Homochiral Ketals in Organic Synthesis. Enantioselective Synthesis of (+)-β-Eudesmol[1]

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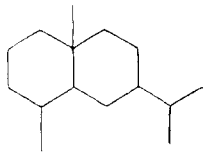
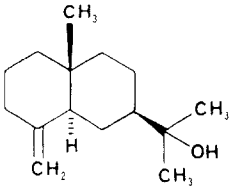
An enantioselective preparation of (+)-β-eudesmol employing a diastereoselective Simmons-Smith cyclopropanation is described. Cyclopropanation of a bicyclic enone precursor is directed by use of the corresponding (2*S*,3*S*)-2,3-butanediol ketal. The overall yield of (+)-β-eudesmol (75% ee) from racemic 7-carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one is 25% over eight steps.

The eudesmane family of sesquiterpenes is comprised of more than 100 naturally occurring bicyclic hydronaphthalenes possessing carbon skeleton A.[2] Members of the family, including (+)-β-eudesmol (**1**),[3] have remained



A



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popular synthetic targets for over 20 years. Although a number of syntheses of racemic eudesmanes have appeared,[4] few syntheses have addressed the problem of enantioselectivity.[4] Most published enantioselective constructions of the eudesmane skeleton proceed from optically active dihydrocarvone or 2-carone[5] via Robinson ring annulation. Other eudesmane syntheses begin with commercially available α-santonin.[4,6] Although these syntheses are highly enantioselective, most are inefficient.[7]

Recently we reported a diastereoselective cyclopropanation process involving homochiral 2-cycloalken-1-one 1,4-di-*O*-benzyl-L-threitol ketals,[8] including bicyclic ketal **2**.[9] Treatment of **2** with the Simmons-Smith reagent provided in 80% yield a 7:1 mixture of diastereomeric cyclopropane ketals **3a** and **3b**. Hydrolysis provided in 92% yield the enantiomerically enriched cyclopropyl ketone **4**, from which decalone **5** might be obtained by reductive ring opening.[10] From these findings an alternative and general approach for construction of eudesmanes based upon enantioselective introduction of the angular methyl substituent was formulated.[11] Pursuit of this approach has resulted in an efficient synthesis of (+)-β-eudesmol, as described below.

Ketalization of racemic 7-carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one (**6**)[3e] using the bis(trimethylsilyl ether) of (2*S*,3*S*)-2,3-butanediol and trimethylsilyl trifluoromethanesulfonate[12] produced in 85% yield an inseparable 1:1 mixture of bicyclic ketal diastereoisomers **7a** and **7b**.[13] Exhaustive methylation (CH_3MgBr, THF, 0 °C) provided in 90% yield a 1:1 mixture of alcohols **8a** and **8b**.[13] Treatment of the mixture of **8a** and **8b** with the Simmons-Smith reagent[14] in refluxing ether gave, after 20 h and in 94% chemical yield, a mixture of diastereomeric cyclopropane ketals **9a-d** in the approximate ratio 8:1:8:1.[13] The two major diastereoisomers were assigned structures **9a** and **9c** on the basis of conversion of this mixture to enantiomerically enriched (+)-β-eudesmol as follows.

Hydrolysis of the mixture of cyclopropane ketals **9a-d** (aqueous HCl, MeOH, room temperature, 35 min) provided in 88% yield enantiomerically enriched cyclopropyl ketones **10a** and **10b**. Surprisingly, these ketones were not chromatographically separable. Fortunately, preparative separation could be effected by selective dehydration of the undesired diastereoisomer **10b**.[15] Treatment of the mixture of tricyclic ketones **10a** and **10b** with ethylene glycol and pyridinium *p*-toluenesulfonate in refluxing benzene for 13 h produced a mixture that included unsaturated ketones **11** and **12**, the corresponding ethylene glycol ketals, and the desired keto alcohol **10a**, which was easily isolated from the mixture by column chromatography.

