Enantiospecific synthesis of (-)-4-thiocyanatoneopupukeanane[†]

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Abstract
Enantiospecific total synthesis of the natural enantiomer of the marine sesquiterpene (-)-4-thiocyanatoneopupukeanane (**6**) is described. The bicyclo[2.2.2]octanonecarboxylate **11**, obtained from (*R*)-carvone and methyl methacrylate *via* Michael-Michael reaction, was transformed into bicyclo[2.2.2]octenecarboxylic acid **8**. Intramolecular cyclopropanation reaction of the diazo ketone **7**, derived from the acid **8**, followed by regioselective reductive cyclopropane ring cleavage generated neopupukeanol **20**, which was transformed into (-)-4-thiocyanatoneopupukeanane **6**.

Keywords: Carvone, marine sesquiterpenes, Michael-Michael reaction, intramolecular cyclopropanation reaction, regioselective cyclopropane ring cleavage

Introduction

In variety of marine organisms, chemical defense *via* secretion of toxic and/or strong smelling organic compounds from their skin glands is a common phenomenon as part of the self-defense mechanism to protect themselves from higher animals. Based on the observation that the nudibranch *Phyllidia varicosa* Lamarck secretes a toxic substance lethal to fish and crustaceans, Scheuer and coworkers investigated on the chemical constituents of the skin extracts of *P. varicosa* and also from its prey, a sponge *Ciocalypta* sp. These investigations led to the isolation[1] of two isotwistane (**1**) based sesquiterpenes, 9- and 2-isocyanopupukeananes **2** and **3**. Subsequently, during their biosynthetic experiments directed towards discovering the origin of the isocyano group in marine sponges, Scheuer and co-workers[2] isolated a new sesquiterpene **4** from the sponge *Ciocalypta* sp. containing a new carbon framework neopupukeanane. Later the research groups of Scheuer and Higa reported[3] the isolation of two thiocyanate containing sesquiterpenes, and assigned the structures as 2- and 4-thiocyanatoneopupukeananes **5a** and **6**, from the sponge *Phycopsis terpnis* (from Okinawa) and from an unidentified species from Pohnpei. Subsequently, Faulkner and co-


[†] Chiral synthons from carvone, Part 56. For part 55, see reference (8o).

workers reported[4] the isolation of 2-thiocyanatoneo-pupukeanane **5b** from *Axinyssa aplysinoides* from Palau, which was found to be identical to that isolated by Scheuer and Higa, and corrected the stereochemistry of the thiocyanate group as *endo*, on the basis of the 2D NMR spectra in C_6D_6. Biosynthetically, origin of pupukeananes and neopupukeananes can be explained by a common pathway *via* cyclization and rearrangement of cadinanes.[2] It is interesting to note that very few (<10) natural products have been reported to contain a thiocyanate group. Even though significant amount of synthetic activity[5] was reported on the synthesis of pupukeananes, there was no report on the synthesis of neopupukeananes prior to 1998.[6,7] In continuation of our interest in the enantiospecific synthesis of natural products,[8] herein we describe the details[6] of the enantiospecific total synthesis of 4-thiocyanatoneopupukeanane **6** starting from (*R*)-carvone employing an intramolecular cyclopropanation reaction based approach.

5a X=SCN; Y=H
5b. X=H; Y=SCN

Results and Discussion

It was envisaged (Scheme 1) that the intramolecular cyclopropanation reaction of the diazo ketone **7**, derived from bicyclo[2.2.2]octenecarboxylic acid **8**, followed by cyclopropane ring cleavage would generate the isotwistanone **9** in a regioselective manner. Whereas, Michael-Michael reaction of (*R*)-carvone (**10**) with methyl methacrylate could be exploited for the generation of the bicyclo[2.2.2]octenecarboxylic acid **8**.

