Enantiospecific Total Synthesis of (−)-4-Thiocyanatoneopupukeanane†

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Received March 12, 2001

Enantiospecific synthesis of the natural enantiomer of the marine sesquiterpene (−)-4-thiocyanatoneopupukeanane (**6**) is described. The bicyclo[2.2.2]octanecarboxylate **14**, obtained from (*R*)-carvone via Michael−Michael reaction, was transformed into neopupukeananedione **12** by employing rhodium acetate catalyzed intramolecular C−H insertion of the diazo ketones **16** or **19** as the key reaction. Regioselective deoxygenation of the C-2 ketone transformed the dione **12** into neopupukean-4-one **10**. Alternately, the keto ester **18** was also transformed into neopupukean-4-one **10** via regioselective deoxygenation of the ketone in **18** followed by intramolecular rhodium carbenoid C−H insertion of the diazo ketone **31**. Finally, neopupukean-4-one **10** was transformed into (−)-4-thiocyanatoneopupukeanane **6** via the alcohol **32** and the mesylate **33**.

Among the natural products, terpenoids occupy a special position on account of their widespread occurrence and the bewildering array of carbocyclic skeleta that they embody.[1] Because of the phenomenal structural diversity, this class of natural products holds special appeal to synthetic chemists and provides a fertile ground for developing and testing new synthetic strategies.[2] In a 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. On the basis of the observation that the nudibranch *Phyllidia varicosa* Lamarck secretes a toxic substance lethal to fish and crustaceans, Scheuer and co-workers 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[3] of two isotwistane (**1**) based sesquiterpenes, 9- and 2-isocyanopupukeananes **2** and **3**. Subsequently, during their biosynthetic experiments directed toward discovering the origin of the isocyano group in marine sponges, Scheuer and co-workers[4] isolated a new sesquiterpene **4** from the sponge *Ciocalypta* sp. containing a new carbon framework neopupukeanane. Later the research groups of Scheuer, Higa, and Faulkner reported[5] the isolation of two thiocyanate containing sesquiterpenes, 2- and 4-thiocyanatoneopupukeananes **5** and **6**, from the sponge *Phycopsis terpnis* (from Okinawa), *Axinyssa aplysinoides* from Palau, and an unidentified species from Pohnpei. Biosynthetically, origin of pupukeananes and neopupukeananes can be explained by a common pathway via cyclization and rearrangement of cadinanes.[4] 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[6,7] was reported on the synthesis of pupukeananes, there was no report on the synthesis of neopupukeananes prior to 1998.[8,9] In continuation of our interest in the enantiospecific synthesis of sesquiterpenes,[10] we embarked on the enantiospecific total synthesis of 4-thiocyanatoneo-

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† Chiral Synthons from Carvone. Part 48. For Part 47, see ref 6m.

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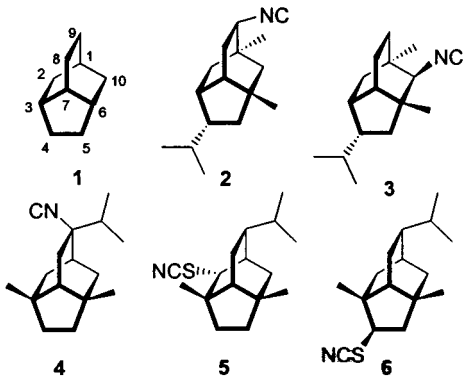
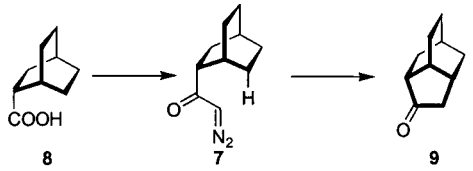
10.1021/jo0102765 CCC: $20.00
Published on Web 05/22/2001

pupukeanane **6** starting from (*R*)-carvone employing an approach based on a regiospecific rhodium carbenoid C−H insertion reaction.[8]



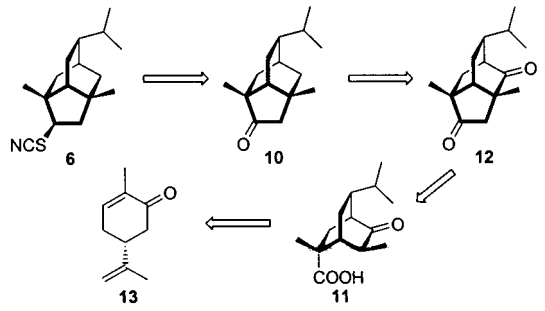
It was envisaged that the rhodium acetate catalyzed reaction of the diazo ketone **7**, derived from bicyclo[2.2.2]-octanecarboxylic acid **8**, would generate the isotwistanone **9** (eq 1) in a regioselective manner via preferential



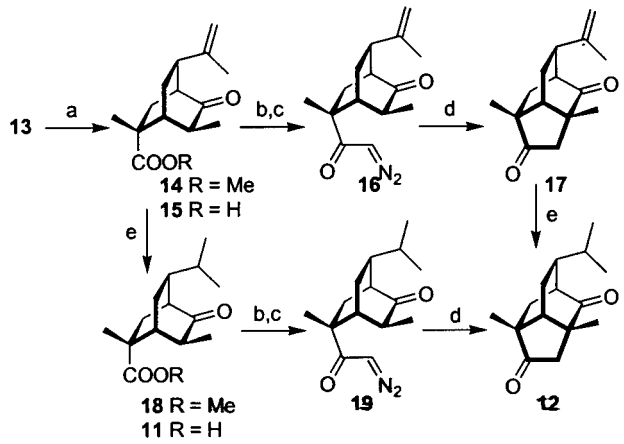
(1)

formation of a five-membered ring by insertion of the intermediate rhodium carbenoid into the only available γ C−H bond,[11] as the other four γ C−H bonds are not approachable as a result of steric reasons. On the basis of this concept, enantiospecific synthesis of 4-thiocyanatoneopupukeanane (**6**) was conceived via neopupukean-4-one **10**, Scheme 1. It was anticipated that rhodium carbenoid C−H insertion of the diazo ketone derived from the acid **11** would generate neopupukeananedione **12**, which could be transformed into neopupukean-4-one **10** via regioselective deoxygenation. Michael−Michael reaction[12] of (*R*)-carvone (**13**) with methyl methacrylate could

Scheme 1



Scheme 2[a]



[a] Reagents: (a) LiHMDS, methyl methacrylate; (b) NaOH; (c) (i) $(COCl)_2$, (ii) CH_2N_2; (d) $Rh_2(OAc)_4$; (e) H_2, 10% Pt/C.

be exploited for the generation of the bicyclo[2.2.2]-octanecarboxylic acid **11**.

