Total Synthesis of 9-Isocyanoneopupukeanane

Tse-Lok Ho* and Gour Hari Jana

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China

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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 and curcudiol,[1] (−)-furodysin,[2] (−)-furodysinin,[3] the enantiomer of herbasolide,[4] and tavacpallescensin.[5] More recently, efforts in attaining the isocyanopupukeananes also bore fruit;[6] we now describe our approach to 9-isocyanoneopupukeanane (**1**), which is a constituent of a *Ciocalypta* sp.[7] Besides the syntheses of 2-isocyanopupukeanane (**2a**, Chart 1)[8] and 9-isocyanopupukeanane (**2b**),[9,10] formal syntheses of the latter that terminated at 9-pupukeanone[11−13] 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 retrosynthetic analysis of isocyanoneopupukeanane, the disconnection of the isopropyl group and functional group interchange at the isocyano-substituted center led to the symmetrical ketone **10**. Further tracking indicated the tricyclic olefin **8**, and the cyclohexadiene **7** to be useful synthetic precursors. To secure these compounds, we started from **3**, which is readily available[15] from a reaction sequence consisting of Birch reduction of *p*-cresyl methyl ether, Diels−Alder reaction with methyl acrylate (after in situ conjugation), and Grignard reaction with MeMgCl. Treatment of **3** with $HClO_4$ led to enone **4** (63%), which was epoxidized at the side chain with hydrogen peroxide−urea in acetic anhydride to give **5** in 70% yield (75% by using *m*-CPBA). Reduction of the epoxy enone with lithium aluminum hydride afforded the diol **6a** (62%, inseparable diastereomers), which was acetylated (Ac_2O, 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 regioisomeric 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/$CeCl_3$[16] (91%) and then Me_3SiCN/H_2SO_4,[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-Isocyanoneopupukeanane 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 isocyanoneopupukeanane. 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 $CDCl_3$ as solvent, at 300 and 74 MHz, respectively for ^1H and ^{13}C absorptions. Chemicals shifts reported in ppm relative to 0 for TMS. Electron 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-butenyl)-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 anhydrous Na_2SO_4, and filtered. The residue obtained on evaporation was passed through a silica gel column (eluent: hexane) to afford the dienone **4** as an oil (8.0 g, 63%): IR (film) 1683 cm^{-1}; ^1H NMR δ 1.04 (3H, s), 1.52 (3H, 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, t, J = 7.2 Hz), 5.80 (1H, d, J = 10.2 Hz), 6.60 (1H, d, J = 10.2 Hz); ^{13}C 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 (EI) 178.1356 (178.1358 calcd for $C_{12}H_{18}O$).

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 extracted with more dichloromethane. The organic solutions were combined, dried over anhydrous Na_2SO_4, and filtered. The residue obtained on evaporation was chromatographed 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); ^{13}C NMR δ 18.7/18.8 (q), 24.6/25.1/25.3 (q), 33.7/33.9 (t), 35.2/35.5 (s), 39.3 (t), 40.0 (t), 57.7 (s), 60.3/60.4 (d), 127.7 (d), 157.7/157.9 (d), 199.1 (s); HRMS (EI) 194.1304 (194.1307 calcd for $C_{12}H_{18}O_2$).

* To whom correspondence should be addressed. E-mail: tlho@cc.nctu.edu.tw.