Scheme 1

   The synthetic sequence is depicted in Scheme 2. Thus, reaction of (*R*)-carvone **10** with lithium hexamethyldisilazide (LiHMDS) in hexane at -78 °C followed by reaction of the resultant kinetic dienolate with one equivalent of methyl methacrylate furnished the bicyclic keto ester **11**, m.p. 59-61 °C (lit.[9] 60-61 °C) *via* the Michael-Michael reaction in a highly regio- and stereoselective manner, which on catalytic hydrogenation generated the keto-ester **12**. For the conversion of the keto group into olefin, reduction-methanesulfonylation-elimination protocol was contemplated. Thus, regioselective reduction of the keto ester **12** with sodium borohydride in methanol at 0 °C furnished the alcohol **13**, m.p. 68-70 °C. Methanesulfonylation reaction   of the   alcohol   **13** with methanesulfonyl   chloride in pyridine in the   presence   of a catalytic amount of DMAP followed by purification over a silica gel column furnished the mesylate **14**, m.p. 67-69 °C, in 60% yield.[10] Treatment of the mesylate **14** with sodium ethoxide in refluxing THF-ethanol furnished the bicyclo[2.2.2]octenecarboxylic acid **8** in moderate yield. In another direction, in an attempt to reductively remove the methanesulfonate group to generate the alcohol **15**, the methanesulfonate **14** was treated with an excess of lithium aluminium hydride (LAH) in refluxing THF, which resulted in the formation of the olefinic alcohol **16** in 80% yield, contrary to the expected alcohol **15**. The structure of the alcohol **16** was derived from its spectral data.
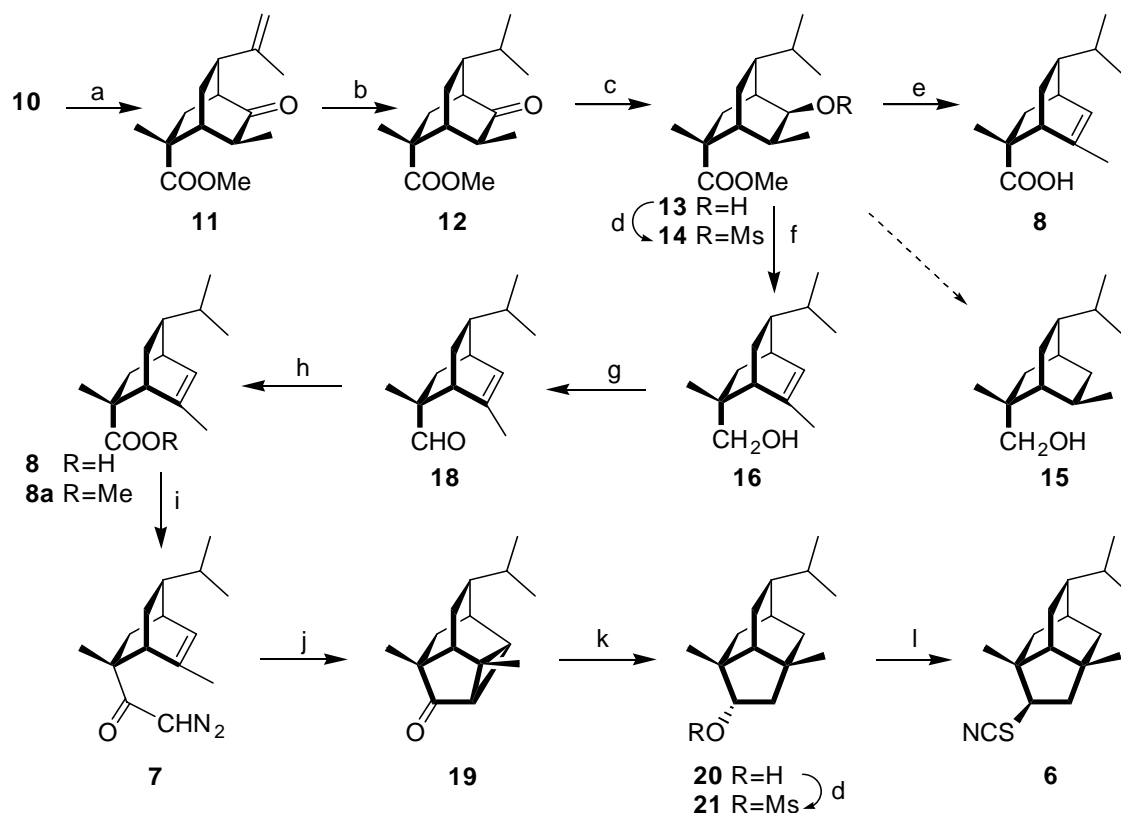

Scheme 2. Reagents**:** (a) LiHMDS, CH_2=C(Me)COOMe; (b) H_2, 10%Pt/C; (c) $NaBH_4$; (d) MsCl, py, DMAP; (e) NaOEt; (f) LAH; (g) PCC, NaOAc; (h) Jones' reagent; (i) $(COCl)_2$; CH_2N_2; (j) $CuSO_4$; (k) Li, liq. NH_3; (l) KSCN.

