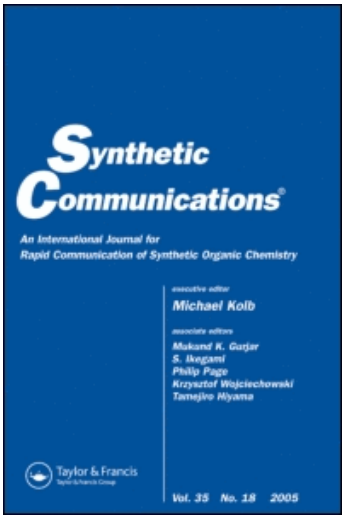

Synthetic Communications
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597304

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To cite this Article Ghosh, Subrata , Roy, Supti Saha and Bhattacharya, Atashi(1989) 'Bicyclo[2.2.1]Heptane as Cyclopentane Precursor. Part 3[1]. A Convenient Route to [3.3.3]Propellanes', Synthetic Communications, 19: 18, 3191 — 3197
To link to this Article: DOI: 10.1080/00397918908052719
URL: http://dx.doi.org/10.1080/00397918908052719

SYNTHETIC COMMUNICATIONS, 19(18), 3191-3197 (1989)

BICYCLO[2.2.1]HEPTANE AS CYCLOPENTANE PRECURSOR. PART 3[1]. A CONVENIENT ROUTE TO [3.3.3]PROPELLANES

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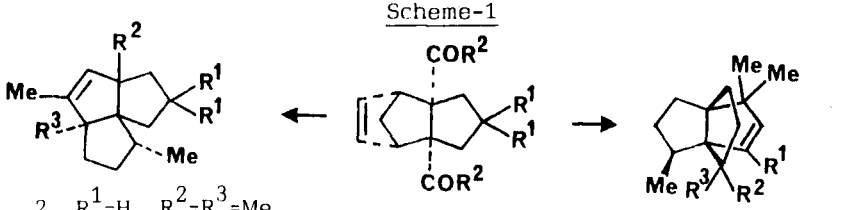
Abstract: A short and convenient strategy to [3.3.3]propellanes 13 and 14 from the readily available bicyclo[2.2.1]heptane precursor 7 is described.

The easy accessibility of bicyclo[2.2.1]heptanes combined with the facile cleavage of these relatively strained derivatives offers an inventive strategy for the synthesis of either condensed[1,2], spiro[3] or bridged ring[4] systems. In connection to an approach toward the synthesis of sesqui- and diterpenes, we have adopted this strategy for the construction of condensed 5-5-6 and 5-7-6[1,5] tricarbocyclic units. To extend this concept to the synthesis of triquinane natural products, we envision that a bicyclo[2.2.1]heptane derivative 1 (Scheme-1), may serve as an

Scheme-1



2, R^1=H, R^2=R^3=Me

3, R^1=Me, R^2=R^3=H

1

4, R^1=Me, R^2=R^3=H

5, R^1=CHO, R^2,R^3=O

6, R^1=COOH, R^2,R^3=O

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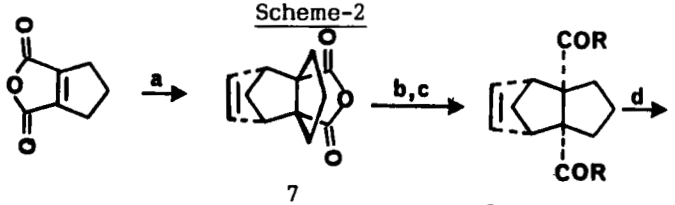
intermediate leading to either angular annelated triquinanes[6a] e.g. isocomene 2[6b], pentalenene 3[6c] or to [3.3.3]propellanes e.g. modhephene 4[6a,b,d], pulicaral 5[7] and pulicaric acid 6[7]. As part of this programme, we report here a short and convenient approach to highly functionalised [3.3.3]propellanes.

The required bicyclo[2.2.1]heptene derivative 7 (Scheme-2) was prepared[8] by aluminium chloride catalysed Diels-Alder cycloaddition of cyclopentene-1,2-dicarboxylic anhydride with cyclopentadiene. To serve as an intermediate for propellane synthesis, the anhydride 7, which have two cyclopentane rings fused together, requires an additional ring to be annulated through the substituents at C_{3a} and C_{6a}. To this end, the anhydride 7 was hydrolysed to the dicarboxylic acid 8.