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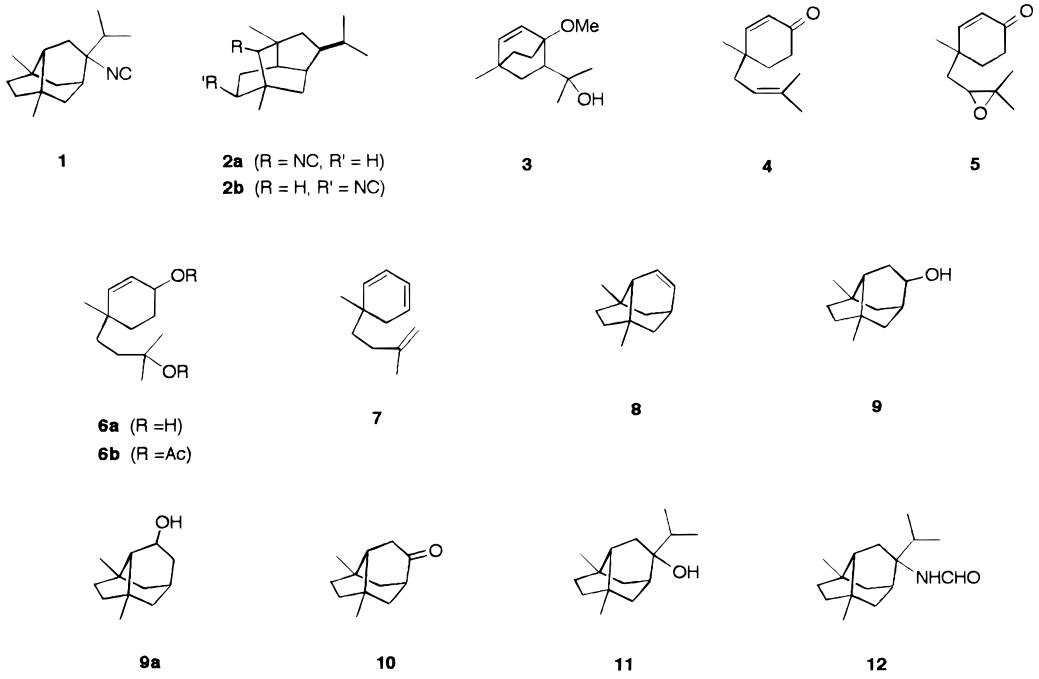
Chart 1



4-Methyl-4-(3-hydroxy-3-methylbutanyl)-2-cyclohexen-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 Na_2SO_4 and filtered. The residue obtained on evaporation was chromatographed over a silica gel column (eluent: hexane/ethyl acetate 2:3) to furnish the diol **6a** as an oil (0.61 g, 62%). The spectral data indicated it to be a mixture of diastereomers, but a sample of one isomer could be obtained: IR (film) 3410 cm^{-1}; ^1H NMR 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); ^{13}C NMR δ 26.5 (q), 28.9 (q), 31.4 (t), 34.1 (s), 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).

4-Methyl-4-(3-acetoxy-3-methylbutanyl)-2-cyclohexen-1-yl Acetate (6b). A mixture of the diol isomers **6a** (0.99 g, 5 mmol), acetic anhydride (5.0 mL, 50 mmol), pyridine (4.0 mL, 50 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.061 g, 0.5 mmol) was stirred at room temperature for 12 h under nitrogen, diluted with dichloromethane, and washed with aqueous sodium carbonate, brine, and water. After drying (Na_2SO_4) and evaporation, the product was isolated by silica gel chromatography (eluent: hexane/ethyl acetate 1:1) to furnish the diastereomeric mixture of the oily diacetate **6b** (1.30 g, 92%): IR (film) 1733 cm^{-1}; ^1H NMR δ 0.88/0.94 (3H, s), 1.20−1.30 (4H, m), 1.34/1.35 (6H, s), 1.60−1.80 (4H, m), 1.89/1.90 (3H, s), 1.98/1.99 (3H, s), 5.10−5.17 (1H, m), 5.50−5.57 (2H, m); ^{13}C NMR δ 21.3 (q), 22.3 (q), 25.0 (t), 25.9 (q), 30.2/31.0 (t), 33.9 (t), 34.0 (t), 34.6/34.7 (s), 35.3/35.4 (t), 67.6/69.0 (d), 141.7 (d), 170.2 (s), 170.7 (s); MS (EI) 282 (M^+, 10), 180 (100).

3,7-Dimethyltricyclo[5.3.1.0^{3,8}]undec-9-ene (8). Diacetate **6b** (2.82 g, 10 mmol) and a trace amount of hydroquinone in hexane (1 mL) was placed in a sealed tube and heated at 450 °C for 1 h. The cooled reaction product was filtered through a short column of silica gel to provide the alkene **8** (0.87 g, 54%) as a colorless liquid: ^1H NMR δ 0.86 (6H, s), 1.04 (2H, d, J = 1.8 Hz), 1.05 (2H, d, J = 1.8 Hz), 1.48−1.51 (4H, m), 1.76 (1H, d, J = 3.0 Hz), 2.34 (1H, m), 6.01 (1H, t, J = 7.0 Hz), 6.30 (1H, t, J = 7.0 Hz); ^{13}C NMR δ 28.5 (q), 31.0 (d), 39.3 (t), 42.0 (s), 44.3 (t), 54.7 (d), 129.2 (d), 135.3 (d); MS (EI) 162 (M^+, 50), 93 (100). Anal. Calcd for $C_{12}H_{18}$: C, 88.88; H, 11.11. Found: C, 88.30; H, 11.38.