In the ^{1}H NMR spectrum, presence of a doublet at δ 5.64 (*J* 6.0 Hz) due to the olefinic proton, a typical AB quartet at 3.19 and 3.09 due to the hydroxymethyl protons, two singlets at 1.78 and 1.07 due to the olefinic and tertiary methyl groups, respectively, established the structure of the alcohol **16**, which was confirmed by the ^{13}C NMR spectrum.
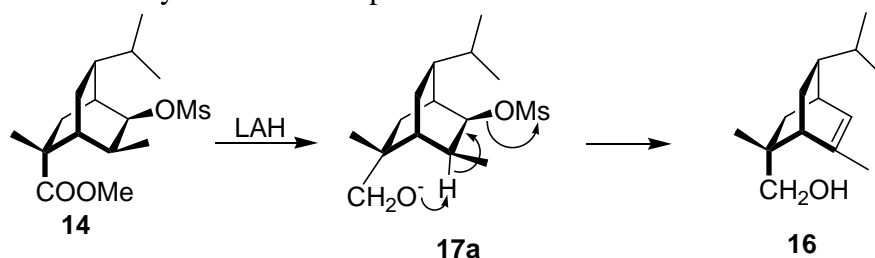

Scheme 3

Formation of the alcohol **16** can be explained as shown in Scheme 3. First reduction of the ester group generates the alkoxide **17a**, which acts as an intramolecular base and brings out the E$_2$-elimination of the mesylate. This was further established by carrying out the reaction in two distinct steps. Thus, reduction of the ester group in the mesylate **14** with LAH at low temperature furnished the hydroxy mesylate **17** in 82% yield. Treatment of the alcohol **17** with one equivalent of *n*-butyllithium in THF furnished the alcohol **16**. It is worth noting that the steric crowding plays an important role in this elimination reaction. For example, elimination of the mesylate was found to be a minor pathway when the isopropyl group in **14** was replaced by the isopropenyl group.

(a) LiAlH$_4$, -70 ^{o}C; (b) *n*-BuLi, rt
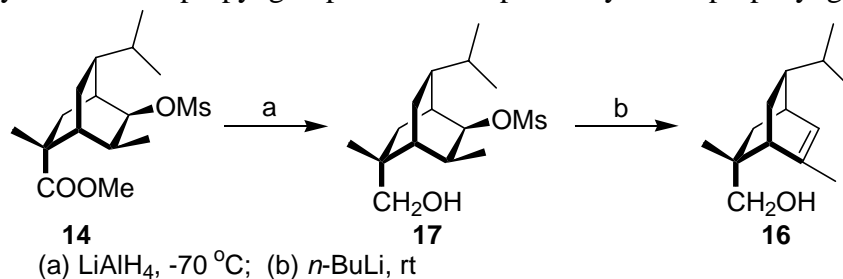
Since the olefinic alcohol **16** was readily available, it was transformed into the acid **8**. Thus, oxidation of the alcohol **16** with PCC and sodium acetate in dichloromethane furnished the aldehyde **18** in 80% yield, which on further oxidation with 1.6 M Jones' reagent in acetone furnished the acid **8** in 98% yield, which was characterized as its methyl ester **8a**. The acid **8** was then transformed into the tetracyclic ketone **19** *via* intramolecular cyclopropanation reaction[11] of the diazo ketone **7**. Thus, reaction of the acid **8** with oxalyl chloride furnished the acid chloride, which upon treatment with an excess of ethereal diazomethane furnished the diazo ketone **7** in 88% yield. Anhydrous copper sulfate catalyzed decomposition of the diazo ketone **7** in refluxing cyclohexane led to the formation of the tetracyclic ketone **19**, m.p. 61-63 °C, *via* stereospecific insertion of the intermediate keto carbenoid, in 60% yield, whose structure was established from its spectral data. It was anticipated that regioselective cyclopropane ring cleavage of the tetracyclic ketone **19** would generate neopupukean-4-one **9**, since it is well established[12] that in the reaction of cyclopropyl

ketones using lithium in liquid ammonia reduction conditions, the cyclopropane bond which has better overlap with the carbonyl π-orbital will be cleaved. Thus, reaction with an excess of lithium in liquid ammonia transformed the tetracyclic ketone **19** directly into the *endo* neopupukean-4-ol **20**, m.p. 57-59 °C, instead of the ketone **9**, in a regio and stereoselective manner. Oxidation of the alcohol **20** with PCC and silica gel in methylene chloride furnished neopupukean-4-one **9**, which exhibited spectral data (IR, ^{1}H and ^{13}C NMR) identical to that of the sample[7e] obtained earlier. Stereoselective reduction of the ketone group in **9** with sodium borohydride in methanol at ice temperature furnished the alcohol **20**, establishing unambiguously the *endo* stereochemistry of the hydroxy group in the alcohol **20**. Reaction of the alcohol **20** with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of DMAP furnished the methanesulfonate **21**, m.p. 52-54 °C, in 84% yield, which on reaction with potassium thiocyanate in acetone in a sealed tube furnished 4-thiocyanatoneopupukeanane **6** in 68% yield $[\alpha]_D^{28}$: -117.6 (c 1.08, CHCl₃), which exhibited optical rotation and spectral data identical to those of the natural product.[3]
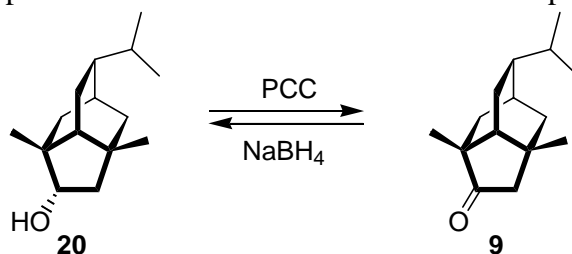
In conclusion, we have developed an enantiospecific approach to the natural enantiomer of the marine sesquiterpene, 4-thiocyanatoneopupukeanane starting from the readily available monoterpene (*R*)-carvone, employing Michael-Michael addition, intramolecular alkoxide mediated E₂-elimination of a mesylate, intramolecular diazo ketone cyclopropanation and regiospecific cyclopropane ring cleavage as key reactions.

