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HOMOCHIRAL KETALS IN ORGANIC SYNTHESIS. ENANTIOSELECTIVE SYNTHESIS OF [m.n.1]PROPELLANONES

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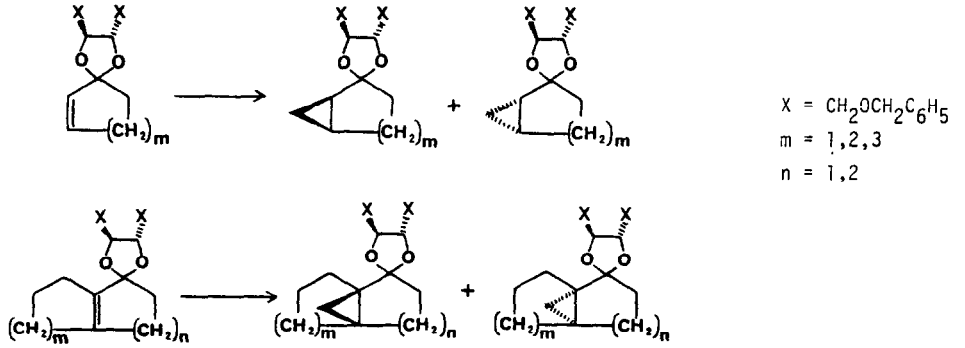
Abstract. Optically active [m.n.1]propellanones have been prepared by diastereoselective cyclopropanation of homochiral ene ketals derived from 1,4-di-*O*-benzyl-*L*-threitol and readily available bicyclic enones.

Propellanones are a synthetically useful subset of the structurally and theoretically interesting propellane family.[1] [m.n.1]Propellanes are most conveniently prepared by cyclopropanation of the corresponding bicyclic alkene.[2] [m.n.1]Propellanones, although more difficult to prepare by direct cyclopropanation, are particularly attractive as precursors of bicyclic ring systems bearing angular methyl[3] or functionalized angular methyl substituents[4] found in a number of natural products. An enantioselective synthesis of such systems would render them all the more attractive as synthetic intermediates. We herein report a general, efficient, enantioselective synthesis of [m.n.1]propellanones which utilizes chiral protecting group methodology.

Recently we described a novel diastereoselective cyclopropanation of homochiral ketals derived from simple monocyclic enones and 1,4-di-*O*-benzyl-*L*-threitol (Scheme I, First Equation).[5] Following this observation, we sought to extend the applicability of the method to more complex bicyclic systems (Scheme I, Second Equation). The results of our survey appear in Table 1.

Scheme I. Diastereoselective Cyclopropanation



The required ene ketals **1**, **4**, **7** and **10** were prepared by direct ketalization of the corresponding enones[6] with 1,4-di-*O*-benzyl-*L*-threitol.[7] Treatment of these ene ketals with an excess of the Simmons-Smith reagent[8] in refluxing diethyl ether gave in good chemical yield mixtures of diastereomers of propellanone ketals **2**, **5**, **8** and **11** ranging from 7:1 to 9:1, as determined by 62.9 MHz ^{13}C NMR spectroscopy.[9] Acid-catalyzed hydrolyses of these propellanone ketals provided propellanones **3**, **6**, **9** and **12** in good to very good chemical yield and in 75-80% ee.[10] Assignments of absolute stereochemistry were based upon CD spectra of the propellanones employing the Reversed Octant Rule[11] and are in accord with previous results on monocyclic systems.[5] Preparation of **3** is representative:

3,4,5,6,7,8-Hexahydronaphthalen-1(2H)-one 1,4-Di-*O*-benzyl-*L*-threitol Ketal **1**

