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α-Hydroxycyclobutane Rearrangement Followed by Retroaldol Cleavage: A Novel and Powerful Technology for the Stereocontrolled Construction of Carbocyclic Systems. An Easy Access to Angularly Functionalised Trans-Fused Cycloheptanoids

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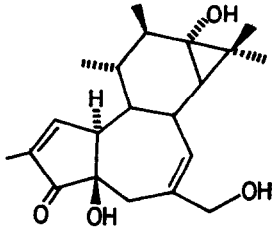
Abstract : Acid-catalysed rearrangement of α-hydroxycyclobutane derivatives **7a-7c** and **11a-11c** followed by retroaldol cleavage and oxidation in a single operation furnish angularly carboxylated trans-fused cycloheptanoid derivatives **9a-9c** and **12a-12c** in good yields.

During the last few years a wide variety of natural products bearing angularly functionalised trans-fused seven-membered ring systems as the core of their polycarbocyclic frameworks have been isolated[1] from marine, plant, insect and microbial sources and many of them have been shown to possess promising biological activities. A few representative examples of current interest are phorboids **1**.[2] virgenes **2**,[3] reiswigins **3**,[4] and helenanolides **4**.[5]



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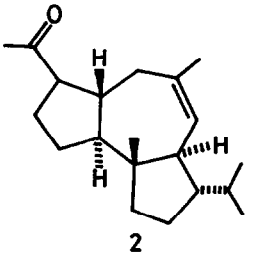

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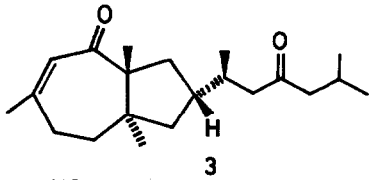

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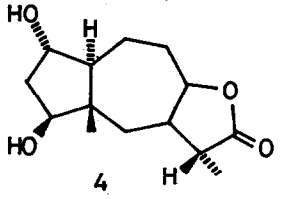

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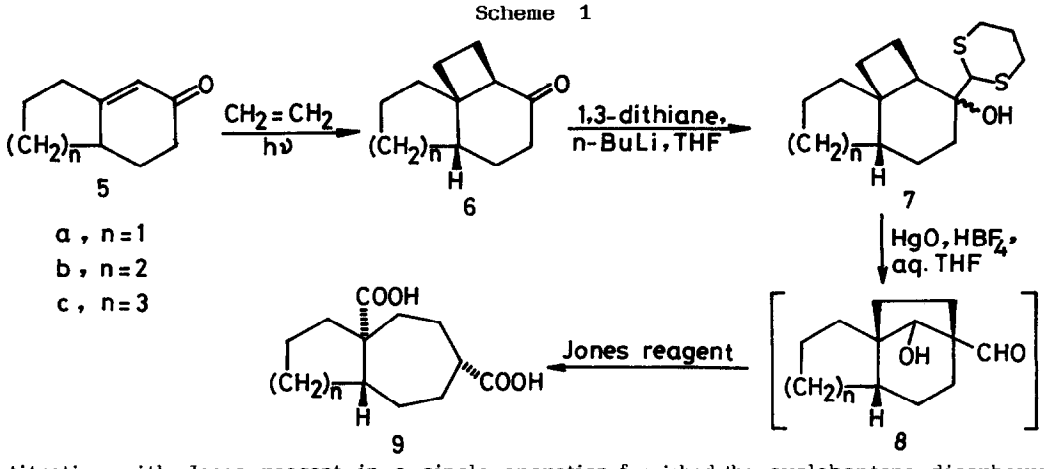
The complexity in chemical structures of these compounds combined with associated biological activities have stimulated immense and persistent interest towards the synthesis of these compounds.[6] An important step in the synthesis of a polycarbocyclic molecule is the basic skeletal construction with appropriate stereochemistry and enough scope for functionalisation in the molecule which often govern the step economy and total yield. Although numerous elegant methodologies for access to the cis-fused cycloheptanoids have been developed during recent times,[7] only

a limited number of strategies for the construction of trans-fused cycloheptanoid compounds have been reported.[8] But, these strategies, often, lack scope for proper functionalisation in the molecule and thus restrict their uses in natural product synthesis. Recently, we have introduced a fundamental strategy for the construction of usefully functionalised six- and seven-membered ring systems via α-hydroxycyclobutane rearrangement followed by retroaldol cleavage.[9] In the present paper[10] we demonstrate an application of this novel technology to address a general method for the stereocontrolled synthesis of angularly functionalised trans-fused cycloheptanoids.