Experimental Section

General Procedures. Melting points are recorded using Tempo and Mettler FP1 melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer 781 and Jasco FTIR 410 spectrophotometers. [1]H (300 MHz) and [13]C (75 and 22.5 MHz) NMR spectra were recorded on Jeol JNM λ-300 and FX-90Q spectrometers. The chemical shifts (ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of CDCl₃ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH₂ or CH₃) was determined by the DEPT-135 experiment, and are given in parentheses. Mass spectra were recorded using Jeol JMS-DX 303 GCMS instrument and relative intensities are given in parentheses. Elemental analyses were carried out using Carlo Erba 1106 CHN analyser. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and [α]_D values are given in units of 10⁻¹ deg cm² g⁻¹. Acme's silica gel (100-200 mesh) was used for column chromatography. All small-scale dry reactions were carried out using standard syringe septum technique. Low

temperature reactions were conducted in a bath made of alcohol and liquid nitrogen. Dry THF was obtained by distillation over sodium-benzophenone ketyl. Dry ether and hexane were obtained by distillation over sodium and stored over sodium wire. Dry dichloromethane was prepared by distilling over calcium hydride. Copper sulfate was dried by irradiation in a microwave oven prior to use. Liquid ammonia was obtained in cylinders from Mysore Ammonia Ltd. and distilled over sodium prior to use.

(-)-Methyl (1R,2R,4S,5S,6S,8S)-5-hydroxy-8-isopropyl-2,6-dimethylbicyclo[2.2.2]octane-2-carboxylate (13). To a cold (0 °C) magnetically stirred solution of the keto ester[7e] **12** (1.0 g, 3.94 mmol) in 5 ml of MeOH was added $NaBH_4$ (200 mg, 5.28 mmol) over a period of 5 min. The reaction mixture was stirred for 15 min at the same temperature and then the solvent was evaporated under reduced pressure. It was then diluted with water (5 ml) and extracted with ether (3 x 10 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the product over a silica gel column using ethyl acetate-hexane as eluent furnished the alcohol **13** (857 mg, 85%), which was recrystallized from hexane. m.p.: 68-70 °C. $[\alpha]_D^{26}$: -79.1 (c 1.82, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 3530, 1725. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.95 (1 H, dd, *J* 11.6 and 3.5 Hz, C*H*OH), 3.67 (3 H, s, COOCH$_3$), 2.33 (1 H, dd, *J* 14.1 and 2.4 Hz), 2.09 (1 H, br s), 2.00-1.50 (5 H, m), 1.43 (1 H, dd, *J* 14.1 and 8.7 Hz), 1.30 (3 H, s, *tert*-CH$_3$), 1.21 (1 H, dd, *J* 14.1 and 4.2 Hz), 1.05-0.90 (1 H, m), 1.01 (3 H, d, *J* 6.9 Hz, *sec*-CH$_3$), 0.92 (3 H, d, *J* 6.0 Hz) and 0.86 (3 H, d, *J* 6.3 Hz) [CH(C*H$_3$*)$_2$]. ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 179.5 (s, O-C=O), 71.1 (d, CHOH), 51.8 (q, COOC*H$_3$*), 45.2 (s, C-2), 42.2 (d), 39.9 (d), 36.1 (t, C-3), 34.4 (d), 33.6 (2 C, d), 26.2 (q), 22.6 (q), 21.8 (t, C-7), 21.1 (q), 12.5 (q, *sec*-CH$_3$). Mass: m/z 254 (M$^+$, 27%), 236 (18), 136 (57), 121 (20), 109 (73), 107 (90), 93 (100), 92 (50). Anal.: For C$_{15}$H$_{26}$O$_3$, Calcd.: C, 70.83; H, 10.30. Found: C, 71.20; H, 10.68%.