To a solution of 3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one[6a] (1.0 g, 6.67 mmol) and 1,4-di-*O*-benzyl-*L*-threitol[7] (1.84 g, 6.09 mmol) in dry benzene (70 mL) was added pyridinium *p*-toluenesulfonate (450 mg, 1.79 mmol) and the mixture heated to reflux under argon. Water was removed azeotropically using a Dean-Stark trap. After 120 hr, the mixture was cooled, diluted with ether, washed with saturated sodium bicarbonate, brine, dried ($MgSO_4$), and filtered. Removal of volatiles gave an oil which was chromatographed on silica gel 60 (100 g) eluted with 20% ethyl acetate/hexanes. Product ene ketal **1** (1.53 g, 3.53 mmol, 58%) eluted first, followed by starting enone (407 mg, 2.71 mmol, 41% recovery) and diol (746 mg, 2.47 mmol, 41% recovery). IR (neat) 3086, 3062, 3029, 2928, 2860, 1495, 1452, 1362, 1292, 1267, 1250, 1184, 1139, 1108, 1028, 1008, 964, 941, 736, and 696 cm^{-1}; ^1H NMR ($CDCl_3$) 1.50-1.95 (12, m), 2.02-2.12 (2, m), 3.65 (4, dd, J = 4.7 Hz, J = 17.1 Hz), 3.98 (1, m), 4.13 (1, m), 4.57 (4, s), and 7.25-7.34 ppm (10, m).

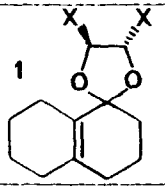
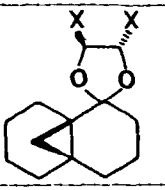
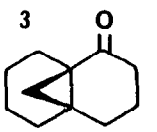
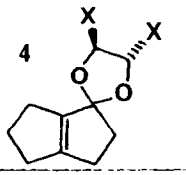
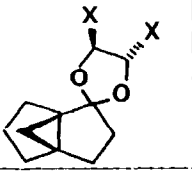
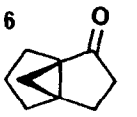
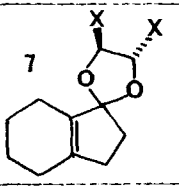
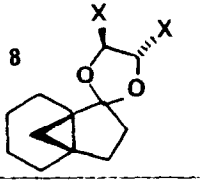
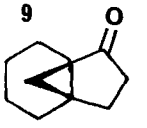
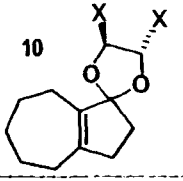
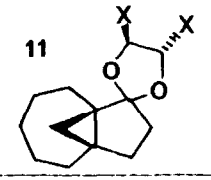
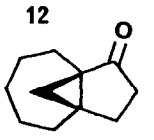
(4a*S*, 8a*R*)-3,4,5,6,7,8-Hexahydro-4a,8a-methanonaphthalen-1(2H)-one 1,4-Di-*O*-benzyl-*L*-threitol Ketal **2**

To a stirred suspension of Zn-Cu couple (1.45 g) and anhydrous potassium carbonate (0.94 g) in diethyl ether (2.8 mL) were added two small crystals of iodine and diiodomethane (0.55 mL, 6.83 mmol). After 30 min at gentle reflux, ene ketal **1** (986 mg, 2.27 mmol) was added as a solution in diethyl ether (1.0 mL). Progress of the reaction was monitored by TLC (69/30/1 dichloromethane/hexanes/methanol). After 2 hr the reaction mixture was cooled to 0°, saturated aqueous potassium carbonate (0.5 mL) added, and the mixture stirred at room temperature for 30 min. Solids were removed by centrifugation and washed well with diethyl ether. The combined extracts were washed with saturated aqueous ammonium chloride, sodium bicarbonate, sodium chloride, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography on silica gel 60 (100 g) eluted with 10% ethyl acetate/hexanes afforded ketal **2** (818 mg, 1.82 mmol, 80%) as a pale yellow oil homogeneous by TLC (R_f 0.48, 20% ethyl acetate/hexanes); IR ($CHCl_3$) 3005, 2931, 2858, 1451, 1210, 1087, 907, and 696 cm^{-1}; ^1H NMR ($CDCl_3$) 0.54 (1, d, $^2J_{HH}$ = 5.0 Hz), 0.69 (1, d, $^2J_{HH}$ = 5.0 Hz), 1.98-2.90 (15, m), 2.18-2.31 (1, m), 3.55-3.77 (4, m), 3.95-4.08 (1, m), 4.09-4.22 (1, m), 4.54-4.66 (4, m), and 7.20-7.50 ppm (10, m); ^{13}C NMR ($CDCl_3$) major diastereomer: 19.5, 21.0, 21.1, 22.4, 24.3, 24.4, 27.2, 30.6, 30.7, 32.3, 70.1, 71.1, 73.3, 73.4, 77.3, 77.8, 113.3, 127.4, 128.2, and 138.1 ppm; minor diastereomer: 19.0, 21.0, 21.1, 22.4, 23.9, 24.1, 27.2, 31.3, 31.6, 32.5, 70.4, 71.1, 73.3, 73.4, 76.4, 78.9, 113.2, 127.4, 128.2, and 138.1 ppm.