The central step is the solvolytic rearrangement of suitably substituted α-hydroxycyclobutane derivatives **7a-7c** in an aqueous acidic medium (Scheme 1). Thus, readily available cycloalkenones **5a-5c**[11] were irradiated with ethylene[12] to give the corresponding cycloadducts **6a-6c** which were then treated with 2-lithio derivative of 1,3-dithiane to give the desired alcohols **7a-7c** in excellent yields. These dithiane alcohols **7a-7c** on reaction with HgO and HBF_4 in aqueous THF for 3-4 h followed by

Scheme 1

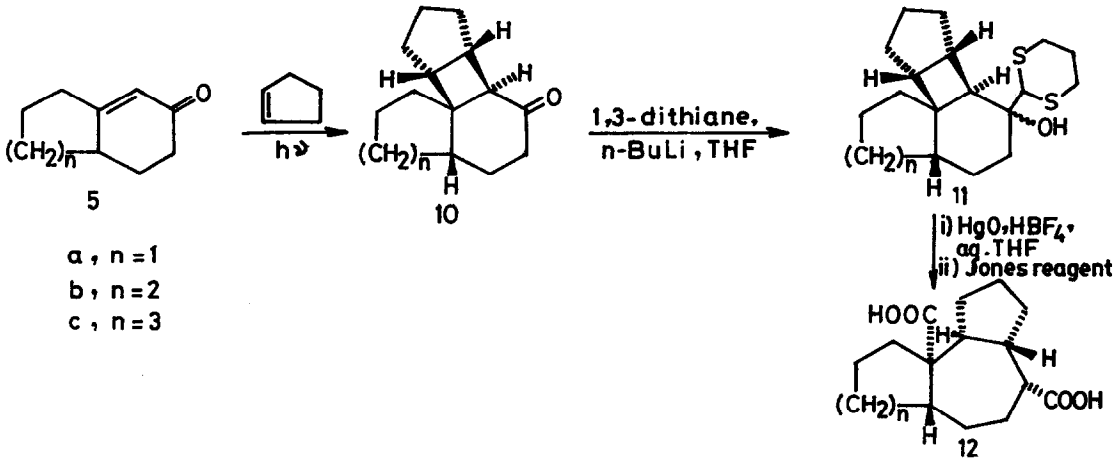


titration with Jones reagent in a single operation furnished the cycloheptane dicarboxylic acid derivatives **9a-9c** as crystalline solids in good yields. The homogeneity and identity of these dicarboxylic acids were confirmed by GC, TLC, ^{1}H NMR and ^{13}C NMR of their methyl esters. The acids **9a-9c** clearly arise[9] by retroaldol cleavages followed by oxidations of the intermediate bicyclo[3.2.1]octane derivatives **8a-8c**, generated by the external bond migration of the α-hydroxycyclobutane derivatives **7a-7c**. The ring juncture stereochemistry of the acids **9a-9c** are trans as established in the photocycloaddition step. The relative stereochemistry of the two CO_2H groups in **9a-9c** were assigned cis on the basis of the quantitative formation of an anhydride (IR 1740, 1785 cm^{-1}) from the acid **9b** and its regeneration to the same acid.

To enter into more complex systems related with natural products we focussed our attention to expand the scope of this technology. Thus the cycloalkenones **5a-5c** were irradiated[12] with cyclopentene to give the corresponding cycloadducts **10a-10c**

(Scheme 2) which are then subjected to the same sequence of reactions as in Scheme 1 to produce the tricyclic dicarboxylic acid derivatives **12a-12c** in similarly good yields.

Scheme 2



The synthesis of trans-fused cycloheptanoids with angular functionalisation has been a continuing challenge to organic chemists over the years because of their presence in a large number of natural products. This converging synthetic strategy, delineated here, provides a solution to this problem addressing a general procedure for facile entry to this class of compounds. The procedure is very simple involving only three steps and the starting compounds are easily available. Particularly noteworthy are the stereocontrolled rearrangement steps and angular functionalisation during rearrangement. Moreover, desired prefunctionalisation in the starting bicyclic cyclohexenone and involvement of varied olefins or cycloalkenes in the photocycloaddition step will tremendously broaden the scope of this methodology for handling complex polycarbocyclic natural products incorporating trans-fused cycloheptanoid subunit.