(-)-Methyl (1R,2R,4S,5S,6S,8S)-8-isopropyl-5-methanesulfonyloxy-2,6-dimethylbicyclo[2.2.2]-octane-2-carboxylate (14). To a magnetically stirred solution of the alcohol **13** (500 mg, 1.97 mmol) in pyridine (3 ml) was added a catalytic amount of DMAP followed by methanesulfonyl chloride (0.16 ml, 2.07 mmol) and the reaction mixture was stirred for 72 h at RT. It was then diluted with 5 ml of water and extracted with CH$_2$Cl$_2$ (3 x 10 ml). The organic layer was washed with 3N aq. HCl, saturated aq. NaHCO$_3$ solution and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10 to 1:5) as eluent furnished the mesylate **14** (390 mg, 60%), which was recrystallized from a mixture of hexane and ether. m.p.: 67-69 °C. $[\alpha]_D^{22}$: -45.7 (c 1.40, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 1720, 1350, 1280, 1210, 1170. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.84 (1 H, dd, *J* 10.5 and 4.0 Hz, C*H*OMs), 3.68 (3 H, s, COOCH$_3$), 2.96 (3 H, s, OSO$_2$CH$_3$), 2.40 (1 H, dd, *J* 14.4 and 2.2 Hz), 2.31 (1 H, br s), 2.05-1.80 (2 H, m), 1.80-1.65 (2 H, m), 1.61 (1 H, br s), 1.50-1.35 (1 H, m), 1.31 (3 H, s, *tert*-CH$_3$), 1.10-1.00 (1 H, m), 1.06 (3 H, d, *J* 7.2 Hz, *sec*-CH$_3$), 0.93 (3 H, d, *J* 6.6 Hz) and 0.88 (3 H, d, *J* 6.3 Hz) [CH(C*H$_3$*)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 178.6 (O-C=O), 81.7 (*C*HOMs), 52.2 (COOC*H$_3$*), 44.9 (*quat*-C), 41.6, 39.5, 37.7, 35.5, 33.5, 33.1, 32.9, 26.1, 22.4, 21.7,

20.9, 13.5 (*sec*-CH$_3$). Mass: m/z 253 (M-SO$_2$CH$_3$, 2%), 237 (62), 177 (25), 136 (100), 107 (47), 93 (95), 92 (65). Anal.: For C$_{16}$H$_{28}$O$_5$S, Calcd.: C, 57.81; H, 8.49. Found: C, 58.04; H, 8.76%.

(+)-(1R,2R,4S,8S)-**8-Isopropyl-2,6-dimethylbicyclo[2.2.2]oct-5-ene-2-methanol** **(16).** To a magnetically stirred solution of the mesylate **14** (150 mg, 0.45 mmol) in THF (2 ml) was added LAH (50 mg, 1.32 mmol) in one portion and the resulting mixture was refluxed for 8 h. It was then cooled, diluted with ether (5 ml) and excess LAH was quenched carefully with a few drops of water. The ethereal layer was separated and aqueous phase was extracted with ether (2 x 10 ml). The combined organic extract was washed with brine and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the alcohol **16** (75 mg, 80%) as oil. $[\alpha]_D^{26}$: 30.6 (c 1.08, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 3360. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.64 (1 H, d, *J* 6.0 Hz, olefinic H), 3.19 (1 H, d, *J* 10.2 Hz) and 3.09 (1 H, d, *J* 10.2 Hz) [C*H$_2$*OH], 2.49 (1 H, m), 2.05 (1 H, br s), 1.97 (1 H, ddd, *J* 12.6, 9.0 and 3.1 Hz), 1.78 (3 H, s, olefinic CH$_3$), 1.51 (1 H, br s, OH), 1.23 (1 H, q, *J* 8.1 Hz), 1.15-0.70 (4 H, m), 1.07 (3 H, s, *tert*-CH$_3$), 0.85 (3 H, d, *J* 6.6 Hz) and 0.78 (3 H, d, *J* 6.6 Hz) [CH(C*H$_3$*)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.0 (*C*=CH), 123.0 (C=*C*H), 72.2 (CH$_2$OH), 45.6, 42.9, 39.4, 37.9 (C-2), 34.0, 33.7, 28.6, 24.1, 21.2, 21.1, 20.4. Mass: 208 (M$^+$, C$_{14}$H$_{24}$O, 16%), 136 (22), 107 (100), 93 (70), 92 (42), 91 (76).