Reductive opening of the cyclopropane ring (Li, *t*-BuOH, liquid NH_3) was accompanied by partial reduction of the ketone. Oxidation of the crude product mixture (PDC,

(1) Portions of this work are taken from the Masters Thesis of James A. Fryling, University of Arizona, 1986.

(2) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. II, pp 137-146.

(3) For previous syntheses of racemic β-eudesmol, see: (a) Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, *31*, 2933-2941. (b) Heathcock, C. H.; Kelly, T. R. *Tetrahedron* **1968**, *24*, 1801-1809. (c) Vig, O. P.; Anand, R. C.; Kumar, B.; Sharma, S. D. *J. Ind. Chem. Soc.* **1968**, *45*, 1033-1036. (d) Huffman, J. W.; Mole, M. L. *J. Org. Chem.* **1972**, *37*, 13-17. (e) Carlson, R. G.; Zey, E. G. *J. Org. Chem.* **1972**, *37*, 2468-2471. (f) Wijnberg, J. B. P. A.; Vader, J.; deGroot, A. *J. Org. Chem.* **1983**, *48*, 4380-4387. (g) Schwartz, M. A.; Willbrand, A. M. *J. Org. Chem.* **1985**, *50*, 1359-1365.

(4) (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley Interscience: New York, 1983; Vol. 5, pp 124-157 and references cited therein. (b) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley Interscience: New York, 1973; Vol. 2, pp 282-330 and references cited therein.

(5) Caine, D.; Gupton, J. T., III *J. Org. Chem.* **1974**, *39*, 2654-2656.

(6) For an enantioselective approach to β-selinene from limonene, see: MacKenzie, B. D.; Angelo, M. M.; Wolinsky, J. *J. Org. Chem.* **1979**, *44*, 4042-4046.

(7) Pinders' synthesis of (+)-β-eudesmol from (-)-dihydrocarvone resulted in an overall yield of approximately 1.5% over nine steps. See: Humber, D. C.; Pinder, A. R.; Williams, R. A. *J. Org. Chem.* **1967**, *32*, 2335-2340, and references cited therein.

(8) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256-8258.

(9) Mash, E. A.; Nelson, K. A. *Tetrahedron Lett.* **1986**, *27*, 1441-1444.

(10) Staley, S. W. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley Interscience: New York, 1972; Vol. 2, pp 309-348.

(11) For a related approach to introduction of an angular methyl via cyclopropanation, see: Sims, J. J.; Selman, L. H. *Tetrahedron Lett.* **1969**, 561-564.

(12) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357-1358.

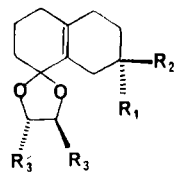
(13) Determined by 62.9-MHz ^{13}C NMR spectroscopy. For previous examples of the use of ^{13}C NMR in the measurement of diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183-2186.

(14) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825-1826.

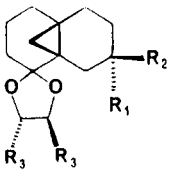
(15) Attempted reketalization of the mixture of cyclopropyl ketones **10a** and **10b** with *dl*-2,3-butanediol (to prepare material for confirmation of NMR assignments) produced a mixture of products which clearly indicated that one of the two cyclopropyl ketones was unstable with respect to elimination of the tertiary alcohol under the conditions employed (benzene, PPTS, reflux). The unstable diastereoisomer proved to be **10b** (see Experimental Section).

0022-3263/87/1952-3000$01.50/0

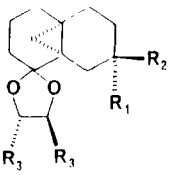
Chart I



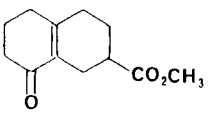
	R_1	R_2	R_3
2	H	H	$CH_2OCH_2C_6H_5$
7a	H	$COOCH_3$	CH_3
7b	$COOCH_3$	H	CH_3
8a	H	$C(CH_3)_2OH$	CH_3
8b	$C(CH_3)_2OH$	H	CH_3



