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A formal total synthesis of (±)-9-isocyanoneopupukeanane

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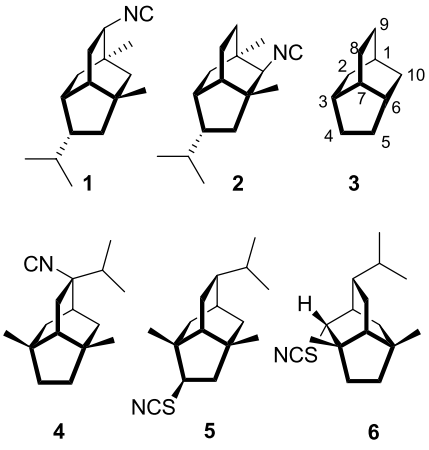
Abstract—A formal total synthesis of the marine sesquiterpene (±)-9-isocyanoneopupukeanane starting from the readily available monoterpene carvone has been accomplished employing a combination of intermolecular Michael addition–intramolecular Michael addition reaction and an intramolecular rhodium carbenoid C–H insertion reaction as key steps, and identifying the isopropenyl group as a masked hydroxy group.

1. Introduction

In a variety of marine organisms, chemical defence via secretion of toxic and/or strong smelling organic compounds from skin glands is a common phenomenon as part of the self-defence 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, investigations on the chemical constituents of the skin extracts of *P. varicosa* and also from its prey, a sponge, *Hymeniacidon* sp. by the research group of Scheuer led to the isolation[1] of two novel sesquiterpenes, 9-isocyano- and 2-isocyanopupukeananes **1** and **2**. The pupukeananes **1** and **2** contain a tricyclo[4.3.1.0^{3,7}]decane (isotwistane **3**) carbon framework, which was observed for the first time among the natural products. 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 the isocyano functionality and a new carbon framework named as neopupukeanane. Later, the research groups of Scheuer, Higa and Faulkner reported[3] the isolation of two more sesquiterpenes belonging to this group, 4- and 2-thiocyanatoneopupukeananes **5** and **6**, from the sponge *Phycopsis terpnis* (from Okinawa) and from an unidentified species from Pohnpei.



The presence of the tricyclo[4.3.1.0^{3,7}]decane carbon framework (isotwistane) incorporating two quaternary carbon centres besides the thiocyanate and isonitrile functionalities made neopupukeananes attractive and challenging synthetic targets. In 1999, Ho and Jana reported[4,5] the first total synthesis of (±)-9-isocyanoneopupukeanane **4** via the symmetric isotwistanone **7**. Herein we report a formal total synthesis of (±)-**4** starting from readily available monoterpene carvone **8**.

2. Results and discussion

It was anticipated (Scheme 1) that the rhodium carbenoid C–H insertion[6] of the diazoketone **10**, derived from bicyclo[2.2.2]octanecarboxylate **11**, would generate the isotwistanedione **9** in a regioselective manner via preferential formation of a five-membered ring by the insertion of the rhodium carbenoid into the only available γ C–H bond,

Keywords: Marine sesquiterpenes; Neopupukeanane; Double Michael reaction; Rhodium CH insertion reaction.
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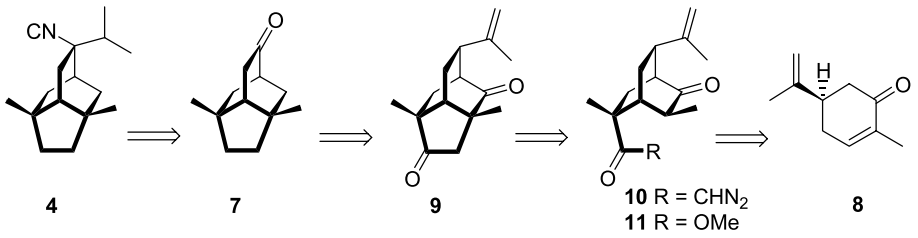
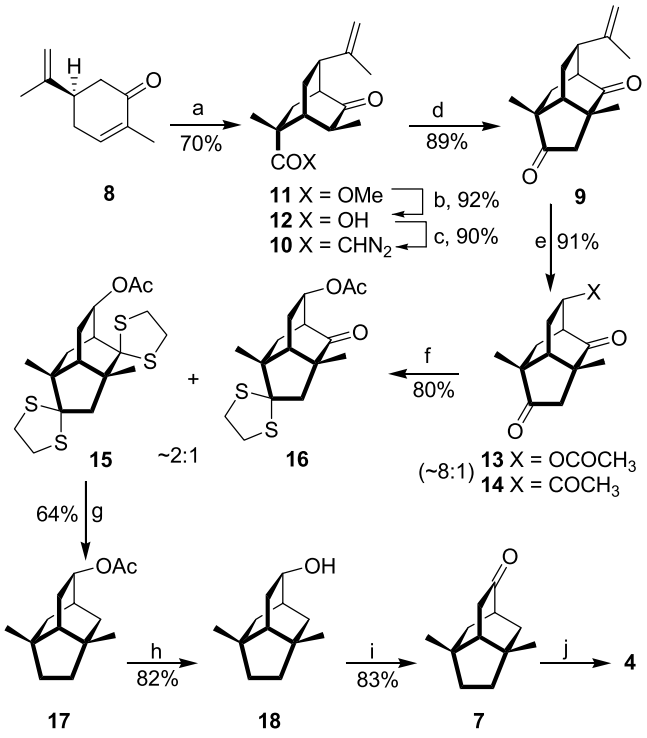