(+)-(1S,2R,4S,8S)-**8-Isopropyl-2,6-dimethylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (8).** To a magnetically stirred solution of the alcohol **16** (75 mg, 0.36 mmol) in CH$_2$Cl$_2$ (1 ml) was added a homogeneous mixture of PCC (155 mg, 0.72 mmol) and NaOAc (155 mg) and the reaction mixture was stirred at RT for 4 h. It was then filtered through a short pad of silica gel and washed with an excess of CH$_2$Cl$_2$. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:10) as eluent furnished the aldehyde **18** (59 mg, 80%). $[\alpha]_D^{27}$: 26.3 (c 1, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 2700, 1720. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.32 (1 H, s, CHO), 5.73 (1 H, d, *J* 6.0 Hz, olefinic H), 2.60 (1 H, br s), 2.23 (1 H, br s), 2.02 (1 H, ddd, *J* 12.6, 8.7 and 3.9 Hz), 1.95 (1 H, dd, *J* 13.2 and 3.9 Hz), 1.74 (3 H, s, olefinic CH$_3$), 1.50-0.85 (4 H, m), 1.12 (3 H, s, *tert*-CH$_3$), 0.86 (3 H, d, *J* 6.6 Hz) and 0.79 (3 H, d, *J* 6.3 Hz) [CH(C*H$_3$*)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.9 (C=O), 141.8 (*C*=CH), 125.0 (C=*C*H), 49.1 (C-2), 46.2, 42.5, 36.8, 33.57, 33.55, 27.7, 21.11, 21.10, 20.7, 20.4. Mass: m/z 206 (M$^+$, C$_{14}$H$_{22}$O, 5%), 136 (10), 107 (100), 93 (26), 91 (40). To a cold (0 °C) magnetically stirred solution of the aldehyde **18** (50 mg, 0.24 mmol) in acetone (1 ml) was added Jones' reagent (0.8 ml, 1.6 M solution, 1.28 mmol) and stirred for 1 h. Isopropyl alcohol (2 ml) was added to consume the excess Jones' reagent. The solvent was then removed under reduced pressure; the residue was taken in 5 ml of water and extracted with CH$_2$Cl$_2$ (3 x 5 ml). The organic phase was washed with brine and dried (Na$_2$SO$_4$). Evaporation of the solvent gave the acid **8** (53 mg, 98%). IR (neat): ν_{max}/cm^{-1} 3100, 1690. ^{1}H NMR (90 MHz, CDCl$_3$): δ 7.40 (1 H, br s, COOH), 5.70 (1 H, d, *J* 6.4 Hz, C=CH), 2.70-2.40 (2 H, m), 2.20 (1 H, dd, *J* 13.0 and 3.5 Hz), 2.10-1.00 (5 H, m), 1.77 (3 H, d, *J* 1.5 Hz, olefinic CH$_3$), 1.35 (3 H, s, *tert*-CH$_3$), 0.87 (3 H, d, *J* 6.3 Hz) and 0.83 (3 H, d, *J* 6.3 Hz) [CH(C*H$_3$*)$_2$]. Mass: 222 (M$^+$, C$_{14}$H$_{22}$O$_2$, 5%), 152 (20), 136 (11), 107 (100), 93 (34). Esterification of a small sample of the acid **8** with ethereal diazomethane gave the ester **8a**. $[\alpha]_D^{26}$: 6.1 (c 1.32, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 1730.

^{1}H NMR (300 MHz, CDCl$_3$): δ 5.68 (1 H, d, J 6.0 Hz, C=CH), 3.62 (3 H, s, COOCH$_3$), 2.49 (2 H, m), 2.23 (1 H, dd, J 13.2 and 4.0 Hz), 1.97 (1 H, ddd, J 12.6, 9.9 and 2.7 Hz), 1.72 (3 H, s, olefinic CH$_3$), 1.30-0.85 (4 H, m), 1.27 (3 H, s, *tert*-CH$_3$), 0.84 (3 H, d, J 6.3 Hz) and 0.78 (3 H, d, J 6.6 Hz) [CH(C*H*$_3$)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 178.8 (O-C=O), 142.7 (*C*=CH), 124.4 (C=*C*H), 51.6 (COO*C*H$_3$), 45.9, 45.3 (C-2), 43.6, 39.6, 33.7, 33.6, 27.2, 25.7, 21.1, 20.4, 20.2. Mass: m/z 236 (M$^+$, C$_{15}$H$_{24}$O$_2$, 9%), 166 (12), 136 (11), 107 (100), 93 (30), 91 (42).