Synthesis of the neopupukeananedione **12** is depicted in Scheme 2. Thus, reaction of (*R*)-carvone **13** with lithium hexamethyldisilazide (LiHMDS) in hexane at −78 °C followed by reaction of the resultant kinetic dienolate with 1 equiv of methyl methacrylate furnished the bicyclic keto ester **14**, mp 59−61 °C (lit.[12a] 60−61 °C) via the Michael−Michael reaction in 60% yield in a highly regio- and stereoselective manner. Refluxing a solution of the keto ester **14** and sodium hydroxide in 1:1 methanol and water led to the hydrolysis of the ester moiety to furnish the keto acid **15**, mp 119−120 °C, in 92% yield. It is worth mentioning that in the keto ester **14** and the keto acid **15**, the stereochemistry of the secondary methyl group at the C-6 carbon (α to the keto group) is *anti* with respect to the acid group, which was ideally suited for the projected C−H insertion reaction for the generation of the isotwistane system. Reaction of the acid **15** with an excess of oxalyl chloride in benzene at room temperature followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane at 0 °C furnished the diazo ketone **16** (2100, 1710, and 1620 cm^{-1}). Treatment of the diazo ketone **16** with a catalytic amount of rhodium acetate in refluxing dichloromethane furnished, as anticipated, the isotwistane dione **17**, mp 111−113 °C, containing the complete carbon framework of neopupukeananes, via regiospecific C−H insertion of the intermediate rhodium carbenoid. The structure of 9-epineopupukean-13-ene-2,5-dione (or neopupukean-13-ene-4,10-dione) **17** was established from its spectral data. Presence of the molecular ion at *m*/*z* 232 ($C_{15}H_{20}O_2$) in the mass spectrum and the presence of

(9) To the best of our knowledge, there is no report on the synthesis of neopupukeananes prior to the publication of our preliminary communication.[8] For the synthesis of (±)-9-isocyanoneopupukeanane, see: (a) Ho, T.-L.; Jana, G. H. *J. Org. Chem.* **1999**, *64*, 8965. For the synthesis of (±)-2-thiocyanatoneopupukeanane, see: (b) Uyehara, T.; Onda, K.; Nozaki, N.; Karikomi, M.; Ueno, M.; Sato, T. *Tetrahedron Lett.*, **2001**, *42*, 699. For the enantiospecific synthesis of 2-thiocyanatoneopupukeanane, see: (c) Srikrishna, A.; Gharpure, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3191. For the enantiospecific synthesis (−)-4-thiocyanatoneopupukeanane, see: (d) Srikrishna, A.; Gharpure, S. J. *Tetrahedron Lett.* **1999**, *40*, 1035.

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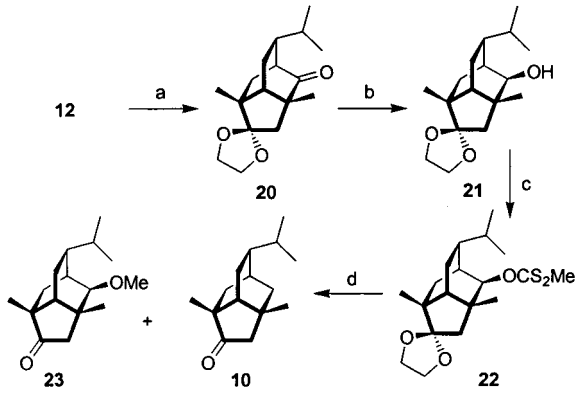
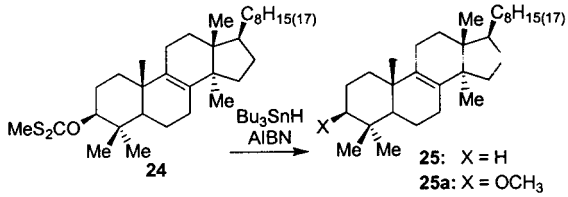
Scheme 3[a]



[a] Reagents: (a) $(CH_2OH)_2$; (b) $LiAlH_4$; (c) NaH; CS_2; MeI; (d) (i) $^nBu_3SnH$, AIBN, (ii) H_3O^+.

carbonyl absorption bands at 1740 and 1720 cm^{-1} due to two ketone groups (a cyclopentanone and a cyclohexanone, respectively) in the IR spectrum indicated the formation of the dione **17**. In the ^1H NMR spectrum, the presence of three singlets at δ 4.83 and 4.79 (olefinic) and 1.76 (methyl) due to the isopropenyl group, two singlets at 1.25 and 1.24 due to two tertiary methyl groups, two doublets at 2.52 and 2.10 (J = 18.9 Hz) due to the H-4 methylene protons ($CH_2C{=}O$), and a multiplet at 2.55−2.50 ppm due to the two bridgehead protons H-1 and H-9 established the structure of the dione **17**. The 15-lines ^{13}C NMR spectrum with characteristic resonances at δ 218.6 and 217.6 due to two carbonyl carbons, a quaternary carbon at 146.8, and a methylene carbon at 110.4 due to the olefinic carbons of the isopropenyl group, two quaternary carbons at 50.9 (C-3) and 48.5 (C-6), three methine signals at 49.0 (C-1), 46.3 and 45.1 (C-7 and 9), three methylene signals at 48.1 (C-4), 35.2 (C-10) and 20.7 (C-8), and three methyl signals at 22.0, 19.5 and 18.1 ppm confirmed the structure of the dione **17**. Hydrogenation of the dione **17** in ethanol with 10% platinum on carbon as the catalyst at 1 atm pressure of hydrogen furnished 9-epineopupukeanane-2,5-dione **12**, mp 131−133 °C, quantitatively. Alternatively, hydrogenation of the keto ester **14** with 10% platinum on carbon as the catalyst in ethanol furnished the keto ester **18**, mp 71−73 °C (lit.[12a] 71.5−73 °C), quantitatively, which on base-catalyzed hydrolysis furnished the keto acid **11**. Treatment of the keto acid **11** with oxalyl chloride in benzene at room temperature, followed by reaction of the resultant acid chloride with an excess of ethereal diazomethane solution, furnished the diazo ketone **19**. Reaction of the diazo ketone **19** in refluxing dichloromethane in the presence of a catalytic amount of rhodium acetate for 4 h also furnished the dione **12** in 63% yield (from the acid **11**).

Next, attention was turned toward the conversion of the dione **12** into neopupukean-4-one **10**, Scheme 3. Since the C-2 ketone is more hindered and less reactive than the C-5 ketone in the dione **12**, for the selective deoxygenation of the C-2 ketone, the C-5 ketone needs to be masked. Thus, refluxing a benzene solution of the dione **12** and ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) using a Dean−Stark water trap furnished the keto ketal **20**, mp 107−108 °C, in 84% yield, in a highly regioselective manner. Since the Wolff−Kishner reduction as well as the Huang−Minlon modified version were unsuccessful, it was decided to use Barton's protocol[13] for deoxygenation of the C-2 ketone. Thus, reduction of the ketone moiety in the keto ketal **20** with LAH in THF at 0 °C followed by basic workup furnished the alcohol **21** in 94% yield. Treatment of the alcohol **21** with sodium hydride in the presence of a catalytic amount of imidazole and reaction of the resultant alkoxide with dry carbon disulfide followed by methyl iodide furnished the xanthate **22** in 80% yield. Reaction of a 0.027 M solution of the xanthate **22** in benzene with tributyltin hydride and a catalytic amount of AIBN at reflux temperature, followed by hydrolysis of the product mixture with 3 N aqueous hydrochloric acid in THF, furnished an ∼3:2 mixture of neopupukean-4-one **10**, mp 66−68 °C, and 10-methoxyneopupukean-4-one **23**, mp 127−128 °C, in 91% yield, which were separated by silica gel column chromatography. The structures of the ketones **10** and **23** were delineated from their spectral data. The structure of the byproduct **23** was confirmed by comparison with an authentic sample obtained by methylation of the hydroxy group in the ketal **21** with sodium hydride and methyl iodide in a mixture of THF and DMF in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) followed by hydrolysis of the ketal moiety. Even though it is not common to obtain the methoxy derivative as a byproduct in Barton's deoxygenation of xanthates using tributyltin hydride and AIBN, in 1997 Cornforth and Hanson reported[14] formation of the methyl ether **25a** as the byproduct in the reaction of the xanthate **24** with an excess of tributyltin hydride and AIBN (eq 2). To suppress the formation of the methyl ether **23**, a few variations in experimental conditions were explored. Thus, increasing the dilution to 0.008 M for the deoxygenation of the xanthate **22** in refluxing benzene, followed by hydrolysis, furnished an ∼4:1 mixture of ketones **10** and **23**. Changing the solvent to toluene, thereby increasing the temperature of the deoxygenation reaction, followed by hydrolysis furnished exclusively neopupukean-4-one **10** in 73% yield.