Scheme 1.

which could be further elaborated to symmetric isotwistanone **7** via reductive deoxygenation of the two ketones and degradation of the isopropenyl group. An intermolecular Michael addition followed by an intramolecular Michael reaction of carvone **8** with methyl methacrylate was exploited for generating the bicyclo[2.2.2]octanone carboxylate **11**.[7] Thus, reaction of carvone **8** with lithium hexamethyldisilazide (LiHMDS) in hexane at −70 °C followed by reaction of the resultant kinetic dienolate with one equivalent of methyl methacrylate furnished the bicyclic keto ester **11** via the Michael–Michael reaction in 70% yield in a highly regio- and stereoselective manner (Scheme 2). Base catalysed hydrolysis of the keto ester **11** furnished the keto acid **12**, which was converted into the diazoketone **10** via the corresponding acid chloride. Treatment of the diazoketone **10** with a catalytic amount of rhodium acetate in dichloromethane at reflux furnished the isotwistane dione **9** in 89% yield, containing the complete carbon framework of neopupukeananes,[8] via regiospecific C–H insertion of the intermediate rhodium carbenoid. As the olefin moiety in the isopropenyl group was found to isomerise under acidic conditions, it was contemplated to degrade the isopropenyl group prior to the reductive deoxygenation of the ketones. Since the ozonolysis followed by Baeyer–Villiger rearrangement would lead to regiochemical problems, a one pot ozonolysis-Criegee rearrangement[9] was chosen for the conversion of the isopropenyl moiety into an acetoxy group. Thus, ozonolysis of the isotwistanedione **9** in methanol–methylene chloride medium followed by treatment of the resultant methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) in benzene at reflux furnished the diketoacetate **13** in 81% yield along with the normal ozonolysis product triketone **14** (11%). For the reductive deoxygenation of the two ketones, a two step protocol was employed via the corresponding bis-dithioketal. Accordingly, treatment of the diketoacetate with ethanedithiol in the presence of a catalytic amount of either iodine[10] or boron trifluoride diethyl etherate furnished a mixture of bis and mono dithioketals **15** and **16** in 52 and 28% yields, respectively. Raney nickel mediated desulfurisation of the bis-dithioketal **15** furnished the 9-isotwistanyl acetate **17**. Hydrolysis of the acetate group in **17** with potassium carbonate in methanol followed by oxidation of the resultant isotwistanol **18** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the isotwistanone **7**. Both the alcohol **18** and the ketone **7** exhibited spectral data, in particular ^{1}H and ^{13}C NMR, identical to those reported by Ho and Jana. Since the conversion of isotwistanone **7** into 9-isocyanoneopupukeanane (±)-**4** has already been accomplished by Ho and Jana,[4] the present sequence constitute a formal total synthesis of the marine sesquiterpene **4**.



Scheme 2. (a) $LiN(TMS)_2$, $CH_2{=}C(Me)COOMe$, hexane; (b) NaOH, MeOH–H_2O, reflux; (c) (i) $(COCl)_2$, C_6H_6; (ii) CH_2N_2, Et_2O; (d) $Rh_2(OAc)_4$, CH_2Cl_2; (e) O_3/O_2, MeOH–CH_2Cl_2, −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux; (f) $(CH_2SH)_2$, I_2, $CHCl_3$; (g) Raney Ni, EtOH, reflux; (h) K_2CO_3, MeOH; (i) PCC, silica gel, CH_2Cl_2; (j) Ref. 4.