	R_1	R_2	R_3
3a	H	H	$CH_2OCH_2C_6H_5$
9a	H	$C(CH_3)_2OH$	CH_3
9c	$C(CH_3)_2OH$	H	CH_3



	R_1	R_2	R_3
3b	H	H	$CH_2OCH_2C_6H_5$
9b	H	$C(CH_3)_2OH$	CH_3
9d	$C(CH_3)_2OH$	H	CH_3



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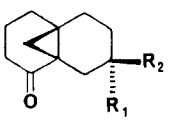
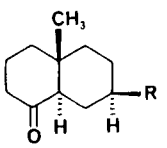
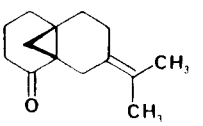


	R_1	R_2
4	H	H
10a	H	$C(CH_3)_2OH$
10b	$C(CH_3)_2OH$	H
11	$C(CH_2)CH_3$	H



	R
5	H
13	$C(CH_3)_2OH$



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CH_2Cl_2, room temperature, 5 h) followed by equilibration of epimers at the ring junction adjacent to the carbonyl (basic alumina, C_6H_6, room temperature, 48 h)[7] provided decalone **13** in 83% yield. Wittig olefination by the literature method[7] gave enantiomerically enriched (+)-β-eudesmol (**1**), mp 73–75 °C (lit.[16] mp 80–81 °C), $[\alpha]^{25}_D$ +43.4° (*c* 0.95, $CHCl_3$) (lit.[16] $[\alpha]^{27}_D$ +58.0° ($CHCl_3$)), in 95% yield from **13**. The yield of (+)-β-eudesmol (75% enantiomeric excess) from racemic 7-carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one (**6**) over eight steps was 25%.

The procedures described herein make accessible the eudesmane skeleton possessing either configuration of the angular methyl substituent since this depends only upon the chirality of the butanediol employed.[17] Eudesmanes functionalized at the angular methyl might also be prepared via this methodology.[18,19]

Reasons for the remarkable diastereoselectivity observed for the cyclopropanation of ketals **8a** and **8b** remain unclear. Most probably, chelation of zinc[20] by dioxolane oxygens of the ketal protecting group results in preferential delivery of the Simmons–Smith reagent to one face of the alkene. Work is in progress to confirm and define the factors responsible for diastereoselection.

Further uses of these and other homochiral protecting groups will be reported in future papers.[21]

Experimental Section

Benzene was distilled from calcium hydride and diethyl ether was distilled from phosphorus pentoxide or sodium benzophenone ketyl under an inert atmosphere. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 3-Å molecular sieves. Liquid ammonia was distilled from lithium immediately before use. 7-Carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one (**6**) was prepared by the method of Carlson and Zey.[3e] Zinc–copper couple was prepared according to the method of Shank and Shechter[14] immediately before use. Proton magnetic resonance spectra were recorded at 250 MHz on a Bruker WM-250 NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) from tetramethylsilane. Carbon-13 magnetic resonance spectra were recorded at 62.9 MHz on a Bruker WM-250 spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) from the center line of the chloroform-*d* triplet (77.0 ppm). Mass spectral determinations were performed at the Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility (Grant CHE-0211164). Elemental analyses were performed by MicAnal Laboratories, Tucson, AZ. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70–230-mesh ASTM). Merck silica gel 60 (70–230-mesh ASTM) was used for column chromatography. Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected.

(16) Varma, K. R.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 2927–2931.

(17) Available from Aldrich Chemical Company. For preparation of (2*S*,3*S*)-2,3-butanediol, see: Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1758–1761.

(18) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412–2414, and references cited therein.

(19) For an example, see: Kupchan, S. M.; Smith, R. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 6667–6668.

(20) For previous examples of chelation-controlled delivery of the Simmons–Smith reagent, see: (a) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721–2724. (b) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892–6894. (c) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290–4291. (d) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React. (N.Y.)* **1972**, *20*, 1–131.

(21) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by the American Heart Association, Arizona Affiliate, is gratefully acknowledged.