3,7-Dimethyltricyclo[5.3.1.0^{3,8}]undecan-10-ol (9) and 3,7-Dimethyltricyclo[5.3.1.0^{3,8}]undecan-9-ol (9a). A solution of boron trifluoride etherate (0.23 g, 0.16 mmol) in THF (5 mL) was slowly introduced to a stirred mixture of alkene **8** (0.650 g, 4 mmol) and sodium borohydride (0.045 g, 1.2 mmol) in THF (10 mL) under nitrogen at room temperature. After 2 h, water was added, which was followed by aqueous sodium hydroxide (3 M, 5 mL) and hydrogen peroxide (28%, 5 mL). At the end of 4 h, the reaction mixture was diluted with water and extracted with ether. On evaporation of the dried extracts, a mixture of two alcohols was obtained. These were separated by silica gel chromatography (eluent: hexane/ethyl acetate 9:1).

Alcohol **9** (0.375 g, 52%): IR (film) 3395 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); ^{13}C 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 $C_{12}H_{20}O$).

Alcohol **9a** (0.072 g, 10%): IR (film) 3480 cm^{-1}; ^1H NMR δ 0.80−0.90 (2H, m), 0.97 (3H, s), 1.00−1.17 (2H, m), 1.18 (3H, m), 1.19−1.80 (4H, m), 1.85−1.87 (2H, m), 1.90−1.98 (2H, m), 4.10−4.17 (1H, m); ^{13}C NMR δ 26.2 (d), 27.1 (q), 29.6 (q), 38.2 (t), 39.6 (s), 40.7 (s), 40.8 (t), 41.7 (t), 42.9 (t), 43.8 (t), 54.3 (d), 66.9 (d); HRMS (EI) 180.1512 (180.1515 calcd for $C_{12}H_{20}O$).

3,7-Dimethyltricyclo[5.3.1.0^{3,8}]undecan-10-one (10). Alcohol **9** (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 4:1) to give ketone **10** as a colorless oil (0.303 g, 85%): IR (film) 1732 cm^{-1}; ^1H NMR δ 1.00 (6H, s), 1.30 (3H, m), 1.51−1.60 (8H, m), 2.00 (1H, m), 2.18−2.19 (2H, m); ^{13}C NMR δ 26.6 (q), 33.0 (t), 39.7 (s), 40.0 (t), 40.3 (t), 43.4 (d), 50.6 (d), 216.8 (s); HRMS (EI) 178.1362 (178.1358 calcd for $C_{12}H_{18}O$).

10-Isopropyl-3,7-dimethyltricyclo[5.3.1.0^{3,8}]undecan-10-ol (11). Cerium trichloride heptahydrate (0.558 g, 1.5 mmol) was dried at 150 °C/0.2 Torr for 4 h, cooled under nitrogen, and suspended and stirred in THF (5 mL). A solution of isopropylmagnesium bromide prepared from Mg (0.048 g, 2 mmol) and 2-bromopropane (0.246 g, 2 mmol) in THF (10 mL) under sonication was added to the cerium chloride at 0 °C. After 1.5 h, ketone **10** (0.178 g, 1 mmol) in THF (2 mL) was added, and the reaction was allowed to proceed for 1 h. After addition of 10% acetic acid, the reaction mixture was extracted with ether and the combined extracts were washed with brine and sodium

bicarbonate. Drying, filtration, and evaporation gave a crude product which was purified by silica gel chromatography (eluent: hexane/ethyl acetate 9:1) to afford alcohol **11** (0.202 g, 91%): IR (film) 3490 cm^{-1}; ^1H NMR δ 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 δ 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 cyanotrimethylsilane (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 (eluent: 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}; ^1H NMR δ 0.74 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz), 0.96 (3H, s), 0.98 (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 δ 16.0 (q), 16.7 (q), 26.3 (q), 26.6 (q), 30.2 (t), 32.1 (d), 35.7 (d), 38.38 (t), 38.4 (t), 39.1 (s), 39.3 (s), 40.8 (t), 41.2 (t), 48.4 (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-Isocyanoneopupukeanane) (1). *p*-Toluenesulfonyl chloride (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_2SO_4), filtered, evaporated, and chromatographed over silica gel (eluent: hexane/ethyl acetate 19:1) to furnish 9-isocyanoneopupukeanane (**1**) (0.085 g, 83%) as a colorless oil: IR (film) 2124 cm^{-1}; ^1H NMR (C_6D_6) δ 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_6D_6) δ 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 Internet at http://pubs.acs.org.

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