In summary, we have developed a convenient approach to 9-isocyanoneopupukeanane starting from readily available monoterpene carvone. The isopropenyl group of carvone has been identified as a masked hydroxy group. A combination of double Michael reaction and a regiospecific intramolecular rhodium carbenoid CH insertion reaction have been employed as key steps for the regio- and stereospecific efficient construction of the isotwistane skeleton.

3. Experimental

3.1. General

Melting points are recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Jasco FTIR

410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75, 22.5 MHz) spectra were recorded on JNM λ-300 or JEOL FX-90Q spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) were determined either by recording the DEPT-135 or off-resonance decoupling, and are given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet (EI) mode. Relative intensities are given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Ozonolysis experiments were carried out using Fischer 502 ozone generator by passing pre-cooled (−70 °C) oxygen (for generating dry ozone). Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium-benzophenone ketyl. Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry dichloromethane was prepared by distilling over calcium hydride. All the commercial reagents were used as such without further purification.

3.1.1. Methyl (1*R*,2*R*,4*S*,6*S*,8*R*)-8-isopropenyl-2,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (11). To a cold (−78 °C), magnetically stirred solution of hexamethyldisilazane (2.02 ml, 9.33 mmol) in dry hexane (20 ml) was slowly added by a syringe a solution of *n*-BuLi (4.56 ml, 1.9 M in hexane, 20 mmol) and the mixture stirred for 15 min. To the LiHMDS thus, formed was added drop wise a solution of (*R*)-carvone **8** (1 g, 6.66 mmol) in dry hexane (5 ml) and continued stirring for 45 min at the same temperature. The enolate was treated with methyl methacrylate (0.78 ml, 7.33 mmol) and stirred for 3 h at rt. 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 **11** (1.16 g, 70%) as a white solid,[7] which was recrystallized from hexanes, mp 59–61 °C (lit.[7] 60–61.5 °C). $[\alpha]_D^{22}$ −43.5 (*c* 3.77, MeOH) [lit.[7] $[\alpha]_D^{25}$ −42.6 (*c* 1.00, MeOH)]. ν_{max} (neat) 1720, 1645, 895 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 4.75 (1H, s), 4.72 (1H, s), 3.71 (3H, s), 2.70 (1H, dd, J=14.5, 2.5 Hz), 2.60–2.40 (2H, m), 2.25–2.00 (3H, m), 1.71 (3H, s), 1.70–1.55 (2H, m), 1.46 (3H, s), 1.10 (3H, d, J=6.9 Hz). δ_C (22.5 MHz, $CDCl_3$) 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 (2C, q and t), 12.3 (q).

3.1.2. (1*R*,2*R*,4*S*,6*S*,8*R*)-8-Isopropenyl-2,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid (12). To a solution of the keto ester **11** (1.0 g, 4 mmol) in 5 ml methanol was added 10% aq NaOH solution (5 ml), and the reaction heated at reflux for 8 h. It was then cooled to rt and washed with CH_2Cl_2 (10 ml). The aqueous layer was acidified with 3 M aq HCl and extracted with CH_2Cl_2 (3×15 ml). The CH_2Cl_2 extract was washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo to furnish the acid **12** (870 mg, 92%) as a sticky solid, which was recrystallized from a mixture of hexane and CH_2Cl_2,[8] mp 119–120 °C. $[\alpha]_D^{26}$ −47.7 (*c* 1.30, $CHCl_3$). ν_{max} (neat) 1720, 1700, 890 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3$+CCl_4) 4.74 (1H, s), 4.72 (1H, s), 2.68 (1H, dd, J=14.7, 2.4 Hz), 2.55–2.45 (2H, m), 2.30–2.10 (3H, m), 1.71 (3H, s), 1.75–1.50 (2H, m), 1.59 (1H, dd, J=14.7, 3.3 Hz), 1.52 (3H, s), 1.12 (3H, d, J=6.9 Hz). δ_C (22.5 MHz, $CDCl_3$) 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 (2C, q and t), 12.5 (q).

3.1.3. (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 (9). To a magnetically stirred solution of the acid **12** (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 rt. Evaporation of benzene and the excess oxalyl chloride in vacuo furnished the acid chloride, which was taken in dry ether (5 ml) and added 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% 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 a neutral alumina column using CH_2Cl_2 as eluent furnished the diazoketone **10** (495 mg, 90%) as yellow oil. IR (neat). ν_{max}/cm^{-1} 2100, 1710, 1620, 890 cm^{-1}.