(2*S*,3*S*)-2,3-Butanediol Bis(trimethylsilyl ether). To a well-stirred mixture of (2*S*,3*S*)-2,3-butanediol (3.0 g, 33.3 mmol) and triethylamine (15 mL, 10.9 g, 107.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Me_3SiCl (8.56 g, 78.8 mmol) dropwise. After 30 min the reaction mixture was filtered, the precipitate was washed well with Et_2O, and volatiles were removed in vacuo. Vacuum distillation gave product, bp_{26} 97–98 °C, as a colorless oil: yield 7.02 g (30 mmol, 90%); ^1H NMR ($CDCl_3$) δ 0.11 (18, s), 1.06 (6, d, J = 6 Hz), 3.59–3.65 (2, m).

7-Carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1-(2*H*)-one (2*S*,3*S*)-2,3-Butanediyl Ketals (7a and 7b). To a well-stirred solution of (2*S*,3*S*)-2,3-butanediol bis(trimethylsilyl ether) (5.5 g, 23.3 mmol) in CH_2Cl_2 (5 mL) at −78 °C were added trimethylsilyl trifluoromethanesulfonate (38 mg, 17 μmol) and 7-carbomethoxy-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one (**6**).[3e] Additional Me_3SiOTf (155 mg, 0.7 mmol) was added after 2 h and the mixture was allowed to attain room temperature and stirred overnight. The reaction was quenched by addition of pyridine (0.5 mL, 0.49 g, 6.2 mmol), volatiles were removed in vacuo, and the residue was chromatographed on silica gel 60 (350 g) eluted with 20% EtOAc/hexanes. Ketals **7a** and **7b** were obtained as a viscous oil homogeneous by TLC (R_f 0.62, 50% EtOAc/hexanes): yield 5.36 g, 19.1 mmol, 85%; IR (neat) cm^{-1} 2932, 2868, 1732, 1437, 1377, 1337, 1312, 1275, 1253, 1227, 1189, 1140, 1095; ^1H NMR ($CDCl_3$) δ 1.20–1.35 (6, m), 1.5–2.6 (13, m), 3.6–3.8 (5, m); ^{13}C NMR ($CDCl_3$) δ 15.84, 15.98, 17.51, 17.66, 20.07, 20.26, 24.45, 24.52, 24.95, 25.13, 29.94, 30.04, 30.15, 35.27, 35.68, 39.63, 39.74, 51.48, 77.53, 77.59, 79.68, 79.79, 106.58, 106.67, 127.87, 127.96, 135.93, 136.01, 176.35, 176.39; mass spectrum (70 eV), m/z (relative intensity) 281 (10), 280 (60), 253 (16), 252 (100), 208 (41), 193 (17), 149 (39), 148 (19), 147 (13), 133 (11), 131 (11), 127 (20), 120 (24), 93 (34), 92 (17), 91 (41), 79 (14), 77 (15), 55 (27); exact mass calcd for $C_{16}H_{24}O_4$ 280.1674, obsd 280.1680.

7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one (2*S*,3*S*)-2,3-Butanediyl Ketals (8a and 8b). To a well-stirred solution of methylmagnesium bromide (44.8 mmol) in THF (80 mL) at 0 °C was added dropwise a solution of esters **7a** and **7b** (5.01 g, 17.9 mmol) in THF (10 mL). Additional methylmagnesium bromide was added to the reaction mixture (16.8 mmol after 45 min and 8.4 mmol after 160 min). After 3.5 h the mixture was poured into crushed ice (75 g) and saturated aqueous sodium bicarbonate (20 mL) and then extracted with ether (4 × 100 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was chromatographed on silica gel 60 (300 g) eluted with 50% EtOAc/hexanes. Product alcohols **8a** and **8b** were obtained as a white solid, mp 82.5–85 °C, homogeneous by TLC (R_f 0.39, 50% EtOAc/hexanes): yield 4.52 g, 16.1 mmol, 90%; IR ($CHCl_3$) cm^{-1} 3605, 3461, 3009, 2975, 2931, 2872, 1454, 1439, 1376, 1212, 1091, 939, 773, 668; ^1H NMR ($CDCl_3$) δ 1.15–1.36 (14, m), 1.45–2.3 (12, m), 3.6–3.8 (2, m); ^{13}C NMR ($CDCl_3$) δ 16.04, 16.16, 17.65, 17.77, 20.24, 20.45, 23.36, 23.45, 26.18, 26.24, 27.37, 29.98, 30.27, 31.48, 31.74, 35.44, 35.89, 45.18, 45.42, 72.76, 77.59, 79.89, 79.97, 107.05, 107.18, 128.66, 128.81, 136.73, 136.79; mass spectrum (70 eV), m/z (relative intensity) 281 (13), 280 (71), 253 (16), 252 (100), 234 (20), 221 (26), 219 (36), 193 (38), 190 (16), 177 (27), 150 (19), 149 (45), 147 (36), 131 (16), 127 (34), 93 (18), 91 (39), 79 (23), 77 (17), 59 (40), 55 (33); exact mass calcd for $C_{17}H_{28}O_3$ 280.2039, obsd 280.2043.