(2)

After successfully accomplishing the synthesis of neopupukean-4-one **10**, before proceeding further, an alternate route was also considered for the synthesis of neopupukean-4-one **10**, Scheme 4. Regioselective reduction of the keto ester **18** with sodium borohydride in methanol at 0 °C furnished the alcohol **26**, mp 68−70 °C. Treatment of the alcohol **26** with sodium hydride in the presence of a catalytic amount of imidazole and reaction of the resultant alkoxide with dry carbon disulfide followed by methyl iodide furnished the xanthate **27** in 80% yield. Treatment of the xanthate **27** with tributyltin hydride and a catalytic amount of AIBN in

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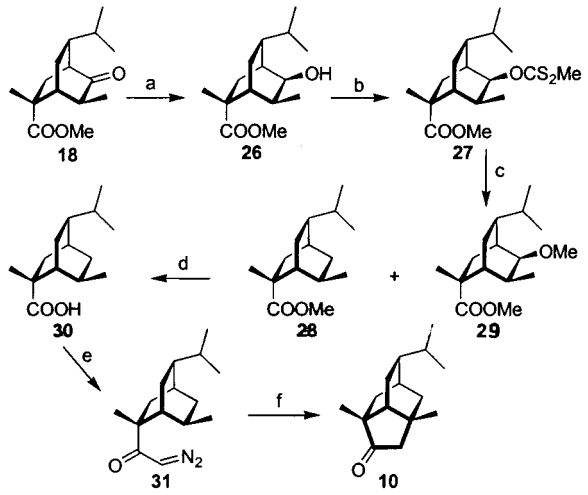
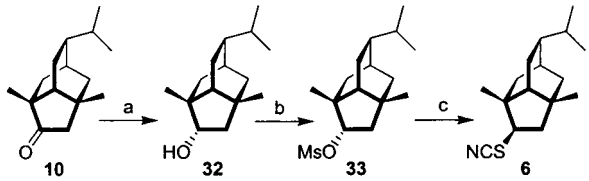
Scheme 4[a]



[a] Reagents: (a) $NaBH_4$; (b) NaH; CS_2; MeI; (c) $^nBu_3SnH$, AIBN; (d) KOH; (e) (i) $(COCl)_2$, (ii) CH_2N_2; (f) $Rh_2(OAc)_4$.

refluxing benzene furnished an ~2:1 mixture of the deoxygenated ester **28** and the methoxy ester **29**, in 90% yield, which was separated by column chromatography on silica gel. As in the earlier case, formation of the methoxy ester **29** could be suppressed by increasing the temperature of the reaction. Refluxing the ester **28** in 2 M methanolic potassium hydroxide furnished the acid **30** in 91% yield. Treatment of the acid **30** with oxalyl chloride followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane solution furnished the diazo ketone **31** in 54% yield. Refluxing a dichloromethane solution of the diazo ketone **31** and a catalytic amount of rhodium acetate furnished neopupukean-4-one **10** in 75% yield.

Stereoselective reduction of the ketone group in **10** with sodium borohydride in methanol at ice temperature furnished the alcohol **32**, which on treatment with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of DMAP cleanly furnished the methanesulfonate **33**, mp 52−54 °C, in 84% yield. Finally, reaction of the methanesulfonate **33** with potassium thiocyanate in acetone (sealed tube) at 80 °C for 5 days furnished 4-thiocyanatoneopupukeanane **6** in 68% yield (40% conversion), $[\alpha]^{28}_D$ −117.6 (*c* 1.08, $CHCl_3$), which exhibited optical rotation and ^1H and ^{13}C NMR spectral data identical[5a] to that of the natural product establishing its absolute configuration as 1*S*,3*R*,4*R*,6*R*,-7*R*,9*S*.



Reagents: (a) $NaBH_4$; (b) MsCl, py, DMAP; (c) KSCN

In conclusion, a short and efficient synthesis of the natural enantiomer of the marine sesquiterpene 4-thiocyanatoneopupukeanane (**6**) has been accomplished starting from the readily available monoterpene (*R*)-carvone. A stereoselective Michael−Michael reaction and a regiospecific intramolecular rhodium carbenoid C−H insertion of a diazo ketone were exploited for the rapid construction of the neopupukeanane carbon framework.

Experimental Section

Melting points are not corrected. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by either recording the off-resonance spectra or the DEPT-135 experiment and are given in parentheses. Values for $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. Silica gel (100−200 mesh) was used for column chromatography. All solvent extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotavapor. All IR spectra were recorded as thin films, and NMR spectra were recorded either in $CDCl_3$ or in a 1:1 mixture of $CDCl_3$ and CCl_4.

(−)-Methyl (1*R*,2*R*,4*S*,6*S*,8*R*)-8-Isopropenyl-2,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (14). To a cold (−78 °C), magnetically stirred solution of hexamethyldisilazane (4.22 mL, 20 mmol) in dry hexane (36 mL) was slowly added *n*-BuLi (12.5 mL of a 1.6 M solution in hexane, 20 mmol), and the mixture was stirred for 15 min. To the LiHMDS thus formed was added, dropwise, a solution of (*R*)-carvone **13** (3.0 g, 20 mmol) in dry hexane (30 mL), and the reaction mixture stirred for 45 min at the same temperature. The enolate was treated with methyl methacrylate (2.14 mL, 20 mmol) and stirred for 3 h at room temperature. The reaction mixture was then filtered through a small silica gel column. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the bicyclic adduct **14** (3.0 g, 60%) as a white solid, which was recrystallized from hexanes. Mp: 59−61 °C (lit.[12a] 60−61.5 °C). $[\alpha]^{22}_D$: −43.5 (*c* 3.77, MeOH) [lit.[12a] $[\alpha]^{25}_D$ −42.6 (*c* 1.00, MeOH)]. IR: ν_{max} 1720, 1645, 895. ^1H NMR (300 MHz): δ 4.75 (1 H, s), 4.72 (1 H, s), 3.71 (3 H, s), 2.70 (1 H, dd, J = 14.5 and 2.5 Hz), 2.60−2.40 (2 H, m), 2.25−2.00 (3 H, m), 1.71 (3 H, s), 1.70−1.55 (2 H, m), 1.46 (3 H, s), 1.10 (3 H, d, J = 6.9 Hz). ^{13}C NMR (22.5 MHz): δ 216.7 (s), 177.5 (s), 146.7 (s), 109.7 (t), 52.0 (q), 47.2 (d), 44.5 (d), 44.2 (s), 42.1 (d), 41.5 (d), 33.9 (t), 26.4 (q), 21.7 (2 C, q and t), 12.3 (q). HRMS: *m*/*z* for $C_{15}H_{22}O_3$ calcd 250.1569, found 250.1556. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 9.00.

