Total Synthesis of 9-Isocyanoneopupukeanane

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Sponges elaborate the largest number of bioactive marine natural products, which often possess fascinating structures of great varieties. Our involvement in this area of chemistry has resulted in the synthesis of curcuphenol structures of great varieties. Our involvement in this area of chemistry has resulted in the synthesis of curcuphenol, 8 and 9-isocyanoneopupukeanane (2a), Chart 1 and 9-isocyanopropenepumpukane (2b), 9,10 formal syntheses of the latter that terminated at 9-pupukeanone11–13 have also been reported. On the other hand, we are not aware of 1, which possesses a rearranged skeleton, having been yielded to synthesis.

This work stemmed from our general interest in synthesis design related to molecular symmetry.14 In a retrospective analysis of isocyanopropenepumpukane, the tricyclic olefin MeMgCl. Treatment of (after in situ conjugation), and Grignard reaction with methyl ether, Diels–Alder reaction sequence consisting of Birch reduction of diol epoxy enone with lithium aluminum hydride afforded the m-hydrogen peroxide (63%), which was epoxidized at the side chain with hydrogen peroxide–urea in acetic anhydride to give 5 in 70% yield (75% by using mp–CPBA). Reduction of the epoxy enone with lithium aluminium hydride afforded the diol 6a (62%, inseparable diastereomers), which was acetylated (Ac2O, py, DMAP) to provide diacetate 6b (92%, inseparable diastereomers). Pyrolysis of 6b in a sealed tube at 450 °C for 1 h furnished directly the desired tricyclic olefin 8 (54%), indicating the generation of 7 as an intermediate.

With the acquisition of 8 the functionalization of its double bond was in order. We expected that hydroboration–oxidation would give rise to 9 predominantly because the formation of the regiosomeric alcohol 9a is less favorable due to steric hindrance from the bridgehead methyl substituents. Indeed, a separable mixture was produced in 52% and 10% yield, respectively. By PCC oxidation of the major alcohol 9 to afford ketone 10 (85%) the work entered its last stage. Thus, after exposure of 10 to i-PrMgBr/ClCeCl316 (91%) and then MeSiCN/H2SO4,17 the formamide 12 was obtained in 42.5% yield. Completion of our synthesis was attained by subjecting 12 to TsCl-py at room temperature. 9-Isocyanopropenepumpukane was isolated in 83% yield. The final product showed spectral data in good agreement with the reported values.

In conclusion, this report delineates the first total synthesis of isocyanopropenepumpukane. It is interesting that we did not isolate the dimethyltwistene isomer from the pyrolysate of 6b.

Experimental Section

General Methods. NMR spectra were recorded with CDCl3 as solvent, at 300 and 74 MHz, respectively for 1H and 13C NMR. Chemical shifts reported in ppm relative to 0 for TMS. Electronic impact mass spectra were measured at 70 eV. Silica gel (70–230 mesh) for chromatography was a Merck product. Melting points, determined with a Laboratory Devices apparatus, were uncorrected.

4-Methyl-4-(3-methyl-2-butanyl)-2-cyclohexenone (4). To a solution of the tertiary alcohol 3 (15.0 g, 71 mmol) in glacial acetic acid (40 mL) was added 70% perchloric acid (1 mL), and the mixture was stirred at room temperature for 45 min and quenched with aqueous sodium bicarbonate. The product was extracted into ether, which was washed with water and brine, dried over Na2SO4, and filtered. The residue obtained on evaporation was chromatographed over a silica gel column (eluent: hexane) to afford the diene 4 as an oil (8.0, 63%): IR (film) 1683 cm−1; 1H NMR δ 1.04 (3H, s), 1.53 (2H, s), 1.70 (3H, s), 1.80–2.00 (1H, m), 2.15–2.20 (3H, m), 2.34–2.40 (2H, m), 5.08 (1H, J = 7.2 Hz), 5.80 (1H, d, J = 10.2 Hz), 6.60 (1H, d, J = 10.2 Hz); 13C NMR δ 17.8 (q), 24.6 (q), 25.9 (q), 33.4 (t), 34.1 (t), 36.5 (s), 39.0 (t), 119.0 (d), 127.3 (d), 135.0 (s), 159.1 (d), 199.6 (s). HRMS (FAB) C17H20O3 (178.1357 calcd for C17H20O3, 178.1358) at 4-Methyl-4-(3-methyl-2,3-epoxybutanyl)-2-cyclohexenone (5). A mixture of 4 (8.2 g, 46 mmol), urea–hydrogen peroxide (13.0 g, 138 mmol), and acetic anhydride (37 mL) in dichloromethane (130 mL) was refluxed for 4 h. The reaction mixture was cooled to room temperature, neutralized with saturated sodium carbonate, and separated into layers. The aqueous solution was washed with dried over sodium hydrogen peroxide, and filtered. The residue obtained on evaporation was photographed over a silica gel column (eluent: hexane/ethyl acetate 9:1) to furnish the oily epoxy enone 5 (6.2 g, 70%): IR (film) 1672 cm−1; 1H NMR δ 1.21 (6H, s), 1.28 (3H, s), 1.40–1.80 (2H, m), 2.00–2.15 (2H, m), 2.25–2.32 (2H, m), 2.59–2.62 (1H, m), 5.70 (1H, d, J = 10.5 Hz), 6.58 (1H, d, J = 10.5 Hz); 13C NMR δ 18.7/18.8 (q), 23.0/23.1 (q), 27.0 (m) (1H, J = 10.5 Hz, 3.0/3.1 (m), 3.9 (t), 40.0 (t), 57.7 (s), 60.3/60.4 (d), 127.7 (d), 157.7/157.9 (d), 199.1 (s); HRMS (FAB) C17H18O5 (194.1304) at 419.1307 calcd for C17H18O5.