(4a*S*,8a*R*)-3,4,5,6,7,8-Hexahydro-4a,8a-methanonaphthalen-1(2H)-one **3**[12]

To a stirred solution of ketal **2** (291 mg, 0.65 mmol) in methanol (3.2 mL) was added 3M hydrochloric acid (0.2 mL). After 45 min saturated aqueous sodium bicarbonate (6 mL) was added and the mixture extracted with pentane (4 x 6 mL). The combined pentane extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* ($\leq$ 25° at ~ 20 mm Hg), affording a mixture of the ketone and diol. Chromatography on silica gel 60 (16 g) eluted with 20% diethyl ether/pentane gave propellanone **3** (98 mg, 0.6 mmol, 92%) as a pale yellow oil homogeneous by TLC (R_f 0.45, 20% ethylacetate/hexanes); IR ($CHCl_3$) 3005, 2931, 2858, 1664, 1451, 1374, 1247, 1144, 1017, 943, 893, and 667 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (1, d, $^2J_{HH}$ = 5.2 Hz), 1.05-2.18 (13, m) and 2.30-2.60 ppm (2, m); ^{13}C NMR ($CDCl_3$) 18.3, 20.6, 21.1, 22.1, 23.8, 29.1, 30.1, 31.0, 35.2, 36.3, and 209.5 ppm.

TABLE 1. Enantioselective Preparation of [m.n.1]Propellanones.

Entry	Ene-Ketal[a,b]	Yield,[c,d] %	$[\alpha]_D^{25}$, deg(c)[e]	Propellanone Ketal	Yield,[c] %	Diastereomer Ratio[f]	Propellanone	Yield,[c] %	$[\alpha]_D^{25}$, deg(c)[e]
1	 1	58 (97)	+25.3 (1.18)	 2	80	7:1	 3	92	+15.0 (2.01)
2	 4	21 (88)	+2.3 (0.65)	 5	78	9:1	 6	77	+15.2 (1.06)[g]
3	 7	66 (100)	+4.3 (3.00)	 8	72	7:1	 9	90	+55.4 (2.80)
4	 10	59 (76)	+2.3 (1.71)	 11	72	9:1	 12	84	-25.9 (2.58)

[a]Prepared by direct ketalization of the corresponding bicyclic enones. [b]X = $CH_2OCH_2C_6H_5$. [c]All yields refer to isolated and purified compounds. Satisfactory IR, NMR, and HRMS data were obtained for all compounds. [d]Yield based on unrecovered diol in parentheses. [e]In $CHCl_3$. [f]Determined by 62.9 MHz ^{13}C NMR spectroscopy. [g]In ether.

Since both enantiomers of 1,4-di-*O*-benzylthreitol are available from the corresponding tartaric acids, production of either propellanone enantiomer is possible. Applications of this new methodology will be reported in future papers.[13]

References and Notes

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