(−)-(1*R*,2*R*,4*S*,6*S*,8*R*)-8-Isopropenyl-2,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic Acid (15). To a solution of the keto ester **14** (1.0 g, 4 mmol) in 5 mL of methanol was added 10% aqueous NaOH solution (5 mL). The reaction mixture was refluxed for 8 h. It was then cooled to room temperature and washed with CH_2Cl_2 (10 mL). The aqueous layer was acidified with 3 N aqueous HCl and extracted with CH_2Cl_2. Evaporation of the solvent furnished the acid **15** (870 mg, 92%) as a sticky solid, which was recrystallized from a mixture of hexane and CH_2Cl_2. Mp: 119−120 °C. $[\alpha]^{26}_D$: −47.7 (*c* 1.30, $CHCl_3$). IR: ν_{max} 3140, 3080, 1720, 1700, 1645, 890. ^1H NMR (300 MHz): δ 4.74 (1 H, s), 4.72 (1 H, s), 2.68 (1 H, dd, J = 14.7 and 2.4 Hz), 2.55−2.45 (2 H, m), 2.30−2.10 (3 H, m), 1.71 (3 H, s), 1.75−1.50 (2 H, m), 1.59 (1 H, dd, J = 14.7 and 3.3 Hz), 1.52 (3 H, s), 1.12 (3 H, d, J = 6.9 Hz). ^{13}C NMR (22.5 MHz): δ 217.7 (s), 183.4 (s), 146.7 (s), 110.0 (t), 47.3 (d), 44.7 (d), 44.1 (s), 42.1 (d), 41.5 (d), 33.7 (t), 26.5 (q), 21.7 (2 C, q and t), 12.5 (q). HRMS: *m*/*z* for $C_{14}H_{20}O_3$ calcd 236.1412, found 236.1402. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.17; H, 8.83.

(−)-(1*S*,3*R*,6*R*,7*S*,9*R*)-9-Isopropenyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decane-2,5-dione (17). To a magnetically stirred solution of the acid **15** (500 mg, 2.12 mmol) in dry benzene (3 mL) was added oxalyl chloride (0.93 mL, 10.6 mmol), and the reaction mixture was stirred for 2 h at room temperature. Evaporation of benzene and the excess oxalyl chloride under reduced pressure furnished the acid chloride, which was taken in dry ether (5 mL) and added dropwise to a cold (0 °C), magnetically stirred solution of diazomethane (25 mL, prepared from 3 g of *N*-nitroso-*N*-methylurea and 30 mL of 60% aqueous KOH solution). The reaction mixture was slowly warmed to room temperature and 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 a neutral alumina column using CH_2Cl_2 as eluent furnished the diazo ketone **16** (495 mg, 90%) as yellow oil. IR: ν_{max}/cm^{-1} 2100, 1710, 1620, 890. To a magnetically stirred, refluxing solution of rhodium acetate (4 mg) in dry CH_2Cl_2 (30 mL) was added, dropwise, a solution of the diazo ketone **16** (495 mg, 1.91 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was refluxed for 4 h. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the dione **17** (392 mg, 89%) as a white solid, which was recrystallized from a mixture of ethyl acetate and hexane. Mp: 111−113 °C. $[\alpha]^{26}_D$: −45.5 (*c* 1.32, $CHCl_3$). IR: ν_{max}/cm^{-1} 1740, 1710, 1640, 890. ^{1}H NMR (300 MHz): δ 4.83 (1 H, s) and 4.79 (1 H, s) [C=CH_2], 2.55−2.50 (2 H, m, H-1 and 9), 2.52 (1 H, d, J = 18.9 Hz, H-4a), 2.21 (1 H, ddd, J = 14.4, 10.5 and 3.3 Hz), 2.10 (1 H, d, J = 18.9 Hz, H-4b), 1.94 (1 H, ddd, J = 14.7, 6.3 and 2.7 Hz), 1.90 (1 H, br s), 1.80 (1 H, dd, J = 14.7 and 4.2 Hz), 1.76 (3 H, s, olefinic CH_3), 1.59 (1 H, d, J = 14.7 Hz), 1.25 (3 H, s) and 1.24 (3 H, s) [2 x *tert*.CH_3]. ^{13}C NMR (75 MHz): δ 218.6 (C) and 217.6 (C) [C-2 and 5], 146.8 (C, *C*=CH_2), 110.4 (CH_2, C=*C*H_2), 50.9 (C, C-3), 49.0 (CH, C-1), 48.5 (C, C-6), 48.1 (CH_2, C-4), 46.3 (CH) and 45.1 (CH) [C-7 and 9], 35.2 (CH_2, C-10), 22.0 (CH_3), 20.7 (CH_2, C-8), 19.5 (CH_3), 18.1 (CH_3). HRMS: *m*/*z* for $C_{15}H_{20}O_2$ calcd 232.1463, found 232.1465. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.51; H, 8.79.

(−)-(1*S*,3*R*,6*R*,7*S*,9*S*)-9-Isopropyl-3,6-dimethyltricyclo-[4.3.1.0^{3,7}]decane-2,5-dione (12). To 10% Pt−C (25 mg) was added a solution of the tricyclic dione **17** (500 mg, 2.16 mmol) in dry ethanol (5 mL). The reaction mixture was stirred for 4 h at room temperature in an atmosphere of hydrogen created by evacuative displacement of air by hydrogen (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the tricyclic dione **12** (484 mg, 96%) as a white solid, which was recrystallized from a mixture of ethyl acetate and hexane. Mp: 131−133 °C. $[\alpha]^{26}_D$: −48.9 (*c* 1.48, $CHCl_3$). IR: ν_{max}/cm^{-1} 1740, 1720. ^{1}H NMR (300 MHz): δ 2.48 (1 H, br s), 2.47 (1 H, d, J = 19.0 Hz), 2.20−2.05 (1 H, m), 2.09 (1 H, d, J = 19.0 Hz), 1.86 (1 H, t, J = 3.0 Hz), 1.78 (1 H, dd, J = 14.7 and 4.5 Hz), 1.75−1.60 (1 H, m), 1.55−1.45 (1 H, m), 1.47 (1 H, d, J = 15.0 Hz), 1.26 (3 H, s), 1.20 (3 H, s), 1.20−1.15 (1 H, m), 0.94 (3 H, d, J = 6.3 Hz), 0.91 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 217.8 (C), 216.9 (C), 50.7 (C), 49.5 (CH), 48.3 (C), 47.7 (CH_2), 47.0 (CH), 45.1 (CH), 34.7 (CH_2), 34.2 (CH), 21.6 (CH_2), 20.8 (CH_3), 20.0 (CH_3), 19.6 (CH_3), 18.2 (CH_3). HRMS: *m*/*z* for $C_{15}H_{22}O_2$ calcd 234.1620, found 234.1615. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.98; H, 9.64.