Experimental

General : Melting points were determined in glass disc with an electrical bath (Reichert, Austria) and are uncorrected. IR spectra were recorded on a Perkin Elmer model 298 spectrometer. ^{1}H NMR spectra were obtained at 60 MHz on Varian EM-360, at 100 MHz on Jeol FX-100 and at 200 MHz on Varian XL-200 spectrometers in CCl_4 or $CDCl_3$ solutions, using tetramethylsilane as an internal standard. ^{13}C NMR was recorded at 75 MHz (300 MHz Brucker instrument) and 25 MHz (Jeol FX-100 spectrometer). Thin layer chromatography was done on precoated silica gel plates (Eastman Kodak Co. and E. Merck). Column chromatography was performed over silica gel (SRL or SD, India). Tetrahydrofuran (THF) was distilled from benzophenone-potassium under nitrogen, immediately before use. Elemental analyses were performed by Mr. S. Sarkar of this laboratory. GLC was done on a Shimadzu GC-9A instrument using column OV-17 (2m)

using nitrogen as carrier gas. A medium pressure 450W Hanovia lamp with pyrex filter is used for irradiation during photolysis. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

The cyclobutyl ketones **6a-6c** and **10a-10c** were prepared following a reported procedure[12] from readily obtainable cycloalkenones.[11]

Preparation of dithiane alcohols 7a-7c and 11a-11c. General procedure : Preparation of **7a.** To a stirred solution of 1,3-dithiane (1.2 g, 10 mmol) in dry THF (10 ml) at -10°C (ice-salt bath) was added n-butyl lithium (12.5 ml of 1 M solution in hexane, 80 mg, 12.5 mmol) dropwise under nitrogen. Stirring was continued at -10°C for 2 h after which the ketone **6a** (1.47 g, 9 mmol) in THF (2.5 ml) was added dropwise. The reaction mixture was allowed to attain room temperature and stirred overnight (18 h). The mixture was then poured into water, saturated with sodium chloride and extracted with ether (4 x 30 ml). The ether extract was dried (Na_2SO_4) and evaporated to leave a yellow viscous liquid which was chromatographed over silica gel to afford the pure alcohol **7a** (2 g, 85%) (some unreacted 1,3-dithiane and ketone **6a** were recovered which was taken into account in calculation of yield) as a pale yellow oil, IR (neat) 3200-3600 (broad), 910 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.9-2.10 (m, 19 H), 2.6-3.0 (m, 4H), 4.13 (s, 1H). Anal. calcd. for $C_{15}H_{24}OS_2$: C, 63.34; H, 8.50. Found: C, 63.51; H, 8.29. **7b** (88%), IR (neat) 3200-3600 (broad), 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9-2.4 (m, 21H), 2.8-3.15 (m, 4H), 4.14 (s, 1H). Anal.calcd.for $C_{16}H_{26}OS_2$: C, 64.38; H, 8.78. Found : C, 64.45; H, 8.81. **7c** (80%), m.p. 123°C, IR (KBr) 3200-3600 (broad), 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.0-2.22 (m, 23H), 2.7-3.1 (m, 4H), 4.2 (s, 1H). Anal. calcd. for $C_{17}H_{28}OS_2$: C, 65.32; H, 9.03. Found: C, 65.43; H, 8.99. **11a** (90%), IR (neat) 3460 (broad), 920 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.72-2.6 (m, 23H), 2.6-3.32 (m, 4H), 4.10 (s, 1H). Anal. calcd. for $C_{18}H_{28}OS_2$: C, 66.62; H, 8.70. Found : C, 66.48; H, 8.91. **11b** (88%), m.p. 176°C, IR (KBr) 3460 (broad), 910 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.04-2.6 (m, 25H), 2.76-3.48 (m, 4H), 4.12 (s, 1H). Anal. calcd. for $C_{19}H_{30}OS_2$: C, 67.40; H, 8.94. Found: C, 67.52; H, 8.88. **11c** (91%), IR (neat) 3450 (broad), 910 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.04-2.70 (m, 27H), 2.76-3.2 (m, 4H), 4.12 (s, 1H). Anal. calcd. for $C_{20}H_{32}OS_2$: C, 68.13; H, 9.15. Found: C, 68.25; H, 9.23.