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4-Methyl-4-(3-hydroxy-3-methylbutanyl)-2-cyclohexen-1-ol (6a). A solution of the epoxy enone 5 (0.97 g, 5 mmol) in anhydrous ether (20 mL) was added to a suspension of lithium aluminum hydride (0.19 g, 5 mmol) in ether (20 mL) at 0 °C and then heated under reflux for 12 h. On cooling, the reaction mixture was quenched with water, neutralized with 3 N sulfuric acid, and separated into layers. The aqueous solution was extracted with more ether, and the combined organic solutions were dried over anhydrous Na2SO4 and filtered. The residue obtained on evaporation was chromatographed over a silica gel column (eluent: hexane/ethyl acetate 1:1) to furnish the diastereomeric mixture of the oily diacetate to furnish the diol as an oil (0.61 g, 62%). The spectral data indicated it to be a diastereomer, but a sample of one isomer could be obtained: IR (film) 3410 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (3H, s), 1.12 (6H, s), 1.15–1.95 (7H, m), 1.96 (1H, m), 2.48 (2H, m), 4.00–4.10 (1H, m), 5.30–5.50 (2H, m); ¹³C NMR δ 26.5 (q), 28.9 (q), 31.4 (t), 36.4 (t), 37.6 (t), 66.2 (d), 70.7 (s), 129.0 (d), 138.3 (d); MS (EI) 198 (M⁺, 3), 111 (100).

3,7-Dimethyltricyclo[5.3.1.0³,8]undecan-10-one (10). A solution of the epoxy enone 5 (0.360 g, 2 mmol) was added to a stirred suspension of PCC (0.862 g, 4 mmol) in dichloromethane (6 mL) at room temperature. After 3 h, the mixture was filtered through Celite and evaporated. The residue was chromatographed over silica gel (eluent: hexane/ethyl acetate 1:1) to give ketone 10 as a colorless oil (0.303 g, 85%): IR (film) 1732 cm⁻¹; ¹H NMR δ 0.80/0.83 (1H, m), 0.95 (3H, s), 1.03 (3H, s), 1.10–1.31 (2H, m), 1.34–1.40 (6H, m), 1.65–1.71 (3H, m), 1.95–2.10 (1H, m), 3.67–3.72 (1H, m); ¹³C NMR δ 26.6 (q), 26.85 (t), 26.9 (q), 33.9 (d), 35.6 (t), 39.1 (s), 39.8 (s), 40.3 (t), 40.7 (t), 41.9 (t), 48.5 (d), 68.9 (d); HRMS (EI) 180.1520 (180.1515 calcd for C₁₂H₂₀O).

10-Isoopropyl-3,7-dimethyltricyclo[5.3.1.0³,8]undecan-10-one (11). Cerium trichloride heptahydrate (0.558 g, 1.5 mmol) was added to a stirred suspension of PCC (0.862 g, 4 mmol) in dichloromethane (6 mL) at room temperature. After 3 h, the mixture was filtered through Celite and evaporated. The residue was chromatographed over silica gel (eluent: hexane/ethyl acetate 1:1) to give ketone 11 as a colorless oil (0.303 g, 85%): IR (film) 1732 cm⁻¹; ¹H NMR δ 0.80/0.83 (1H, m), 0.95 (3H, s), 1.03 (3H, s), 1.10–1.31 (2H, m), 1.34–1.40 (6H, m), 1.65–1.71 (3H, m), 1.95–2.10 (1H, m), 3.67–3.72 (1H, m); ¹³C NMR δ 26.6 (q), 26.85 (t), 26.9 (q), 33.9 (d), 35.6 (t), 39.1 (s), 39.8 (s), 40.3 (t), 40.7 (t), 41.9 (t), 48.5 (d), 68.9 (d); HRMS (EI) 178.1358 (178.1352 calcd for C₁₂H₂₀).
bicarbonate. Drying, filtration, and evaporation gave a crude product which was purified by silica gel chromatography (elu-
ent: hexane/ethyl acetate 9:1) to afford alcohol 11 (0.202 g,
91%): IR (film) 3490 cm\(^{-1}\); \(^1\)H NMR \(\delta 0.77 (3H, d, J = 6.9 Hz),
0.93 (3H, d, J = 6.9 Hz), 0.96 (3H, s), 1.05 (3H, s), 1.10–1.95
(13H, m); \(^{13}\)C NMR \(\delta 16.05 (q), 16.07 (q), 26.3 (q), 27.0 (q), 32.1
(t), 34.1 (d), 37.6 (t), 38.77 (s), 38.83 (s), 39.6 (t), 41.0 (t), 41.0
(t), 49.4 (d), 72.8 (s); HRMS (EI) 222.1980 (222.1985 calcd for
C\(_{15}\)H\(_{26}\)O).