(−)-Methyl (1*R*,2*R*,4*S*,6*S*,8*S*)-8-Isopropyl-2,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (18). To 10% Pt−C (50 mg) was added a solution of the keto ester **14** (1.0 g, 4 mmol) in dry ethanol (5 mL). The reaction mixture was stirred for 4 h at room temperature in an atmosphere of hydrogen (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the keto ester **18** (986 mg, 96%) as a white solid, which was recrystallized from hexane. Mp: 71−73 °C (lit.[12a] 71.5−73 °C). $[\alpha]^{23}_D$: −46.9 (*c* 1.94, MeOH) [lit.[12a] $[\alpha]^{25}_D$: −41.1 (*c* 1.10, MeOH)]. IR: ν_{max}/cm^{-1} 1720. ^{1}H NMR (300 MHz): δ 3.67 (3 H, s), 2.64 (1 H, dd, J = 14.7 and 2.7 Hz), 2.41 (1 H, br s), 2.14 (1 H, br s), 2.10−1.95 (2 H, m), 1.55−1.30 (3 H, m), 1.37 (3 H, s), 1.30−1.00 (1 H, m), 1.05 (3 H, d, J = 7.5 Hz), 0.86 (3 H, d, J = 6.6 Hz), 0.85 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 218.1 (C), 178.2 (C), 52.2 (CH_3), 46.3 (CH), 44.9 (CH), 44.4 (C), 43.9 (CH), 42.1 (CH), 33.7 (CH_2), 33.6 (CH), 26.7 (CH_3), 22.9 (CH_2), 20.5 (2 C, CH_3) 12.2 (CH_3). HRMS: *m*/*z* for $C_{15}H_{24}O_3$ calcd 252.1725, found 252.1735. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.82.

(−)-(1*S*,3*R*,6*R*,7*S*,9*S*)-9-Isopropyl-3,6-dimethyltricyclo-[4.3.1.0^{3,7}]decane-2,5-dione (12). Hydrolysis of the keto ester **18** (1.0 g, 3.96 mmol) with 5% NaOH in 1:1 MeOH−water (10 mL) furnished the keto acid **11** (878 mg, 93%) as a viscous oil. $[\alpha]^{21}_D$: −49.9 (*c* 4.10, $CHCl_3$). IR: ν_{max}/cm^{-1} 3000, 1720, 1700. ^{1}H NMR (300 MHz): δ 2.66 (1 H, dd, J = 14.4 and 2.4 Hz), 2.45 (1 H, br s), 2.20−2.00 (3 H, m), 1.55−1.30 (3 H, m), 1.47 (3 H, s), 1.20−1.05 (1 H, m), 1.11 (3 H, d, J = 6.9 Hz), 0.97 (1 H, dd, J = 6.6 and 2.1 Hz), 0.89 (6 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 217.3 (C), 184.2 (C), 46.3 (CH), 45.1 (CH), 44.4 (C), 44.1 (CH), 42.1 (CH), 33.7 (CH), 33.5 (CH_2), 26.8 (CH_3), 23.1 (CH_2), 20.72 (CH_3), 20.68 (CH_3), 12.4 (CH_3). Mass: *m*/*z* 239 (M + 1, 4%), 135 (8), 123 (8), 109 (100), 108 (15). Reaction of the acid **11** (1.0 g, 4.2 mmol) with oxalyl chloride (1.83 mL, 21 mmol) in dry benzene (3 mL) followed by treatment of the resultant acid chloride with an ice-cold solution of an excess of ethereal diazomethane (50 mL, prepared from 5 g of *N*-nitroso-*N*-methylurea and 60 mL of 60% aqueous KOH solution) furnished the diazo ketone **19** (1.0 g, 90%) as yellow oil. IR: ν_{max}/cm^{-1} 2100, 1710, 1620. Decomposition of the diazo ketone **19** (1.0 g, 3.82 mmol) in the presence of rhodium acetate (8 mg) in refluxing CH_2Cl_2 (70 mL) and purification of the product on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the tricyclic dione **12** (625 mg, 70%), which was identified by comparison of TLC and spectral data (IR and ^{1}H and ^{13}C NMR) with those of the sample obtained by hydrogenation of the dione **17**.

(−)-(1*S*,3*R*,6*R*,7*S*,9*S*)-5,5-Ethylenedioxy-9-isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decan-2-one (20). To a magnetically stirred refluxing solution of the dione **12** (300 mg, 1.28 mmol) and ethylene glycol (0.1 mL, 1.79 mmol) in benzene (20 mL) was added a catalytic amount of PTSA, and the reaction mixture was refluxed for 10 h with a Dean−Stark water trap. Excess benzene was distilled off, and the residue was diluted with 5 mL of saturated aqueous $NaHCO_3$ and extracted with ether. Purification of the residue on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the ketal **20** (300 mg, 84%) as a white solid, which was recrystallized from a mixture of hexane and CH_2Cl_2. Mp: 107−108 °C. $[\alpha]^{23}_D$: −111.0 (*c* 0.93, $CHCl_3$). IR: ν_{max}/cm^{-1} 1717. ^{1}H NMR (300 MHz): δ 3.95−3.80 (4 H, m), 2.32 (1 H, br s), 2.26 (1 H, dd, J = 14.7 and 3.8 Hz), 2.00−1.90 (1 H, m), 1.95 (1 H, d, J = 14.7 Hz), 1.90−1.80 (1 H, m), 1.77 (1 H, d, J = 14.4 Hz), 1.40−1.00 (3 H, m), 1.23 (1 H, d, J = 14.7 Hz), 1.09 (3 H, s), 1.06 (3 H, s), 0.90 (3 H, d, J = 6.0 Hz), 0.88 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 219.9 (C), 117.3 (C), 65.1 (CH_2), 64.7 (CH_2), 51.6 (C), 49.0 (CH), 47.9 (CH_2), 47.2 (CH), 45.3 (C), 44.9 (CH), 34.2 (CH), 33.5 (CH_2), 22.6 (CH_2), 20.8 (CH_3), 20.5 (CH_3), 19.5 (CH_3), 18.3 (CH_3). HRMS: *m*/*z* for $C_{17}H_{26}O_3$ calcd 278.1882, found 278.1869. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.42; H, 9.57.

(−)-(1*S*,2*R*,3*R*,6*R*,7*R*,9*S*)-5,5-Ethylenedioxy-9-isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decan-2-ol (21). To a cold (0 °C) magnetically stirred solution of the keto ketal **20** (200 mg, 0.72 mmol) in 2 mL of THF was added LAH (40 mg, 1.05 mmol) in one portion. The reaction mixture was then stirred for 2 h at the same temperature. It was then diluted with ether and quenched carefully with a few drops of water. The ether layer was separated, and the aqueous phase was extracted with ether. Purification of the residue on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the alcohol **21** (190 mg, 94%) as an oil. $[\alpha]^{23}_D$: −101.0 (*c* 3.04, $CHCl_3$). IR: ν_{max}/cm^{-1} 3520. ^{1}H NMR (300 MHz): δ 3.90−3.75 (4 H, m), 3.57 (1 H, d, J = 4.4 Hz), 2.05 (1 H, m), 1.90−1.75 (3 H, m), 1.80 (1 H, d, J = 14.3 Hz), 1.66 (1 H, d, J = 14.3 Hz), 1.50−1.30 (3 H, m), 1.05−0.80 (2 H, m), 1.03 (3 H, s), 0.94 (3 H, s), 0.90 (3 H, d, J = 6.3 Hz), 0.84 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 118.2 (C), 82.1 (CH), 64.9 (CH_2), 64.6 (CH_2), 54.1 (CH_2), 45.8 (CH), 45.1 (C), 43.6 (CH), 41.2 (C), 36.8 (CH_2), 34.0 (CH), 33.7 (CH), 22.8 (CH_2), 22.1 (CH_3), 21.3 (CH_3), 20.0 (CH_3), 19.5 (CH_3). Mass: *m*/*z* 280 (M^+, $C_{17}H_{28}O_3$).