Preparation of dicarboxylic acids 9a-9c and 12a-12c. General Procedure : Preparation of **9a.** The alcohol **7a** (560 mg, 2 mmol) in THF (5 ml) was added dropwise to a stirred suspension of HgO (red) (850 mg, 3.9 mmol) and fluoboric acid (48%) (0.8 ml, 350 mg, 4 mmol) in aqueous THF (85%, 5 ml) under nitrogen at room temperature. Stirring was continued for 3 h (as indicated by TLC showing the disappearance of starting alcohol). The reaction mixture was cooled to 0°C and titrated with Jones reagent till the colour of Jones reagent persisted for 5 mins. After being stirred for another 30 min, the reaction mixture was diluted with water (10ml), saturated with sodium chloride, and extracted with ether (4 x 30 ml). The ether extract was washed with

brine until inorganic acid free and then extracted with aqueous sodium bicarbonate solution (5%). The bicarbonate washings were then acidified with dilute (1:1) HCl and extracted with ether (3 x 25 ml). The ether extract was washed with water, dried (Na_2SO_4) and evaporated to furnish a solid which was recrystallised from ethyl acetate-petroleum ether to produce pure dicarboxylic acid **9a** (298 mg, 66%), m.p. 130°C, IR (KBr) 1705 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.00-3.12 (m, 16H), 8.43 (broad; 2H). Anal. calcd. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.71; H, 8.02. A methyl ester was prepared using a standard procedure (CH_2N_2), IR (neat) 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18-2.4 (m, 15H), 2.86-2.98 (m, 1H), 3.62 (s, 3H), 3.72 (s, 3H). **9b** (70%), m.p. 168°C, IR (KBr) 3520 (broad), 1705 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.03-3.13 (m, 18H), 10.03 (broad, 2H). Anal. calcd. for $C_{13}H_{20}O_4$: C, 64.97; 8.38. Found: C, 64.89; H, 8.31. A methyl ester was prepared: IR (neat) 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.2-2.4 (m, 17H), 2.4-2.8 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (t), 18.4 (t), 22.2 (t), 22.3 (t), 26.7 (t), 28.1 (t), 34.0 (t), 36.8 (d), 37.8 (s), 46.6 (t), 47.4 (d), 51.3 (q), 51.4 (q), 174.72 (s), 174.75 (s). **9c** (56%), m.p. 177°C, IR (KBr) 3200 (broad), 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.05-3.15 (m, 20H), 9.30 (broad, 2H). Anal. calcd. for $C_{14}H_{22}O_4$: C, 66.10; H, 8.72. Found: C, 66.12; H, 8.73. A methyl ester was prepared: IR (neat) 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43-2.4 (m, 19H), 2.66-2.76 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H). **12a** (60%), m.p. 145°C, IR (KBr) 1695, 1715 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.69-2.52 (m, 19H), 2.72-3.16 (m, 1H), 9.0 (broad, 2H). Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.82; H, 8.42. A methyl ester was prepared: IR (neat) 1730 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.08-2.64 (m, 19H), 2.84-3.16 (m, 1H), 3.66 (s, 6H), ^{13}C NMR (25 MHz, $CDCl_3$) δ 20.2 (t), 26.2 (t), 28.1 (t), 28.9 (t), 31.5 (t), 33.2 (t), 34.9 (t), 36.3 (t), 44.7 (3d), 48.1 (d), 51.9 (s), 180.1 (s), 181.4 (s). **12b** (50%), m.p. 210°C, IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-3.13 (m, 22H), 5.56 (broad, 2H). A methyl ester was prepared: IR (neat) 1730 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.08-2.72 (m, 21H), 2.76-3.12 (m, 1H), 3.64 (s, 3H), 3.68 (s, 3H). Anal. calcd. for $C_{18}H_{28}O_4$:C,70.10; H, 9.15. Found: C, 69.81; H, 9.04. **12c** (75%), m.p. 176°C, IR (KBr) 1690, 1725 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.16-3.26 (m, 24H), 8.82 (broad, 2H). A methyl ester was prepared; IR (neat) 1730 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.08-2.68 (m, 23H), 2.8-3.12 (m, 1H), 3.64, 3.66 (2s, 6H). Anal. calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.54; H, 9.29.

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References and Notes

1. Glasby, J.S 'Encyclopedia of the Terpenoids', Wiley Interscience, New York, **1982**, (b) Rahman, A. Ed., 'Studies in Natural Product Chemistry', Elsevier, **1990**, Vols. 1-6.

