviews[2] and papers[3] have recently been published on this subject. Uskokovic[4] et al. have reported the synthesis of very useful synthon **1** which was transformed into Grundmann ketone **2** and into its hydroxylated derivatives **2a** (Scheme I).

The synthesis of synthon **1** described by Uskokovic[4] et al. started from easily synthesized[5] enedione **3** and required 13 steps. We present a simpler six-step synthesis of synthon **1**, starting from enedione **3**. Recently we reported[6]

Scheme I



Scheme II



the stereoselective reductive addition of electrophiles to enedione **3**, which led to *trans*-7a-methyloctahydro-1*H*-indene-1,5-dione derivatives. This reductive additions involve hydride transfer from the complex of *tert*-butyl-

(1) Holik, M. F.; DeLuca, H. F. *Annu. Rev. Med.* **1974**, *25*, 349. DeLuca, H. F.; Schoes, H. K. *Annu. Rev. Biochem.* **1976**, *45*, 631. DeLuca, H. F.; Paaren, H. E.; Schos, H. K. *Top. Curr. Chem.* **1979**, *83*, 3.
(2) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. Lythgoe, B. *Chem. Soc. Rev.* **1980**, *84*, 449. Yakhimovich, R. I. *Russ. Chem. Rev.* **1980**, *49*, 371. Jones, M.; Rasmusson, G. U. *Fortschr. Chem. Org. Naturst.* **1980**, *39*, 64. Kametani, T.; Furuyama, H. *Med. Res. Rev.* **1987**, *7*, 147.
(3) Sardina, F. J.; Mourino, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264. Mascarenas, J. L.; Mourino, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1269. Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819. Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. Nemoto, H.; Kusobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311. Castedo, L.; Mourino, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523. Baggiolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskokovic, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. Castedo, L.; Mascarenas, J. L.; Mourino, A. *Tetrahedron Lett.* **1987**, *28*, 2099. Sterling, J.; Slovin, E.; Barasch, D. *Tetrahedron Lett.* **1987**, *28*, 1685. Solladie, G.; Hutt, J. *J. Org. Chem.* **1987**, *52*, 35.
(4) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283.

(5) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(6) Daniewski, A. R.; Kiegiel, J.; Piotrowska, E.; Warchoł, T.; Wojciechowska, W. *Liebigs Ann. Chem.* **1988**, 593.

0022-3263/88/1953-5534$01.50/0

copper with DIBAH to enedione **3** and simultaneous generation of the diisobutylaluminum enolate, which is trapped by electrophiles. In the present studies bromine was used for trapping of the aluminum enolate **4**, and crystalline bromodione **5** was obtained in a 57% yield (Scheme II). Reduction of **5** with lithium (tri-*tert*-butoxyalumino)hydride led to bromo diol **6**, which was transformed into epoxy alcohol **7** after treatment with potassium hydride in HMPA. Oxidation of compound **7** with PDC afforded epoxy ketone **8**, which was reacted with ethyltriphenylphosphonium iodide and potassium *tert*-butoxide in THF to yield epoxy olefin **9**. Treatment of **9** with LAH in THF heated at reflux afforded synthon **1**. Multiplication of given yields results in a 22% overall yield. Synthon **1** and the material reported by Uskokovic[4] have almost identical spectra.

Experimental Section

THF, HMPA, and CuI were anhydrous. All reactions were carried out under argon. The reaction were monitored by TLC. The IR spectra were taken on Beckman 4240 spectrophotometer, and the NMR spectra on a Bruker WP 100 FY spectrometer in $CDCl_3$ unless otherwise noted. The MS spectra were determined with a LKB-9000S apparatus. The starting enedione **3** had optical rotation $[\alpha]_D$ +364° (1.0 in benzene), ee 99%.