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.94; H, 10.40.

7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydro-4a,8a-methanonaphthalen-1(2*H*)-one (2*S*,3*S*)-2,3-Butanediyl Ketals (9a–d). To a well-stirred suspension of freshly prepared Zn–Cu couple[14] (8.26 g) and anhydrous potassium carbonate (3.76 g, 27.2 mmol) in ether (80 mL) under argon were added several small crystals of I_2 and CH_2I_2 (16.6 g, 62 mmol). After 30 min at reflux (external heating), ketals **8a** and **8b** (1.96 g, 7.0 mmol) were added as a solution in THF (5 mL). Progress of the reaction was monitored by TLC (50% EtOAc/hexanes). After 20 h the mixture was cooled to 0 °C and quenched with saturated aqueous K_2CO_3 (15 mL). After stirring at room temperature for 45 min, the gray-black precipitate was removed by filtration and washed well with ether. The combined organic extracts were washed with 30-mL portions of saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (400 g) eluted with 20% EtOAc/hexanes gave cyclopropane ketals **9a-d** as a pale yellow oil homogeneous by TLC (R_f 0.42): yield 1.94 g, 6.59 mmol, 94%; IR (neat) cm^{-1} 3455, 3059, 2934, 1454, 1375, 1284, 1190, 1096, 1032, 967, 936, 916, 842, 755, 666; ^1H NMR ($CDCl_3$) δ 0.49–0.59 (1, m), 0.65–0.75 (1, m), 1.0–2.5 (26, m), 3.6–3.8 (2, m); ^{13}C NMR ($CDCl_3$) δ (major diastereoisomers only) 15.96, 16.29, 17.77, 18.17, 19.25, 19.77, 20.86, 21.31, 21.46, 23.15, 24.03, 24.40, 24.61, 25.56, 27.19, 27.25, 27.50, 27.66, 28.24, 30.24, 30.86, 31.19, 32.13, 32.98, 41.51, 45.94, 72.53, 72.83, 77.87, 79.30, 79.41, 111.37, 111.79; mass spectrum (70 eV), m/z (relative intensity) 294 (6), 235 (5), 207 (4), 145 (3), 141 (3), 128 (9), 127 (100), 114 (3), 105 (4), 93 (4), 91 (7), 79 (5), 77 (3), 73 (3), 67 (3), 59 (14), 57 (3), 55 (23); exact mass calcd for $C_{18}H_{30}O_3$ 294.2196, obsd 294.2192.