2. (a) Crombie, L.; Games, M.L.; Pointer, D.J. J. Chem. Soc., C **1968**, 1347. (b) Wender, P.A.; Kogen, H.; Lee, H.Y.; Munger, J.D. Jr.; Wilhelm, R.S.; Williams, P.D. J. Am. Chem. Soc., **1989**, 111, 8957. (c) Wender, P.A.; McDonald, F.E. J. Am. Chem. Soc. **1990**, 112, 4956. (d) Harwood, L.M.; Jones, G.; Pickard, J.; Thomas, R.M.; Watkin, D. J. Chem. Soc. Chem. Commun. **1990**, 605.

3. Uegaki, R.; Fujimori, T.; Ueda, N.; Ohnishi, A. Phytochemistry **1987**, 3029.

4. Kashman, Y.; Hirsch, S.; Koehn, F.; Cross, S. Tetrahedron Lett. **1987**, 28, 5461.

5. Harimaya, K.; Arai, N.; Inayama, S. Chem. Pharm. Bull. **1989**, 37, 2525.

6. (a) Ho, T.-L. Ed., 'Carbocyclic construction in Terpene Synthesis', VCH, Deerfield Beach, **1988**. (b) Heathcock, C.H. in 'The Total Synthesis of Natural products', Ed. Apsimon, J., Wiley, New York, **1973** , Vol.2.

7. (a) Lee, T.V.; Porter, J.R.; Roden, F.S. Tetrahedron, **1991**, 47, 139. (b) Marson, C.M.; Benzies, D.W.M.; Hobson, A.D.; Adams, H.; Bailey, N.A. J. Chem. Soc. Chem. Commun. **1990**, 1516. (c) Rosenblum, M.R.; Watkins, J.C. J. Am. Chem. Soc. **1990**, 112, 5985. (d) Paquette, L.A.; Shi, Y.-J. J. Am. Chem. Soc. **1990**, 112, 8478. (e) Rawal, V.H.; Newton, R.C.; Krishnamurthy, V. J. Org. Chem. **1990**, 55, 5181. (f) Hirst, G.C.; Howard, P.N.; Overman, L.E. J. Am. Chem. Soc. **1989**, 111, 1515. (g) Reydellet, V.; Helquist, P. Tetrahedron Lett. **1989**, 30, 6837. (h) Majetich, G.; Defauw, J.; Ringold, C. J. Org. Chem. **1988**, 53, 50 and references cited therein.

8. (a) Majetich, G.; Song, J.S.; Ringold, C.; Nemeth, G.A. Tetrahedron Lett. **1990**, 31, 2239 (b) Sathyamoorthi, G.; Thangaraj, K.; Srinivasan, P.C.; Swaminathan, S. Tetrahedron **1990**, 46, 3559. (c) Snider, B.B.; Yang, K. J. Org. Chem. **1990**, 55, 4392. (d) Kennedy, M.; McKervey, M.A. J. Chem. Soc. Chem. Commun. **1988**, 1028. (e) Tanis, S.P.; Johnson, G.M.; McMills, M.C. Tetrahedron Lett. **1988**, 29, 4521. (f) Welch, M.C.; Bryson, T.A. Tetrahedron Lett. **1988**, 29, 521. (g) Mehta, G.; Krishnamurthy, N. Tetrahedron Lett. **1987**, 28, 5945. (h) Sworin, M.; Lin, K.C. J. Org. Chem. **1987**, 52, 5640. (i) Wender, P.A.; Fisher, K. Tetrahedron Lett. **1986**, 27, 1857. (j) Ghosh, S.; Saha Roy, S.; Saha, G. Tetrahedron **1988**, 44, 6235 and references cited therein.

9. (a) Ranu, B.C.; Sarkar, D.C. J. Chem. Soc. Chem. Commun. **1988**, 245. (b) Ranu, B.C.; Sarkar, D.C.; Basu, M.K. Tetrahedron **1989**, 45, 3107.

10. A preliminary communication with a part of this work appeared in: Ranu, B.C.; Basu, M.K. Tetrahedron Lett. **1991**, 32, 4177.

11. Aumiller, J.C.; Whittle, J.A. J. Org. Chem. **1976**, 41, 2955.

12. Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. J. Am. Chem. Soc. **1989**, 111, 3707.