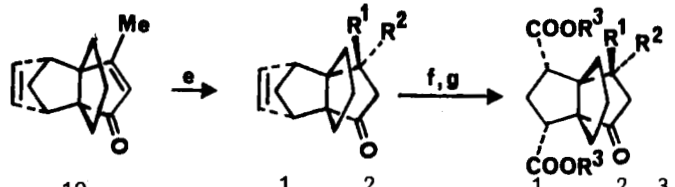
Scheme-2



7

8, R=OH

9, R=Me



10

11, R^1=Me, R^2=H

12, R^1=H, R^2=Me

13a, R^1=Me, R^2=R^3=H

13b, R^1=R^3=Me, R^2=H

14a, R^1=R^3=H, R^2=Me

14b, R^1=H, R^2=R^3=Me

Reagents: a, Cyclopentadiene, THF, $AlCl_3$, 0^oC.
b, $NaHCO_3$-EtOH-H_2O, Reflux then HCl. c, MeLi, Et_2O, 0^o to rt. d, t-BuOK, t-BuOH, rt. e, Li-NH_3, NH_4Cl.
f, $RuCl_3$,·$NaIO_4$, H_2O-acetone. g, CH_2N_2, Et_2O.

Treatment of the dicarboxylic acid 8 in ether solution with two equivalent of methyl lithium smoothly transformed it to the diketone 9 in 91% yield. The diketone 9 is now ready for ring closure to provide the required third cyclopentane ring for propellane synthesis.

Brief exposure of 9 to potassium tert-butoxide in tert-butanol at room temperature effected the ring closure to afford 10 in excellent yield. That cyclisation has taken place is clearly established by the appearance of a olefinic singlet at δ 5.78 in ^{1}H NMR of 10, in addition to a pair of doublet of doublet at δ 5.94 and 6.08 for the isolated olefinic protons. Selective reduction of the enone double bond in 10 with lithium-liquid ammonia afforded a mixture of 11 and 12 in almost equal amount as evidenced by the appearance of two methyl doublets at δ 1.06 and 1.11 (J=6.9 and 6.7Hz respectively). An attempted separation of this mixture either through crystallisation, column or gas chromatography was unsuccessful. The mixture of 13 and 14 was subjected to oxidative fission of the double bond by ruthenium trichloride-sodium metaperiodate to afford a mixture of the propellanes 13a and 14a which were characterised as their dimethyl esters 13b and 14b.

Thus, the efficacy of the bicyclo[2.2.1]heptene 7 to provide the highly functionalised propellane derivatives through short and simple sequence of reactions is clearly established. Subsequently the diketone 12 will be utilised as a key intermediate for the total synthesis of the naturally occuring propellanes e.g. 4, 5 and 6.

Experimental Section

Melting points were taken in open capillary in a sulphuric acid bath. IR spectra were recorded on a Perkin-Elmer 298 spectrometer in $CHCl_3$ solution. ^{1}H NMR were recorded in $CDCl_3$ solution at 200 MHz on Varian XL-200 spectrometer using TMS as

internal standard. Organic extracts were dried over anhydrous sodium sulphate. Column chromatography was performed in silica gel column. Petroleum and light petroleum refers to fractions of petroleum ether boiling in the ranges 60^{o}-80^{o}C and 40^{o}-60^{o}C respectively.

4α,6α-Etheno- hexahydro pentalene-3aα,6aα-dicarboxylic acid (8). The dicarboxylic acid (8) was prepared with slight modification of the reported procedure[8]. To a solution of cyclopentene-1,2-dicarboxylic anhydride (7g, 50.7 mmol) in THF (20 ml) cooled to 0^{o}C was added with stirring freshly distilled cyclopentadiene (20 ml) followed by aluminium chloride (160 mg). After standing at 0-5^{o}C for 12-14 h the reaction mixture was diluted with ether and washed with brine. The organic layer after drying was concentrated to afford a solid which was crystallised from ether-light petroleum to afford (7) (9.2 g, 90%); mp 154^{o}C. Hydrolysis of the anhydride (7) (3 g, 14.4 mmol) was accomplished by mild refluxing in aqueous ethanol (150 ml, 4:1) with sodium bicarbonate (5.2 g) for 2 h. The cold reaction mixture after extraction with ether to remove any unhydrolysed material was acidified with 6N HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried. Removal of solvent in vacuo afforded the dicarboxylic acid (8) (2.98 g, 92%); mp 173-174^{o}C (dec.). ^{1}H NMR of the methyl ester (diazomethane) of this acid is identical with the reported value[8].

3aα,6aα-Diacetyl-4α,6α-etheno-hexahydro pentalene (9). To a magnetically stirred solution of the diacid 8 (220 mg, 1 mmol) in ether (20 ml) cooled to -10^{o}C under N_2 atmosphere, was added an ethereal solution of methyl lithium (3.3 ml, 4 mmol, 1.2 M) dropwise. After complete addition, the reaction mixture was stirrred at 0^{o}C for 1 h and at room temperature for 16 h during which the initially formed white precipitate disappeared to produce a clear solution. The reaction mixture was poured into

iced-HCl. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extract was washed successively with saturated aqueous sodium bicarbonate, 2% aqueous sodium thiosulphate, brine and dried. Removal of solvent afforded (9) (200 mg, 91%) as a solid. An analytical sample was made by its crystallisation from petroleum, mp 60°C; IR 1690cm^{-1}; ^{1}H NMR δ 1.4-1.94 (4H), 2.08 (6 H, s), 2.06-2.40 (4H), 2.8 (2H, m) and 6.27 (2H, t, J=2Hz). Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.69; H, 8.73.