(4a*R*,7*RS*,8a*R*)-7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydro-4a,8a-methanonaphthalen-1(2*H*)-ones (10a and 10b). To a well-stirred solution of ketals **9a–d** (1.94 g, 6.59 mmol) in CH_3OH (35 mL) at room temperature was added slowly 2.7 M aqueous HCl (2 mL). Progress of the reaction was monitored by TLC (50% EtOAc/hexanes). After 35 min the solution was poured into saturated aqueous $NaHCO_3$ (50 mL) and the mixture extracted with ether (7 × 50 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (325 g) eluted with 50% EtOAc/hexanes gave a 1:1 mixture of enantiomerically enriched ketones **10a** and **10b** as a pale yellow oil homogeneous by TLC (R_f 0.20): yield 1.29 g, 5.81 mmol, 88%; IR (neat) cm^{-1} 3455, 3070, 2934, 1736, 1673, 1464, 1450, 1374, 1324, 1275, 1238, 1212, 1148, 1048, 1015, 988, 975, 937, 898, 875, 857; ^1H NMR ($CDCl_3$) δ 0.8–1.08 (2, m), 1.1–1.3 (8, m), 1.5–1.85 (7, m), 1.89–2.17 (4, m), 2.25–2.95 (1, m); ^{13}C NMR ($CDCl_3$) δ 17.92, 18.22, 19.58, 20.63, 21.42, 23.42, 24.98, 25.51, 25.60, 25.80, 27.56, 27.80, 27.91, 29.42, 29.77, 31.42, 31.93, 35.04, 36.04, 36.18, 36.48, 42.98, 45.68, 72.32, 72.59, 209.45, 210.48; mass spectrum (70 eV), m/z (relative intensity) 222 (1), 204 (21), 189 (12), 164 (26), 161 (27), 160 (11), 149 (22), 148 (15), 146 (13), 143 (33), 135 (20), 133 (19), 131 (18), 123 (20), 122 (13), 119 (11), 108 (32), 107 (14), 105 (24), 93 (25), 91 (31), 79 (24), 77 (14), 67 (13), 59 (100), 55 (16); exact mass calcd for $C_{14}H_{22}O_2$ 222.1620, obsd 222.1615.

(4a*R*,7*R*,8a*R*)-7-(1-Methyl-1-hydroxyethyl)-3,4,5,6,7,8-hexahydro-4a,8a-methanonaphthalen-1(2*H*)-one (10a). To a well-stirred solution of ketones **10a** and **10b** (1.18 g, 5.3 mmol) in benzene (500 mL) under argon were added ethylene glycol (590 mg, 9.5 mmol) and pyridinium *p*-toluenesulfonate (1.9 g, 7.56 mmol). The mixture was heated to reflux for 13 h, then cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel 60 (80 g) eluted with 50% EtOAc/hexanes. Early fractions contained mixtures of ketones **11** and **12** as well as the corresponding ethylene glycol ketals. Later fractions contained alcohol **10a**, which was obtained as a colorless oil: $[\alpha]^{23}_D$ +19.3° (*c* 0.72, $CHCl_3$); yield 596 mg, 2.68 mmol, 50%; IR ($CHCl_3$) cm^{-1} 3602, 3460, 3010, 2939, 2854, 1666, 1465, 1452, 1373, 1346, 1325, 1276, 1233, 1220, 1212, 1147, 1036, 937, 905, 761, and 668; ^1H NMR ($CDCl_3$) δ 0.8–1.0 (2, m), 1.06–1.35 (8, m), 1.35–1.85 (7, m), 1.90–2.50 (4, m), 2.85 (1, m); ^{13}C NMR ($CDCl_3$) δ 18.27, 20.69, 21.46, 25.57, 25.66, 27.89, 29.48, 31.48, 35.07, 36.27, 45.75, 72.47, 209.51; mass spectrum (70 eV) m/z (relative intensity) 222 (0.1), 207 (5), 205 (5), 204 (28), 189 (13), 164 (25), 161 (29), 160 (13), 149 (21), 148 (19), 147 (13), 146 (18), 145 (10), 143 (38), 135 (15), 133 (18), 131 (21), 123 (23), 119 (15), 117 (11), 108 (34), 105 (30), 99 (49), 93 (32), 91 (36), 79 (26), 59 (100); exact mass calcd for $C_{14}H_{22}O_2$ 222.1620, obsd 222.1632.