(−)-(1*S*,3*R*,6*R*,7*R*,9*S*)-9-Isopropyl-3,6-dimethyltricyclo-[4.3.1.0^{3,7}]decan-4-one (10). To a magnetically stirred suspension of NaH (34 mg, 55% dispersion in oil, 0.71 mmol, washed with dry hexane) in THF (1 mL) was added a solution of the alcohol **21** (50 mg, 0.18 mmol) in 1 mL of THF followed by a catalytic amount of imidazole (∼10 mg). The reaction mixture was heated to 60 °C for 1 h. It was then cooled to room temperature, dry CS_2 (0.11 mL, 1.8 mmol) was added, and the mixture was heated to 60 °C for 15 min. It was recooled to room temperature, and MeI (0.11 mL, 1.8 mmol)

was added. The reaction mixture was then refluxed for 3 h. It was then cooled to room temperature, diluted with 5 mL of water, and extracted with ether. Evaporation of the solvent and rapid purification of the product on a silica gel column using ethyl acetate−hexane (1:20) furnished the xanthate **22** (53 mg, 80%). IR: ν_{max}/cm^{-1} 1224. ^{1}H NMR (300 MHz): δ 5.58 (1 H, d, J = 4.8 Hz), 3.95−3.80 (4 H, m), 2.56 (3 H, s), 2.35−2.25 (1 H, m), 2.05−1.90 (2 H, m), 1.97 (1 H, d, J = 14.7 Hz), 1.86 (1 H, d, J = 14.7 Hz), 1.70−1.45 (3 H, m), 1.42 (1 H, ddd, J = 14.2, 9.4 and 1.5 Hz), 1.11 (1 H, dd, J = 14.7 and 3.3 Hz), 1.02 (3 H, s), 0.98 (3 H, s), 0.88 (3 H, d, J = 6.6 Hz), 0.80 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 215.9 (C), 117.8 (C), 92.0 (CH), 65.0 (CH_2), 64.7 (CH_2), 53.8 (CH_2), 45.9 (CH), 45.2 (C), 43.3 (CH), 41.8 (C), 36.1 (CH_2), 34.0 (CH), 31.3 (CH), 23.1 (CH_2), 22.2 (CH_3), 21.2 (CH_3), 20.2 (CH_3), 19.5 (CH_3), 19.2 (CH_3). A solution of the xanthate **22** (30 mg, 0.08 mmol), ^{n}Bu$_3$SnH (0.05 mL, 0.19 mmol), and a catalytic amount of AIBN (∼5 mg) in 3 mL of benzene was refluxed for 4 h. The reaction mixture was cooled, diluted with ether, washed successively with 1% aqueous NH_4OH solution, water, and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a mixture of ketals, which was taken in THF (2 mL), and 3 N aqueous HCl was added and stirred for 4 h at room temperature. It was then diluted with ether and washed with water and brine. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished, first, 4-neopupukeanone **10** (10 mg, 56% from xanthate) as a white solid, which was recrystallized from a mixture of hexane and ether. Mp: 66−68 °C. $[\alpha]^{22}_D$: −56.6 (*c* 0.76, $CHCl_3$). IR: ν_{max}/cm^{-1} 1740. ^{1}H NMR (300 MHz): δ 2.22 (1 H, d, J = 18.9 Hz), 1.97 (1 H, d, J = 18.9 Hz), 1.90 (1 H, ddd, J = 14.7, 11.1 and 4.2 Hz), 1.75 (1 H, br s), 1.64 (1 H, dd, J = 14.1 and 4.2 Hz), 1.58 (1 H, d, J = 13.2 Hz), 1.50−1.15 (5 H, m), 1.16 (3 H, s), 1.04 (3 H, s), 0.95−0.80 (1 H, m), 0.94 (3 H, d, J = 6.6 Hz), 0.83 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 222.3 (C), 54.4 (CH_2), 48.3 (C), 46.4 (CH), 43.3 (CH), 40.0 (CH_2), 35.8 (CH_2), 35.3 (C), 32.5 (CH), 28.3 (CH), 25.9 (CH_3), 22.5 (CH_2), 21.1 (CH_3), 20.8 (CH_3), 19.8 (CH_3). Mass: *m*/*z* 220 (M^+). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.78; H, 11.28. Further elution of the column with ethyl acetate−hexane (1:20 to 1:10) furnished the methoxy ketone **23** (7 mg, 35%) as a white solid, which was recrystallized from a mixture of hexane and ether. Mp: 127−128 °C. $[\alpha]^{22}_D$: −46.9 (*c* 1.45, $CHCl_3$). IR: ν_{max}/cm^{-1} 1737. ^{1}H NMR (300 MHz): δ 3.32 (3 H, s), 3.02 (1 H, d, J = 3.6 Hz), 2.28 (1 H, d, J = 18.6 Hz), 2.18 (1 H, br s), 2.04 (1 H, d, J = 18.6 Hz), 2.00−1.75 (2 H, m), 1.65−1.50 (1 H, m), 1.49 (1 H, dd, J = 14.5 and 3.5 Hz), 1.35 (1 H, m), 1.22 (1 H, dd, J = 14.5 and 3.5 Hz), 1.15 (3 H, s), 1.05 (3 H, s), 1.00−0.85 (1 H, m), 0.90 (3 H, d, J = 6.6 Hz), 0.86 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 219.6 (C), 89.1 (CH), 59.1 (CH_3), 54.3 (CH_2), 47.9 (C), 47.3 (CH), 43.4 (CH), 40.4 (C), 38.7 (CH_2), 33.0 (CH), 31.3 (CH), 22.4 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 19.7 (CH_3), 19.4 (CH_3). Mass: *m*/*z* 250 (M^+). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47, found C, 76.83; H, 10.66. Reaction of the xanthate **22** (30 mg, 0.08 mmol) with ^{n}Bu$_3$SnH (0.05 mL, 0.19 mmol) and a catalytic amount of AIBN (∼5 mg) in refluxing toluene (3 mL) followed by hydrolysis gave exclusively 4-neopupukeanone **10** (13 mg, 73%).

(−)-(1*S*,3*R*,6*R*,7*R*,9*S*,10*R*)-9-Isopropyl-10-methoxy-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decan-4-one (23). To a magnetically stirred suspension of NaH (20 mg, 55% dispersion in oil, 0.42 mmol, washed with dry hexane) and tetrabutylammonium iodide (∼10 mg) in THF (1 mL) was added a solution of the alcohol **21** (50 mg, 0.18 mmol) in THF (1 mL) and DMF (0.5 mL), and the reaction mixture was stirred for 1 h at room temperature. To the reaction mixture was then added MeI (0.1 mL, 1.61 mmol) and stirred for 20 h at room temperature. It was then quenched with a few drops of water and extracted with ether. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the methyl ether (25 mg, 48%) as an oil. $[\alpha]^{22}_D$: −83.3 (*c* 0.90, $CHCl_3$). ^{1}H NMR (300 MHz): δ 3.90−3.75 (4 H, m), 3.27 (3 H, s), 2.96 (1 H, d, J = 4.5 Hz), 2.12 (1 H, m), 1.90−1.65 (3 H, m), 1.82 (1 H, d, J = 14.1 Hz), 1.70 (1 H, d, J = 14.1 Hz), 1.45−1.25 (2 H, m), 1.10−0.80 (1 H, m), 1.05 (1 H, dd, J = 14.3 and 3.3 Hz), 0.99 (3 H, s), 0.94 (3 H, s), 0.89 (3 H, d, J = 6.3 Hz), 0.81 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 118.3 (C), 91.8 (CH), 64.9 (CH_2), 64.6 (CH_2), 58.6 (CH_3), 55.0 (CH_2), 46.2 (CH), 45.3 (C), 44.0 (CH), 41.8 (C), 36.8 (CH_2), 32.5 (CH), 30.4 (CH), 22.6 (CH_2), 21.8 (2 C, CH_3), 20.6 (CH_3), 19.6 (CH_3). Mass: *m*/*z* 294 (M^+, $C_{18}H_{30}O_3$). Further elution of the column with ethyl acetate−hexane (1:10) gave the unreacted starting alcohol **21** (25 mg, 50%). To a magnetically stirred solution of methyl ether (20 mg, 0.07 mmol) was added a drop of 3 N aqueous HCl, and the reaction mixture was stirred at room temperature for 3 h. It was then diluted with ether (10 mL) and washed with brine. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the methoxy ketone **23** (16 mg, 94%), which was found to be identical (TLC, IR, and ^{1}H NMR) to the sample obtained via the ^{n}Bu$_3$SnH reaction of the xanthate **22**.