4,6-Dihydro-4α,6α-etheno-3-methyl-3aβ,6aβ-propanopentalen-1(5H)-one (10). To a solution of potassium tert-butoxide in tert-butanol [made from potassium (150 mg, 3.84 mg atom) and tert-butanol (9 ml)], a solution of the diketone (9) (650 mg, 2.98 mmol) in tert-butanol (4 ml) was added dropwise under N_2 atmosphere. The purple reaction mixture after 30 min at room temperature was diluted with water and extracted with ether (3 x 20 ml). The ether extract was washed with aq. 2% HCl (2 x 10 ml), brine (2 x 10 ml) and dried. Removal of solvent gave a viscous liquid which on column chromatography (5% ethylacetate-petroleum) afforded the pure enone (10) (490 mg, 82%), mp 74°C; IR 1695, 1615cm^{-1}; ^{1}H NMR δ 1.3-2.11 (8H), 1.93 (3H, s), 2.71 (H, brs) 2.83 (H, brs), 5.78 (H, s), 5.94 (H, dd, J=5.7 and 2.8Hz) and 6.08 (H, dd, J=5.1 and 2.5Hz). Anal. calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.93; H, 8.16.

3β-Methyl-4α,6α-etheno-2,3,4,6-tetrahydro-3aβ,6aβ-propanopentalen-1(5H)-one (11) and 3α-methyl-4α,6α-etheno-2,3,4,6-tetrahydro-3aβ,6aβ-propanopentalen-1(5H)-one (12). To a solution of lithium metal (380 mg, 54 mg atom) in distilled ammonia was added with stirring a solution of the enone (10) (350 mg, 1.75 mmol) in ether (10 ml). Stirring was continued for another 30 min after which ammonium chloride was added to quench the reaction. After evaporation of ammonia the residue was acidified with 6N HCl and extracted with ether (3 x 30 ml). The ether extract was washed with brine (3 x 10 ml) and dried.

Removal of solvent afforded a solid which was chromatographed (5% ethylacetate-petroleum) giving a mixture of (11) and (12) (250 mg, 70%) as a white solid, mp 152°C; IR 1720cm^{-1}; ^{1}H NMR 1.06 and 1.11 (3H, d, J=6.9 and 6.7 Hz, for CH_3 of 11 and 12), 1.3-2.04 (11H), 2.6-2.88 (2H), 6.06 (0.5H, dd, J=5.7 and 3.1Hz), 6.22 (0.5H, dd, J=5.7 and 3.4Hz), 6.3 (0.5H, dd, J=5.4 and 3.4Hz) and 6.43 (0.5H, dd, J=5.4 and 3.3Hz). Anal. calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.10; H, 8.86.

3 β -Methyl-1(5H)-oxo-2,3,4,6-tetrahydro-3a β ,6a β -propanopentalene-4α,6α-dicarboxylic acid (13a) and 3α-methyl-1(5H)-oxo-2,3,4,6-tetrahydro-3a β ,6a β -propanopentalene-4α ,6α -dicarboxylic acid (14a) and their dimethyl esters (13b and 14b). To a magnetically stirred cold (5°C) solution of the ketone mixture (11) and (12) (100 mg, 0.5 mmol) in aqueous acetone (2 ml, 1:1), $RuCl_3$, $3H_2O$ (3 mg) was added. To this an aqueous solution of sodium metaperiodate (620 mg, 2.9 mmol) in water (4.2 ml) was added dropwise. Stirring was continued at 5°C for 30 min and then at room temperature for 1.5 h. After filtering off the white precipitate, the filtrate was extracted with ethylacetate (3 x 15 ml). The ethylacetate extract was washed with brine (2 x 10 ml) and dried. Removal of solvent afforded a mixture of the dicarboxylic acids (13a) and (14a) (100 mg, 76%); mp 198°C (crystallised from tetrahydrofuran-light petroleum). The mixture could not be purified to the pure acids by crystallisation.

A mixture of the dicarboxylic acids (13a) and (14a) (90 mg) was esterified with ethereal diazomethane to afford a mixture of the diesters (13b) and (14b) (80 mg, 80%) as a solid. Recrystallisation from ether-light petroleum gave the analytical sample, mp 90°C; IR 1730cm^{-1}; ^{1}H NMR δ 0.94, 0.96, 0.97 (3H, 3s, CH_3), 1.2-2.92 (13H), 3.76, 3.78, 3.8 (6H, 3s, $COOCH_3$). Anal. calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.06; H, 7.51.

Acknowledgement: S.S.R. (RA) and A.B. (JRF) thank CSIR (New Delhi) for fellowship.

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(Received in UK 20 June, 1989)