(-)-(1R,2S,3R,4S,6R,8S,9S)-9-Isopropyl-2,6,dimethyltetracyclo[4.4.0.0^{2,4}0^{3,8}]decan-5-one   (19).
To a magnetically stirred solution of the acid **8** (160 mg, 0.72 mmol) in dry benzene (1 ml) was added oxalyl chloride (0.31 ml, 3.6 mmol) and the reaction mixture was stirred for 2 h at RT. Evaporation of benzene and the excess oxalyl chloride under reduced pressure furnished the acid chloride, which was taken in dry ether (2 ml) and added, dropwise, to a cold (0 °C) magnetically stirred solution of diazomethane (10 ml, prepared from 1.0 g of *N*-nitroso-*N*-methylurea and 15 ml of 60% aq. KOH solution). The reaction mixture was slowly warmed up to RT, stirred for 2 h and the excess diazomethane and ether were carefully evaporated on a water bath. Rapid purification by filtration of the crude product through neutral alumina using CH$_2$Cl$_2$ as eluent furnished the diazo ketone **7** (156 mg, 88%) as yellow oil. IR (neat): ν$_{max}$/cm^{-1} 2100, 1630. To a magnetically stirred, refluxing (by keeping two 100 W tungsten lamps near the flask) suspension of anhydrous copper sulfate (680 mg) in 20 ml of dry cyclohexane was added, dropwise, a solution of the diazo ketone **7** (156 mg, 0.63 mmol) in cyclohexane (5 ml) over a period of 15 min and the reaction mixture was refluxed for 4 h. It was then cooled and copper sulfate was filtered off using a sintered funnel. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:10) as eluent furnished the tetracyclic ketone **19** (83 mg, 60%), which was recrystallized from a mixture of hexane and ether. m.p.: 61-63 °C. [α]$_D^{26}$: -17.9 (c 1.40, CHCl$_3$). IR (neat): ν$_{max}$/cm^{-1} 1720. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.25-2.15 (1 H, m), 1.80-1.65 (4 H, m), 1.60-1.40 (3 H, m), 1.30 (3 H, s, *tert*-CH$_3$), 1.25-1.05 (2 H, m), 0.96 (3 H, d, J 6.6 Hz) and 0.94 (3 H, d, J 6.9 Hz) [CH(C*H*$_3$)$_2$], 0.91 (3 H, s, *tert*-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 214.4 (C, C=O), 46.8 (CH), 45.6 (C, C-6), 43.8 (CH$_2$, C-7), 41.3 (CH), 33.7 (CH), 33.2 (CH), 31.7 (CH), 31.6 (C, C-2), 25.7 (CH), 21.3 (CH$_3$) and 21.2 (CH$_3$) [*C*H$_3$-CH-*C*H$_3$], 21.1 (CH$_2$, C-10), 17.8 (CH$_3$), 15.9 (CH$_3$). Mass: m/z 218 (M$^+$, 52%), 190 (M-CO, 43), 175 (35), 147 (62), 135 (26), 119 (39), 107 (100), 105 (70), 95 (40), 93 (45), 91 (50). Anal.: For C$_{15}$H$_{22}$O, Calcd.: C, 82.52; H, 10.16. Found: C, 81.93; H, 10.62%.

(-)-(1S,3R,4S,6R,7R,9S)-9-Isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decan-4-ol   (20).   To a magnetically stirred solution of lithium (10 mg, 1.43 mmol) in 30 ml of freshly distilled (over sodium) ammonia was added, dropwise, a solution of the tetracyclic ketone **19** (65 mg, 0.3 mmol) in THF (1 ml). The reaction mixture was stirred for 30 min and then quenched with ammonium chloride. Ammonia was evaporated; the reaction mixture was diluted with 5 ml of water and extracted with ether (3 x 5 ml). The ether extract was washed with brine and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished neopupukean-4-ol **20** (55 mg, 83%), which was recrystallized from a mixture of hexane and ether.[7e] m.p.: 57-59 °C. [α]$_D^{26}$: -66.1 (c 1.12, CHCl$_3$). IR (neat):

ν_{max}/cm^{-1} 3360. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.62 (1 H, dd, J 9.9 and 6.6 Hz, H-4), 2.03 (1 H, dd, J 13.8 and 9.9 Hz), 1.91 (1 H, dd, J 13.8 and 3.5 Hz), 1.74 (1 H, ddd, J 14.4, 9.9 and 4.5 Hz), 1.66 (1 H, br s), 1.58 (1 H, br s, OH), 1.40 (1 H, d, J 15.0 Hz), 1.35-0.80 (7 H, m), 1.01 (3 H, s) and 0.96 (3 H, s) [2 x $tert$-CH$_3$], 0.89 (3 H, d, J 6.6 Hz) and 0.83 (3 H, d, J 6.6 Hz) [CH(CH_3)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 78.8 (CH, CHOH), 50.4 (CH$_2$), 46.7 (CH), 44.6 (CH), 42.9 (C, C-3), 39.6 (CH$_2$), 38.2 (C, C-6), 34.7 (CH$_2$), 31.9 (CH), 27.5 (CH), 26.8 (CH$_3$), 24.5 (CH$_3$), 23.0 (CH$_2$, C-8), 21.2 (CH$_3$), 21.0 (CH$_3$). Mass: m/z 222 (M$^+$, C$_{15}$H$_{26}$O, 1%), 205 (M-OH, 20), 204 (M-H$_2$O, 22), 161 (35), 136 (44), 119 (32), 107 (100), 105 (50), 93 (56).