(4a*R*,7*R*,8a*R*)-4a-Methyl-7-(1-methyl-1-hydroxyethyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (13). To a well-stirred solution of Li metal (90 mg, 12.9 mmol) in liquid ammonia (10 mL) at −78 °C was added a solution of *t*-BuOH (0.685 mL) and ketone **10a** (580 mg, 2.61 mmol) in ether (3 mL). The cold bath was removed and the mixture allowed to reflux (−33 °C). Progress of the reaction was monitored by TLC (50% EtOAc/hexanes). After 1 h, the reaction mixture was cooled to −78 °C, quenched with solid NH_4Cl (1 g), diluted with ether (20 mL), and warmed to room temperature, and the ammonia was allowed to evaporate. The mixture was filtered and the filtrate

concentrated in vacuo, leaving an oil.

To a well-stirred solution of the above oil in CH_2Cl_2 (15 mL) at room temperature was added pyridinium dichromate (7.0 g, 18.6 mmol). After 5 h, the mixture was filtered through a short plug of silica gel (elution with ether). The eluent was concentrated in vacuo, and the residue was redissolved in benzene and loaded onto a column of basic alumina (30 g). After 48 h, the product was eluted from the column with 50% $CHCl_3$/benzene, volatiles were removed in vacuo, and the residue (565 mg) was chromatographed on silica gel 60 (50 g) eluted with 50% EtOAc/hexanes. The desired decalone **13** was obtained as a colorless oil contaminated with approximately 10% of the cis-fused isomer: yield 485 mg, 2.17 mmol, 83%; $[\alpha]^{24}_D$ +8.46° (*c* 1.75, $CHCl_3$), lit.[7] $[\alpha]^{25}_D$ +7.1° (*c* 2, $CHCl_3$); IR (neat) cm^{-1} 3460, 2939, 2847, 1707, 1466, 1446, 1380, 1307, 1252, 1184, 1153, 1085, 1043, 951, 916, 836, 781; ^1H NMR ($CDCl_3$) δ 0.77 (3, s), 1.19 (3, s), 1.21 (3, s), 1.2–2.0 (12, m), 2.1–2.4 (3, m); ^{13}C NMR ($CDCl_3$) δ (major diastereoisomer) 16.87, 21.39, 21.83, 22.59, 26.61, 27.25, 39.27, 40.26, 40.69, 41.15, 48.35, 57.33, 72.59, 212.92; mass spectrum (70 eV), *m/z* (relative intensity) 224 (0.5), 209 (2), 207 (6), 206 (6), 191 (5), 166 (16), 152 (5), 151 (38), 123 (6), 112 (7), 111 (100), 107 (5), 98 (5), 97 (5), 95 (6), 93 (7), 91 (6), 79 (7), 67 (10), 59 (35); exact mass calcd for $C_{14}H_{24}O_2$ 224.1777, obsd 224.1786.

(+)-β-Eudesmol (1). Ketone **13** (320 mg, 1.43 mmol) was converted to (+)-β-eudesmol (**1**), mp 73–75 °C, lit.[16] mp 80–81 °C (301 mg, 1.36 mmol, 95%) by following the literature procedure:[7] $[\alpha]^{25}_D$ +43.4° (*c* 0.95, $CHCl_3$), lit.[16] $[\alpha]^{27}_D$ +58.0° ($CHCl_3$); IR ($CHCl_3$) cm^{-1} 3605, 3455, 3079, 3020, 2975, 2933, 2867, 2844, 1642, 1455, 1439, 1408, 1378, 1188, 1151, 1122, 1091, 1047, 987, 958, 933, 914, 889, 613; ^1H NMR ($CDCl_3$) δ 0.70 (3, s), 1.20 (6, s), 1.1–2.4 (15, m), 4.44 (1, d, *J* = 1.6 Hz), 4.72 (1, d, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 16.28, 22.35, 23.45, 24.99, 27.11, 35.86, 36.86, 41.10, 41.81, 49.42, 49.76, 72.86, 105.30, 151.11; mass spectrum (70 eV), *m/z* (relative intensity) 222 (0.4), 204 (4), 189 (6), 165 (3), 164 (20), 161 (7), 150 (5), 149 (31), 135 (7), 133 (6), 123 (13), 122 (12), 121 (12), 119 (5), 109 (18), 108 (17), 107 (12), 105 (11), 95 (15), 93 (17), 91 (12), 82 (13), 81 (20), 79 (15), 69 (13), 67 (14); exact mass calcd for $C_{15}H_{26}O$ 222.1985, obsd 222.1976.