(3a*R*,4*S*,7a*S*)-4-Bromooctahydro-7a-methyl-1*H*-indene-1,5-dione (5). *tert*-Butyllithium (2.6 mL, 3.66 mmol, 1.4 M in pentane) was added dropwise to a stirred slurry of CuI (0.58 g, 3.04 mmol) in THF (30 mL) at −40 °C. The reaction mixture was stirred at that temperature for an additional 15 min, and then HMPA (12 mL, 68.9 mmol) was added at −40 °C. The reaction mixture was cooled to −78 °C, and the solution of enedione **3** (1.0 g, 6.1 mmol) in THF (5 mL) was added. To this mixture was added a solution of DIBAH (1.3 mL, 7.3 mmol) in THF (5 mL) and in HMPA (5 mL) slowly during 15 min at −78 °C. The reaction mixture was stirred at −78 °C for an additional 15 min, and the temperature was allowed to raise to −40 °C. Bromine (0.4 mL, 1.27 g, 7.93 mmol) was added to this mixture at −78 °C, and stirring was continued for 5 min. Then an aqueous solution of $CuSO_4$ (100 mL, 10%) was added, and the mixture was extracted with ether (4 × 60 mL). The extract was dried with $MgSO_4$ and chromatographed on a silica gel column with a hexane–ethyl acetate (2:1) mixture as an eluent. Collection of the proper fraction afforded bromo dione **5**, which was crystallized from an ethyl acetate–ether mixture to yield **5** (0.852 g, 57%): mp 133–154 °C; $[\alpha]_D$ +113.9° (1.0, $CHCl_3$); IR (KBr) 1740, 1715 cm^{-1}; ^1H NMR δ 1.19 (s, 3 H, CH_3), 4.71 (d, 1 H, CHBr, J = 12.5 Hz); MS (70 eV), m/e 244, 246. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.34. Found: C, 49.12; H, 5.45.

(1*S*,3a*R*,4*S*,5*S*,7a*S*)-4-Bromooctahydro-7a-methyl-1*H*-indene-1,5-diol (6). Lithium (tri-*tert*-butoxyalumino)hydride (4.57 g, 18.0 mmol) was added in six portions to a solution of bromo dione **5** (2.0 g, 8.16 mmol) in THF (60 mL) at room temperature during 1 h, whereupon the reaction mixture was heated at reflux for 10 min. After the mixture was cooled to 0 °C, acetic acid (4.3 mL, 72 mmol) was added, and the reaction mixture was filtered through a silica gel layer (2 cm), which was then washed with ethyl acetate (60 mL). After evaporation of the solvent from the filtrate, the residue was crystallized from ethyl acetate to yield bromo diol **6** (1.77 g, 84%): mp 226–227 °C; $[\alpha]_D$ −32.7° (1.0, CH_3OH); IR (KBr) 3240, 3340 cm^{-1}; ^1H NMR (CD_3OD) δ 0.81 (s, 3 H, CH_3), 3.3–4.09 (m, 3 H); MS (70 eV), m/e 248, 250. Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.20; H, 6.88. Found: C, 48.28; H, 6.84.

(1*S*,3a*R*,4*R*,5*S*,7a*S*)-4,5-Epoxyoctahydro-7a-methyl-1*H*-inden-1-ol (7). Potassium hydride (20% suspension in oil, 0.6 g, 3.0 mmol) was added in four portions to a stirred solution of compound **6** (0.30 g, 1.2 mmol) in dry HMPA (6 mL) under argon at 10–15 °C during 1 h. Then the reaction mixture was neutralized with acetic acid (0.3 mL), and an aqueous solution of $CuSO_4$ (40 mL, 10%) was added. The mixture was extracted with ethyl ether (2 × 30 mL). The organic phase was dried with $MgSO_4$ and concentrated, whereupon it was chromatographed on a silica gel column with a hexane–ethyl acetate mixture as an eluent. Compound **7** (0.18 g, 89%) was obtained as an oil: $[\alpha]_D$ +24.8° (1.4, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR δ 0.87 (s, 3 H, CH_3), 2.95–3.2 (m, 2 H, C_4 and C_5H), 3.57 (t, 1 H, C_1H, J = 8.0 Hz); MS (70 eV), m/e 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.45; H, 9.65.