To a magnetically stirred, refluxing solution of rhodium acetate (4 mg) in dry CH_2Cl_2 (30 ml) was added drop wise a solution of the diazoketone **71** (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 **9** (392 mg, 89%) as a white solid, which was recrystallized from a mixture of ethyl acetate/hexane,[8] mp 111–113 °C. $[\alpha]_D^{26}$ −45.5 (*c* 1.32, $CHCl_3$). ν_{max} (neat) 1740, 1710, 890 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 4.83 (1H, s), 4.79 (1H, s), 2.55–2.50 (2H, m), 2.52 (1H, d, J=18.9 Hz), 2.21 (1H, ddd, J=14.4, 10.5, 3.3 Hz), 2.10 (1H, d, J=18.9 Hz), 1.94 (1H, ddd, J=14.7, 6.3, 2.7 Hz), 1.90 (1H, br s), 1.80 (1H, dd, J=14.7, 4.2 Hz), 1.76 (3H, s), 1.59 (1H, d, J=14.7 Hz), 1.25 (3H, s), 1.24 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3$+CCl_4) 218.6 (C), 217.6 (C), 146.8 (C), 110.4 (CH_2), 50.9 (C), 49.0 (CH), 48.5 (C), 48.1 (CH_2), 46.3 (CH), 45.1 (CH), 35.2 (CH_2), 22.0 (CH_3), 20.7 (CH_2), 19.5 (CH_3), 18.1 (CH_3).

3.1.4. (1*S*,3*R*,6*R*,7*S*,9*R*)-9-Acetoxy-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decane-2,5-dione (13). Dry ozone in oxygen gas was passed through a cold (−70 °C) solution of the diketone **9** (215 mg, 0.92 mmol) and $NaHCO_3$ (100 mg) in 1:9 MeOH/CH_2Cl_2 (10 ml) until (ca. 4.5 min) pale blue colour appeared. Excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue was dissolved in dry benzene (30 ml). Acetic anhydride (0.61 ml, 6.49 mmol), triethylamine (1.29 ml, 9.26 mmol) and a catalytic amount of DMAP (10 mg) were added to the reaction mixture and heated at reflux for 10 h. It was then cooled, diluted with water (10 ml) and extracted with ether (3×5 ml). The ether extract was washed with

3 M aqueous HCl, water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:5) as eluent furnished the diketoacetate **13** (187 mg, 81%) as colourless solid, which was recrystallised from a mixture of CH_2Cl_2/hexane, mp 73–75 °C. $[\alpha]_D^{24}-5.8$ (*c* 5.5, $CHCl_3$). ν_{max} (neat) 1740, 1729 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 5.09 (1H, ddd, *J*=9.0, 4.2, 2.1 Hz, C*H*OAc), 2.56 (1H, t, *J*=4.2 Hz), 2.44 (1H, d, *J*=18.9 Hz), 2.37 (1H, ddd, *J*=16.5, 9.3, 3.0 Hz), 2.10 (1H, d, *J*=18.9 Hz), 2.08 (1H, d, *J*=4.8 Hz), 2.03 (3H, s), 2.00–1.85 (1H, m), 1.76 (1H, dd, *J*=14.4, 4.8 Hz), 1.46 (1H, d, *J*=14.4 Hz), 1.33 (3H, s), 1.16 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 216.6 (C), 214.5 (C), 169.4 (C), 71.6 (CH), 50.9 (C), 48.8 (CH), 48.0 (CH_2), 47.7 (C), 46.4 (CH), 30.5 (CH_2), 24.0 (CH_2), 20.9 (CH_3), 19.6 (CH_3), 17.9 (CH_3). *m/z* 250 (M^+, 22), 234 (12), 208 (14), 191 (20), 190 (100), 175 (14), 162 (32), 147 (68), 134 (32), 121 (43), 119 (43), 105 (22), 93 (82%). HRMS: M^++Na, found 273.1095. $C_{14}H_{18}O_4Na$ requires 273.1103.