(−)-Methyl (1*R*,2*R*,4*S*,5*S*,6*S*,8*S*)-5-Hydroxy-8-isopropyl-2,6-dimethylbicyclo[2.2.2]octane-2-carboxylate (26). To a cold (0 °C) magnetically stirred solution of the keto ester **18** (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 and extracted with ether. Evaporation of the solvent and purification of the product over a silica gel column using ethyl acetate−hexane as eluent furnished the alcohol **26** (857 mg, 85%) as a white solid, which was recrystallized from hexane. Mp: 68−70 °C. $[\alpha]^{26}_D$: −79.1 (*c* 1.82, $CHCl_3$). IR: ν_{max}/cm^{-1} 3530, 1725. ^{1}H NMR (300 MHz): δ 3.95 (1 H, dd, J = 11.6 and 3.5 Hz), 3.67 (3 H, s), 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), 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), 0.92 (3 H, d, J = 6.0 Hz). 0.86 (3 H, d, J = 6.3 Hz). ^{13}C NMR (22.5 MHz): δ 179.5 (s), 71.1 (d), 51.8 (q), 45.2 (s), 42.2 (d), 39.9 (d), 36.1 (t), 34.4 (d), 33.6 (2 C, d), 26.2 (q), 22.6 (q), 21.8 (t), 21.1 (q), 12.5 (q). Mass: *m*/*z* 254 (M^+). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.20; H, 10.68.

(−)-Methyl (1*R*,2*R*,4*S*,5*S*,7*R*)-5-Isopropyl-2,7-dimethylbicyclo[2.2.2]octane-2-carboxylate (28). To a magnetically stirred suspension of NaH (66 mg, 55% dispersion in oil, 1.38 mmol, washed with dry hexane) in THF (2 mL) was added a solution of the alcohol **26** (175 mg, 0.69 mmol) in 1 mL of THF, followed by a catalytic amount of imidazole (∼10 mg). The reaction mixture was heated to 60 °C for 1 h. It was then cooled to room temperature, and dry CS_2 (0.42 mL, 6.9 mmol) was added and heated to 60 °C for 15 min. It was recooled to room temperature, MeI (0.42 mL, 6.9 mmol) was added, and the reaction mixture was refluxed for 3 h. It was then cooled to room temperature, diluted with 5 mL of water, and extracted with ether. Evaporation of the solvent and rapid purification of the product on a short silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the xanthate **27** (190 mg, 80%). IR: ν_{max}/cm^{-1} 1730, 1283, 1218. ^{1}H NMR (300 MHz): δ 5.77 (1 H, dd, J = 9.5 and 3.5 Hz), 3.69 (3 H, s), 2.56 (3 H, s), 2.50−2.30 (2 H, m), 2.05−1.90 (2 H, m), 1.80−1.60 (2 H, m), 1.50−1.00 (3 H, m), 1.32 (3 H, s), 0.98 (3 H, d, J = 7.2 Hz), 0.89 (3 H, d, J = 6.3 Hz), 0.81 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 215.8 (C), 178.5 (C), 83.1 (CH), 52.1 (CH_3), 45.0 (C), 41.9 (CH), 39.8 (CH), 35.6 (CH_2), 33.8 (CH), 33.3 (CH), 31.9 (CH), 26.5 (CH_3), 22.9 (CH_2), 22.1 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 13.2 (CH_3). A solution of the xanthate **27** (150 mg, 0.44 mmol), ^{n}Bu$_3$SnH (0.3 mL, 1.12 mmol), and a catalytic amount of AIBN (∼5 mg) in 10 mL of benzene was refluxed for 4 h. The reaction mixture was cooled, diluted with ether, and washed successively with 1% aqueous NH_4OH solution and water. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the ester **28** (65 mg, 63%) as an oil. $[\alpha]^{24}_D$: −121.0 (*c* 1.08, $CHCl_3$). IR: ν_{max}/cm^{-1} 1732. ^{1}H NMR (300 MHz): δ 3.66 (3 H, s), 2.39 (1 H, dd, J = 14.0 and 2.6 Hz), 1.85−1.65 (2 H, m), 1.65−1.55 (1 H, m), 1.55−1.35 (3 H, m), 1.26 (3 H, s), 1.30−1.10 (2 H, m), 1.05−0.90 (2

H, m), 0.93 (3 H, d, J = 6.6 Hz), 0.90 (3 H, d, J = 6.6 Hz), 0.82 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 179.4 (C), 51.8 (CH_3), 45.5 (C), 42.7 (CH), 39.2 (CH), 37.1 (CH_2), 31.7 (CH), 28.6 (CH), 28.5 (CH_2), 28.4 (CH), 26.8 (CH_3), 22.8 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 20.4 (CH_3). Mass: 238 (M^+, $C_{15}H_{26}O_2$). Further elution of the column with the same solvent gave methoxy ester **29** (32 mg, 27%) as an oil. $[\alpha]^{24}_D$: −64.2 (*c* 1.76, $CHCl_3$). IR: ν_{max}/cm^{-1} 1732. ^{1}H NMR (300 MHz): δ 3.66 (3 H, s), 3.29 (1 H, dd, J = 13.2 and 4.5 Hz), 3.27 (3 H, s), 2.28 (1 H, dd, J = 14.1 and 2.4 Hz), 2.15 (1 H, m), 1.90−1.60 (4 H, m), 1.40 (1 H, ddd, J = 13.5, 8.7 and 1.2 Hz), 1.28 (3 H, s), 1.20 (1 H, dd, J = 14.1 and 4.0 Hz), 1.10−0.90 (1 H, m), 0.95 (3 H, d, J = 7.2 Hz), 0.89 (3 H, d, J = 6.3 Hz), 0.82 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 179.3 (C), 81.0 (CH), 58.3 (CH_3), 51.9 (CH_3), 45.3 (C), 42.6 (CH), 40.3 (CH), 36.3 (CH_2) 33.7 (CH), 32.5 (CH), 30.8 (CH), 26.4 (CH_3), 22.4 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 13.1 (CH_3). Mass: *m*/*z* 268 (M^+, $C_{16}H_{28}O_3$). Reaction of the xanthate **27** (50 mg, 0.14 mmol) with ^{n}Bu$_3$SnH (0.1 mL, 0.37 mmol) and a catalytic amount of AIBN (∼5 mg) in refluxing toluene (10 mL) for 4 h furnished the esters **28** (28 mg, 81%) and **29** (6 mg, 15%).