N-Formyl-10-isopropyl-3,7-dimethyltricyclo[5.3.1.0\(^3,8\)]-
undecan-10-ylamine (12). Concentrated sulfuric acid (0.25 mL,
4.5 mmol) was added in small portions to a stirred, ice-cooled
solution of alcohol 10 (0.111 g, 0.5 mmol) and cyanotrimethyl-
silane (0.4 mL, 2.5 mmol) in acetic acid (1.0 mL) under nitrogen.
The ice bath was removed, and the mixture was stirred at room
temperature for 24 h, neutralized with 10% sodium hydroxide,
and extracted with ethyl acetate. The product was purified by
silica gel chromatography (elu-
ent: hexane/ethyl acetate 3:2) to
furnish the crystalline formamide
12 (0.053 g, 42.5%): mp 78–
80 °C; IR (film) 3213, 1683 cm\(^{-1}\); \(^1\)H NMR \(\delta 0.74 (3H, d, J = 6.6
Hz), 0.87 (3H, d, J = 6.6 Hz), 0.96 (3H, s), 1.15–2.25 (4H, m), 1.30–1.42 (3H, m), 1.46–1.60 (2H, m), 1.74–1.80
(1H, m), 1.84–1.85 (1H, m), 6.30 (1H, br.s), 8.07 (1H, d, J = 12.0 Hz); \(^{13}\)C
NMR \(\delta 16.0 (q), 16.7 (q), 26.3 (q), 26.6 (q), 30.2 (t), 32.1 (d), 35.7 (d), 36.38 (t), 38.4 (t), 39.1 (s), 39.3 (s), 40.8 (t),
41.2 (t), 46.4 (d), 56.9 (s), 164.1 (d); HRMS (EI) 249.2101
(249.2094 calcd for C\(_{16}\)H\(_{27}\)NO).

\(10\)-Isocyano-10-isopropyl-3,7-dimethyltricyclo[5.3.1.0\(^3,8\)]-
undecane (9-Isocyanoneopukane). Concentrated sulfuric acid
(0.200 g, 1.05 mmol) was added to formamide 12
(0.110 g, 0.44 mmol) in pyridine (3.0 mL) at 0 °C. After a few
minutes, the ice bath was removed, and the mixture was stirred
at room temperature for 3 h, quenched with water (1 mL), and
extracted with hexane. The extracts were dried (Na\(_2\)SO\(_4\)),
filtered, evaporated, and chromatographed over silica gel (elu-
ent: hexane/ethyl acetate 19:1) to furnish 9-isocyanoneopuke-
anane (1) (0.085 g, 83%) as a colorless oil: IR (film) 2124 cm\(^{-1}\);
\(^1\)H NMR (C\(_{6}\)D\(_6\)) \(\delta 0.55 (1H, m), 0.73 (3H, d, J = 6.6 Hz), 0.74
(3H, s), 0.75–0.90 (2H, n), 0.95 (3H, d, J = 6.6 Hz), 1.09
(3H, s), 1.20–1.60 (7H, m), 1.65–1.80 (2H, m), 2.00–2.10 (1H, m); \(^{13}\)C
NMR (C\(_{6}\)D\(_6\)) \(\delta 16.5 (q), 17.0 (q), 26.3 (q), 26.7 (q), 31.4 (t), 33.2
(d), 34.6 (d), 38.0 (t), 38.7 (t), 39.0 (s), 39.1 (s), 40.1 (t), 48.3 (d),
64.4 (s), 157.0 (s); HRMS (EI) 231.1985 (231.1988 calcd for
C\(_{16}\)H\(_{25}\)N).

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Supporting Information Available: Copies of \(^{13}\)C NMR spectra. This material is available free of charge via the
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