Further elution of the column with ethyl acetate/hexane (1:3) furnished the triketone **14** (21 mg, 10%) as a colourless solid, which was recrystallized from a mixture of CH_2Cl_2/hexane, mp 68–70 °C. $[\alpha]_D^{27}-70.0$ (*c* 2.8, $CHCl_3$). ν_{max} (neat) 1742, 1713 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 3.40–3.25 (1H, m), 3.00–2.88 (1H, m), 2.70–2.52 (2H, m), 2.42 (1H, d, *J*=19.2 Hz), 2.18 (3H, s), 2.07 (1H, d, *J*=19.2 Hz), 1.95–1.75 (2H, m), 1.59 (1H, d, *J*=14.7 Hz), 1.27 (3H, s), 1.20 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 216.6 (C), 215.4 (C), 206.1 (C), 51.6 (CH), 51.2 (C), 48.8 (CH), 48.3 (C), 47.9 (CH_2), 44.9 (CH), 34.0 (CH_2), 28.0 (CH_3), 19.6 (CH_3), 18.0 (CH_3), 15.5 (CH_2). *m/z* 234 (M^+, 46), 219 (16), 206 (36), 191 (29), 164 (14), 163 (13), 149 (26), 135 (20), 123 (62), 121 (44), 110 (72), 109 (100), 93 (73%). HRMS: M+Na, found 257.1148. $C_{14}H_{18}O_3Na$ requires 257.1154.

3.1.5. (1*S*,3*R*,6*R*,7*S*,9*R*)-9-Acetoxy-3,6-dimethyltricyclo[4.3.1.0^{3,7}]decane-2,5-dione bis-dithioketal (15). To a cold (0 °C) magnetically stirred solution of the diketone **13** (50 mg, 0.20 mmol) and ethanedithiol (0.33 ml, 4.0 mmol) in dry $CHCl_3$ (5 ml) was added a catalytic amount of iodine (10 mg) and stirring continued for 16 h at rt. It was then diluted with ether (10 ml), washed with 5% aqueous NaOH solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:40) as eluent first furnished the bis-thioketal **15** (42 mg, 52%) as oil. $[\alpha]_D^{23}-45.0$ (*c* 5.8, $CHCl_3$). ν_{max} (neat) 1731 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 4.76 (1H, t, *J*=9.3 Hz), 3.43 (1H, d, *J*=16.5 Hz), 3.35–3.10 (6H, m), 3.12–2.90 (2H, m), 2.40 (1H, d, *J*=16.5 Hz), 2.28 (1H, s), 2.20–1.80 (2H, m), 2.04 (3H, s), 1.89 (1H, ddd, *J*=14.4, 9.0, 1.2 Hz), 1.75–1.50 (2H, m), 1.31 (3H, s), 1.21 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 170.2 (C), 79.1 (C), 78.0 (C), 72.4 (CH), 60.8 (CH_2), 50.6 (CH), 49.3 (C), 48.3 (CH), 47.7 (C), 40.6 (CH_2), 40.5 (CH_2), 40.4 (CH_2), 39.4 (CH_2), 37.0 (CH_2), 24.5 (CH_3), 22.9 (CH_2), 21.7 (2C, CH_3). *m/z* 402 (M^+, 34), 374 (29), 158 (13), 145 (36), 119 (100), 105 (22%). HRMS: M+Na, found 425.0694. $C_{18}H_{26}O_2S_4Na$ requires 425.0713.

Further elution of the column using ethyl acetate/hexane (1:20) as eluent furnished monodithioketal **16** (18 mg, 28%) as a colourless solid, which was recrystallized from a mixture of CH_2Cl_2/hexane, mp 123–125 °C. $[\alpha]_D^{27}-103.2$ (*c* 5.8, $CHCl_3$). ν_{max} (neat) 1736, 1716 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 5.00–4.90 (1H, m), 3.40–3.10 (4H, m), 2.64 and 2.47 (2H, 2×d, *J*=15.6 Hz), 2.42–2.30 (2H, m), 2.13–2.00 (1H, m), 2.10–1.95 (1H, m), 2.02 (3H, s), 1.70–1.50 (2H, m), 1.32 (3H, s), 1.19 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 214.9 (C), 169.8 (C), 79.1 (C), 72.4 (CH), 56.0 (CH_2), 52.2 (C), 50.7 (CH), 48.8 (C), 46.6 (CH), 40.7 (CH_2), 39.7 (CH_2), 34.1 (CH_2), 25.0 (CH_2), 22.2 (CH_3), 21.1 (CH_3), 17.8 (CH_3). *m/z* 328 (M^++2, 9), 326 (82), 298 (34), 270 (46), 239 (27), 238 (31), 237 (30), 210 (37), 199 (45), 145 (100), 105 (41), 91 (26%). HRMS: M+Na, found 349.0912. $C_{16}H_{22}O_3S_2Na$ requires 349.0908.