(−)-(1*S*,3*R*,6*R*,7*R*,9*S*)-9-Isopropyl-3,6-dimethyltricyclo-[4.3.1.0^{3,7}]decan-4-one (10). A magnetically stirred solution of the ester **28** (50 mg, 0.21 mmol) in 1 mL of 2 M methanolic KOH was refluxed for 15 h. It was then cooled, diluted with water, and washed with CH_2Cl_2. The aqueous phase was acidified with 3 N aqueous HCl and extracted with CH_2Cl_2. Evaporation of the solvent gave acid **30** (43 mg, 91%). IR: ν_{max}/cm^{-1} 1697. ^{1}H NMR (300 MHz): δ 2.37 (1 H, dd, J = 14.0 and 2.2 Hz), 1.90−1.10 (9 H, m), 1.34 (3 H, s), 1.05−0.95 (2 H, m), 0.96 (3 H, d, J = 6.6 Hz), 0.91 (3 H, d, J = 6.3 Hz), 0.83 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 186.1 (C), 45.5 (C), 42.7 (CH), 39.0 (CH), 36.8 (CH_2), 31.7 (CH), 28.6 (CH), 28.54 (CH_2), 28.49 (CH), 26.9 (CH_3), 22.8 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 20.4 (CH_3). To a magnetically stirred solution of the acid **30** (20 mg, 0.09 mmol) in dry benzene (1 mL) was added oxalyl chloride (0.04 mL, 0.45 mmol). The reaction mixture was stirred for 2 h at room temperature. 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 (5 mL, prepared from 500 mg of *N*-nitroso-*N*-methylurea and 10 mL of 60% aqueous KOH solution). The reaction mixture was slowly warmed to room temperature and stirred for 2 h, and the excess diazomethane and ether were carefully evaporated on a water bath. Rapid purification of the crude product through a neutral alumina column using CH_2Cl_2 as eluent furnished the diazo ketone **31** (12 mg, 54%) as a yellow oil. IR: ν_{max}/cm^{-1} 2094, 1624. To a magnetically stirred, refluxing solution of rhodium acetate (2 mg) in dry CH_2Cl_2 (5 mL) was added, dropwise, a solution of the diazo ketone **31** (12 mg, 0.048 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was refluxed for 4 h. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:20) as eluent furnished the 4-neopupukeanone **10** (8 mg, 75%), which exhibited TLC, IR, and ^{1}H NMR spectra identical to those of the sample obtained earlier.

(−)-(1*S*,3*R*,4*S*,6*R*,7*R*,9*S*)-9-Isopropyl-3,6-dimethyltricyclo[4.3.1.0^{3,7}]dec-4-yl methanesulfonate (33). To a cold (0 °C), magnetically stirred solution of the ketone **10** (48 mg, 0.22 mmol) in 1 mL of MeOH was added $NaBH_4$ (10 mg, 0.26 mmol). The reaction mixture was stirred for 15 min at the same temperature, and then solvent was evaporated under reduced pressure. It was then diluted with water and extracted with ether. Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate−hexane (1:10) as eluent furnished the alcohol **32** (44 mg, 91%). Mp: 57−59 °C. $[\alpha]^{27}_D$: −66.1 (*c* 1.12, $CHCl_3$). IR: ν_{max}/cm^{-1} 3360. ^{1}H NMR (300 MHz): δ 3.62 (1 H, dd, J = 9.9 and 6.6 Hz), 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), 1.40 (1 H, d, J = 15.0 Hz), 1.35−0.80 (7 H, m), 1.01 (3 H, s), 0.96 (3 H, s), 0.89 (3 H, d, J = 6.6 Hz), 0.83 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 78.8 (CH), 50.4 (CH_2), 46.7 (CH), 44.6 (CH), 42.9 (C), 39.6 (CH_2), 38.2 (C), 34.7 (CH_2), 31.9 (CH), 27.5 (CH), 26.8 (CH_3), 24.5 (CH_3), 23.0 (CH_2), 21.2 (CH_3), 21.0 (CH_3). Mass: *m*/*z* 222 (M^+, $C_{15}H_{26}O$). To a magnetically stirred solution of the alcohol **32** (44 mg, 0.19 mmol) in 1 mL of pyridine were added MsCl (0.02 mL, 0.26 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 10 h at room temperature. It was then diluted with 5 mL of water and extracted with CH_2Cl_2. The organic extract was washed successively with 3 N aqueous HCl and saturated aqueous $NaHCO_3$ solution. 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 **33** (50 mg, 84%) as a white solid, which was recrystallized from a mixture of hexane and ether. Mp: 52−54 °C. $[\alpha]^{22}_D$: −21.0 (*c* 1.49, $CHCl_3$). IR: ν_{max}/cm^{-1} 1350, 1170. ^{1}H NMR (300 MHz): δ 4.44 (1 H, dd, J = 9.9 and 6.3 Hz), 3.00 (3 H, s), 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), 0.99 (3 H, s), 0.95−0.85 (2 H, m), 0.89 (3 H, d, J = 6.3 Hz), 0.83 (3 H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz): δ 87.9 (CH), 47.8 (CH_2), 45.6 (CH), 44.0 (CH), 43.0 (C), 39.2 (CH_2), 38.6 (C), 38.1 (CH_3), 35.6 (CH_2), 31.9 (CH), 27.1 (CH), 26.5 (CH_3), 24.3 (CH_3), 22.6 (CH_2), 21.1 (CH_3), 21.0 (CH_3). Mass: *m*/*z* 205 (M − OMs). Anal. Calcd for $C_{16}H_{28}O_3S$: C, 63.96; H, 9.39. Found: C, 64.19; H, 9.76%.

(−)-(1*S*,3*R*,4*R*,6*R*,7*R*,9*S*)-4-Thiocyanatoneopupukeanane (6). A solution of the mesylate **33** (25 mg, 0.08 mmol) and KSCN (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_2Cl_2, and washed with water. 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%, 68% based on the starting material consumed) as an oil. The synthetic sample exhibited spectral data identical to that of the natural product reported by Scheuer and Higa.[5a] $[\alpha]^{28}_D$: −117.6 (*c* 1.08, $CHCl_3$) [lit.[5a] $[\alpha]^{23}_D$: −120.5 (*c* 1.44, $CHCl_3$)]. IR: ν_{max}/cm^{-1} 2160. ^{1}H NMR (300 MHz): δ 3.47 (1 H, dd, J = 8.4 and 3.3 Hz), 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), 1.05 (3 H, s), 0.90−0.80 (1 H, m), 0.90 (3 H, d, J = 6.6 Hz), 0.81 (3 H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz): δ 113.8 (C), 60.1 (CH), 50.5 (CH_2), 45.7 (CH_2), 45.1 (CH), 44.8 (C), 43.1 (CH), 39.1 (C), 37.8 (CH_2), 31.8 (CH), 27.8 (CH), 26.7 (CH_3), 24.0 (CH_3), 22.4 (CH_2), 21.0 (2 C, CH_3). Mass: *m*/*z* 205 (M − SCN, $C_{15}H_{25}$). Further elution of the column with ethyl acetate−hexane (1:10) furnished the unreacted mesylate **33** (15 mg, 60%).

Acknowledgment. We thank Professor T. Higa, University of Ryukyus, and Professor P. J. Scheuer, University of Hawaii at Manoa for providing the copies of the ^{1}H and ^{13}C NMR spectra of natural (−)-4-thiocyanatoneopupukeanane, the Department of Science and Technology, New Delhi for financial support, and the Council of Scientific and Industrial Research, New Delhi, for the award of a research fellowship to SJG.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **21** and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0102765