(-)-(1S,3R,4S,6R,7R,9S)-9-Isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]dec-4-yl methanesulfonate (21). To a magnetically stirred solution of the alcohol **20** (44 mg, 0.19 mmol) in 1 ml of pyridine were added methanesulfonyl chloride (0.02 ml, 0.26 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 10 h at RT. It was then diluted with 5 ml of water and extracted with CH$_2$Cl$_2$ (3 x 5 ml). The organic extract was washed successively with 3N aq. HCl, saturated aq. NaHCO$_3$ solution and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the mesylate **21** (50 mg, 84%), which was recrystallized from a mixture of hexane and ether. m.p.: 52-54 °C. [α]$_D^{22}$: -21.0 (c 1.49, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 1350, 1170. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.44 (1 H, dd, J 9.9 and 6.3 Hz, H-4), 3.00 (3 H, s, OSO$_2$CH$_3$), 2.17 (1 H, dd, J 14.4 and 9.9 Hz), 1.95 (1 H, dd, J 13.8 and 3.6 Hz), 1.77 (1 H, ddd, J 14.4, 9.9 and 4.5 Hz), 1.68 (1 H, br s), 1.61 (1 H, dd, J 14.4 and 6.3 Hz), 1.45 (1 H, d, J 14.1 Hz), 1.40-1.10 (4 H, m), 1.10 (3 H, s) and 0.99 (3 H, s) [2 x $tert$-CH$_3$], 0.95-0.85 (2 H, m), 0.89 (3 H, d, J 6.3 Hz) and 0.83 (3 H, d, J 6.3 Hz) [CH(CH_3)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$, DEPT): δ 87.9 (CH, CHOMs), 47.8 (CH$_2$, C-5), 45.6 (CH), 44.0 (CH), 43.0 (C, C-3), 39.2 (CH$_2$), 38.6 (C, C-6), 38.1 (CH$_3$, OSO$_2$CH$_3$), 35.6 (CH$_2$), 31.9 (CH), 27.1 (CH), 26.5 (CH$_3$), 24.3 (CH$_3$), 22.6 (CH$_2$, C-8), 21.1 (CH$_3$), 21.0 (CH$_3$). Mass: m/z 205 (M-OMs, 26%), 204 (100), 161 (62), 119 (31), 107 (40), 105 (37), 93 (36). Anal.: For C$_{16}$H$_{28}$O$_3$S, Calcd.: C, 63.96; H, 9.39. Found: C, 64.19; H, 9.76%.

(-)-(1S,3R,4R,6R,7R,9S)-4-Thiocyanatoneopupukeanane (6). A solution of the mesylate **21** (25 mg, 0.08 mmol) and potassium thiocyanate (50 mg, 0.51 mmol) in acetone (1 ml) was placed in a Carius tube and heated to 80 °C for 5 days. The reaction mixture was then cooled, diluted with CH$_2$Cl$_2$ (10 ml), washed with water and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished 4-thiocyanatoneopupukeanane **6** (6 mg, 27%) as oil. The synthetic sample exhibited spectral data identical to that of the natural product reported[3] by Scheuer and Higa. [α]$_D^{28}$: -117.6 (c 1.08, CHCl$_3$). IR (neat): ν_{max}/cm^{-1} 2160. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.47 (1 H, dd, J 8.4 and 3.3 Hz, H-4), 2.24 (1 H, dd, J 15.3 and 8.1 Hz), 1.76 (1 H, ddd, J 14.4, 10.2 and 4.5 Hz), 1.70-1.60 (1 H, m), 1.68 (1 H, dd, J 15.3 and 3.3 Hz), 1.50-1.10 (7 H, m), 1.21 (3 H, s) and 1.05 (3 H, s) [2 x $tert$-CH$_3$], 0.90-0.80 (1 H, m), 0.90 (3 H, d, J 6.6 Hz) and 0.81 (3 H, d, J 6.6 Hz) [CH(CH_3)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ 113.8 (C, SCN), 60.1 (CH, CHSCN), 50.5 (CH$_2$, C-5), 45.7 (CH$_2$), 45.1 (CH), 44.8 (C, C-3), 43.1 (CH), 39.1 (C, C-6), 37.8 (CH$_2$), 31.8 (CH), 27.8 (CH), 26.7 (CH$_3$), 24.0 (CH$_3$), 22.4 (CH$_2$, C-8), 21.0 (2 C, CH$_3$). Mass: m/z 205 (M-SCN, C$_{15}$H$_{25}$, 100%), 149 (20), 107

(32), 93 (23). Further elution of the column with ethyl acetate-hexane (1:10) furnished the unreacted starting mesylate **21** (15 mg, 60%).

Acknowledgements

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