3.1.6. (*R*)-3,6-Dimethyltricyclo[4.3.1.0^{3,7}]decan-9-yl acetate (17). To a magnetically stirred solution of the bis-dithioketal **15** (34 mg, 0.08 mmol) in dry ethanol (3 ml) was added Raney nickel (150 mg, excess) and the reaction heated at reflux for 5 h. The reaction mixture was then cooled and filtered through a short silica gel column to remove the catalyst. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:30) as eluent furnished the acetate **17** (12 mg, 64%) as oil. $[\alpha]_D^{27}-13.0$ (*c* 3.0, $CHCl_3$). ν_{max} (neat) 1737 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 4.70–4.55 (1H, m), 2.14–1.90 (2H, m), 2.03 (3H, s), 1.75–1.22 (10H, m), 1.05 (3H, s), 1.01 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 170.4 (C), 71.9 (CH), 48.3 (CH), 41.7 (CH_2), 40.9 (CH_2), 40.4 (CH_2), 39.8 (C), 39.4 (C), 36.4 (CH_2), 30.4 (CH), 27.1 (CH_3), 26.6 (CH_3), 24.2 (CH_2), 21.4 (CH_3). *m/z* 162 (M^+−AcOH, 91), 147 (21), 106 (80), 95 (100), 93 (47%). HRMS: M+Na found 245.1515. $C_{14}H_{22}O_2Na$ requires 245.1517.

3.1.7. (*R*)-3,7-Dimethyltricyclo[4.3.1.0^{3,7}]decan-9-ol (18). To a magnetically stirred solution of the acetate **17** (12 mg, 0.05 mmol) in methanol (1 ml) was added K_2CO_3 (50 mg) and the reaction stirred for 10 h at rt. The reaction mixture was then filtered through a short silica gel column using ethyl acetate/hexane (1:5). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:10) as eluent furnished the alcohol **18** (8 mg, 82%) as oil.[4] $[\alpha]_D^{23}-15.8$ (*c* 1.2, $CHCl_3$). ν_{max} (neat) 3276 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 3.75–3.65 (1H, m), 1.98 (1H, ddd, *J*=14.7, 9.6, 3.3 Hz), 1.76 (1H, d, *J*=13.5 Hz), 1.60–1.10 (11H, m), 1.06 (3H, s), 0.98 (3H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 68.7 (CH, CHOH), 48.6 (CH), 42.0 (CH_2), 40.8 (CH_2), 40.4 (CH_2), 39.9 (C), 39.2 (C), 35.6 (CH_2), 33.9 (CH), 27.0 (CH_3), 26.9 (CH_2), 26.6 (CH_3). *m/z* 162 (M^+-H_2O, 62), 149 (8), 107 (100), 106 (68), 105 (37), 95 (52), 93 (50), 91 (40%).

3.1.8. 3,7-Dimethyltricyclo[4.3.1.0^{3,7}]decan-9-one (7). To a magnetically stirred solution of the alcohol **18** (6 mg, 0.03 mmol) in dry CH_2Cl_2 (1 ml) was added a homogeneous mixture of PCC (71 mg, 0.33 mmol) and silica gel (71 mg) and the reaction stirred for 90 min at rt. The reaction mixture was then filtered through a short silica gel column and eluted with excess CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:30) as eluent furnished the ketone **7**

(5 mg, 83%) as oil.[4] ν_{max} (neat) 1732 cm^{-1}. δ_H (300 MHz, 1:1 $CDCl_3+CCl_4$) 2.26 (2H, d, $J=3.3$ Hz), 2.20–2.14 (1H, m), 1.73–1.55 (8H, m), 1.31 (1H, t, $J=3.3$ Hz), 1.08 (6H, s). δ_C (75 MHz, 1:1 $CDCl_3+CCl_4$) 217.0 (C), 50.8 (CH), 43.6 (CH), 40.5 (2C, CH_2), 40.1 (2C, CH_2), 39.8 (2C, C), 33.1 (CH_2), 26.7 (2C, CH_3). *m/z* 178 (M^+, 18%), 149 (100), 135 (7), 121 (10), 107 (21), 105 (73). HRMS: M+Na, found 201.1263. $C_{12}H_{18}ONa$ requires 201.1255.

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