Stereochemistry of Long-Lasting Opiates. 2. δ-Selective Opiate Antagonists and Their Agonist Analogues†

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We have discovered novel δ-selective opiate antagonists of a non-peptide nature. Our lead compound at the present time is the mixed azine between estrone and naloxone (**16**). In this work we describe syntheses and stereochemical determinations of several antagonist and agonist analogues of **16**, all of which are mixed azines between steroids and opiates. For example, we have prepared the mixed azine between pregnenolone and naltrexone (**17**). A ^{13}C NMR stereochemical analysis showed that **17** was formed as a mixture of two azine isomers: 20(steroid)anti-6(opiate)anti and 20(steroid)anti-6(opiate)syn. The X-ray structural analysis of pregnenolone hydrazone (**8**) (from which **17** was formed) showed 20 anti hydrazone. The X-ray analysis of a single crystal of **17** showed the 20(steroid)anti-6(opiate)anti azine. The C=N—N=C torsion angle was −123°, indicating gauche geometry of the azine bond.

Introduction

Opioid receptors have been pharmacologically classified into several types.[1] Investigation of the physiological significance and molecular properties of different opioid receptor types requires development of type-specific probes. Much information can be obtained by the use of antagonists specifically blocking a certain receptor type. We have synthesized a series of opioid–steroid hybrid azines as potential opioid receptor probes and found them to show long-lasting in vitro activity at the μ binding sites in rat brain membranes.[2-4] Some compounds showed enhanced δ receptor selectivity in vitro.[5,6]

In this study we describe syntheses and detailed stereochemical determinations of several opiate–steroid hybrid azines and steroidal hydrazones they were made from. The latter hydrazones were coupled with opiate ketones oxymorphone, naloxone, or naltrexone (Figure 1). The uncatalyzed coupling between steroidal hydrazones and opiate ketones is quite slow. An attempt to catalyze the latter coupling with catalytic amounts of HCl lead to a rearrangement of the initially formed desired mixed opiate–steroid azine to a mixture of the undesired symmetrical azines, i.e. opiate–opiate and steroid–steroid azines.

Experimental Section

The melting points, elemental analyses, IR, NMR, and mass spectra, and the TLC's were done as described in ref 2. In addition, several ^{13}C and ^1H NMR spectra were obtained on a JEOL FX 200-MHz instrument at the University of Wisconsin—Madison. Thanks are expressed to Dr. Bruce Adams for allowing us to use the latter instrument.

Androstenedione (Δ^4-androstene-3,17-dione, **1**) and pregnenolone (**5**) were obtained from G. D. Searle. Estrone (**3**) was

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(1) Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W. *Br. Med. Bull.* **1983**, *39*, 31.

(2) Kolb, V. M.; Hua, D. H. *J. Org. Chem.* **1984**, *49*, 3824.

(3) Koman, A.; Kolb-Meyers, V.; Terenius, L. "Affinity Probes for Opioid Receptors in Synaptosomes" In *Investigation of Membrane-Located Receptors*, Reid, E., Cook, G. M. W., and Morre, D. J., Eds.; Meth. Surv. Biochem. Anal. Plenum: New York, 1984; Vol. 13, pp 497–498.

(4) Koman, A.; Kolb, V. M.; Terenius, L. *Pharm. Res.* **1986**, *3*, 56.

(5) Koman, A. Ph.D. Dissertation, Uppsala University, Sweden, 1985 (ISSN 0282-7484; ISBN 91-554-1753-1).

(6) Koman, A.; Kolb, V. M.; Terenius, L. *Pharm. Res.* **1987**, *4*, 147.

0022-3263/87/1952-3003$01.50/0