(3a,*R*,4*R*,5*S*,7a*S*)-4,5-Epoxyoctahydro-7a-methyl-1*H*-inden-1-one (8). PDC (1.34 g, 3.56 mmol) was added to a stirred solution of **7** (0.15 g, 0.89 mmol) in methylene chloride (30 mL), and stirring was continued at room temperature for 1 h. The mixture was filtered through a silica gel layer (2 cm) and washed with methylene chloride (50 mL). The filtrate was concentrated and chromatographed on a silica gel column with a hexane–ethyl acetate mixture as an eluent, to afford 96 mg of **8** (65%) as a volatile liquid: $[\alpha]_D$ + 42.7° (1.0, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 1.07 (s, 3 H, CH_3), 3.1-3.2 (m, 1 H, C_5H), 3.3 (d, 1 H, C_4H, J = 4.0 Hz); MS (70 eV), m/e 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.52.

(3a*R*,4*R*,5*S*,7a*S*)-(*Z*)-4,5-Epoxy-7a-methyl-1-ethylideneoctahydro-1*H*-indene (9). Compound **8** (0.2 g, 1.2 mmol) was added to a stirred mixture of ethyltriphenylphosphonium iodide (2.0 g, 4.8 mmol) and potassium *tert*-butoxide (0.564 g, 5.04 mmol) in THF (10 mL) at room temperature. The mixture was stirred at this temperature for 20 h, and then another portion of ethyltriphenylphosphonium iodide (1.0 g, 2.4 mmol) and of potassium *tert*-butoxide (282 mg, 2.52 mmol) was added, and stirring was continued for 30 h. Acetic acid (0.4 mL) in water (20 mL) was added to the reaction mixture, which was then extracted with hexane (2 × 10 mL). After drying with $MgSO_4$ and concentration, the residue was purified by chromatography on a silica gel column, with a pentane–ethyl ether mixture as an eluent. Compound **9** was obtained (196 mg, 92%) as a volatile liquid: $[\alpha]_D$ −58.2° (0.7, $CHCl_3$); IR (neat) vw 1680 cm^{-1}; ^1H NMR δ 1.06 (s, 3 H, CH_3), 1.63 (d, 3 H, CH_3, J = 6 Hz), 2.97–3.38 (m, 2 H, C_4 and C_5H), 5.10 (qt, 1 H, CH=, J = 8 and 2 Hz); MS (70 eV), m/e 178. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.80; H, 10.23.

(3a*R*,4*S*,7a*S*)-(*Z*)-1-Ethylideneoctahydro-7a-methyl-1*H*-4-indenol (1). Lithium aluminum hydride (42.6 mg, 1.12 mmol) was added to a solution of **9** (0.1 g, 0.56 mmol) in THF (15 mL), and the mixture was heated at reflux for 45 min. Water-saturated ethyl ether and subsequently aqueous sodium hydroxide (20%) were added until a white precipitate formed. After filtration, the filtrate was evaporated to dryness on a rotary evaporator; the residue was dissolved in hexane; and the solution was filtered through a silica gel layer (1 cm). The product **1** (88.2 mg, 87%) was obtained as an oil: $[\alpha]_D$ −19.7° (1.0, $CHCl_3$); IR (neat) 3430 and vw 1686 cm^{-1} (lit.[4] Raman IR 1688 cm^{-1}); ^1H NMR δ 1.14 (s, 3 H, CH_3), 1.65 (dm, 3 H, CH_3, J = 8.0 Hz), 4.14 (m, 1 H, CHOH), 5.06 (qt, 1 H, CH=, J = 8 and 2 Hz) (Chemical shifts and coupling constants are consistent with the literature[4] values); MS (70 eV), m/e 180; HRMS calcd 180.1520, found 180.1524.

Acknowledgment. We are thankful to the Polish Academy of Sciences for financial support (Grant CPBP 01.13.2.25).

Registry No. **1**, 93489-58-8; **3**, 17553-86-5; **5**, 113726-26-4; **6**, 115340-15-3; **7**, 115340-16-4; **8**, 115340-17-5; **9**, 115340-18-6; vitamin D, 1406-16-2.

A Facile Total Synthesis of Estrogens

Andrzej Robert Daniewski* and Jarosław Kiegiel

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, ul. Kasprzaka 44, Poland

Received April 23, 1988

Although the total syntheses of estrogens have been relatively well described,[1] there is still a chance of either improving them or devising some better ones. In consequence of the discovery of an efficient chiral synthesis of

(1) Groen, M. M.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465 and references therein.

0022-3263/88/1953-5535$01.50/0