

A stereoselective total synthesis of (–)-seychellene

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Abstract

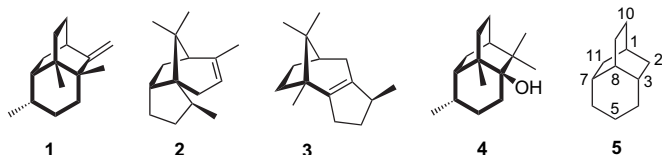
A stereoselective total synthesis of the tricyclic sesquiterpene (–)-seychellene, starting from (*R*)-carvone via (*R*)-3-methylcarvone has been accomplished, employing a combination of intermolecular Michael addition–intramolecular Michael addition sequence, a stereoselective hydrogenation, and an intramolecular alkylation reaction.

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Keywords: Seychellene; Sesquiterpene synthesis; Intramolecular alkylation; Carvone; Double Michael reaction

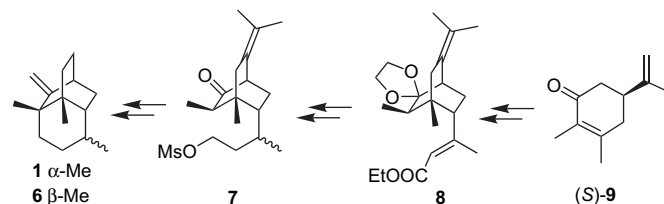
1. Introduction

The structurally novel tricyclic sesquiterpene (–)-seychellene **1** was first isolated from the patchouli oil (from the leaves of *Pogostemon cablin* Benth obtained from the Seychelles Islands) as one of the minor components along with α - and β -patchoulene **2** and **3** and patchouli alcohol **4**.¹ It was subsequently isolated from a variety of species belonging to *Pogostemon* and *Nardostachys jatamansi*. The relative structure as well as the absolute configuration of seychellene **1** was established by Ourisson and Wolff based on the degradation studies.¹ Structurally and biogenetically, seychellene **1** is closely related to the tricyclic alcohol patchouli alcohol **4**.



The tricyclic structure containing a carbon framework tricyclo[5.3.1.0^{3,8}]undecane (homoisotwistane **5**) incorporating two vicinal quaternary carbon atoms attracted the attention of

synthetic chemists and a number of reports appeared on the synthesis of seychellene **1** in its racemic form.² As a part of our interest in the enantiospecific synthesis of tricyclic sesquiterpenes starting from the readily available monoterpene (*R*)-carvone, such as neopupukeananes, pupukeananes, valeriananoids, patchouli alcohol, etc.,³ we have recently reported⁴ the first enantiospecific synthesis of *ent*-seychellene **1** and *epi*-seychellene **6** via intramolecular alkylation of ketomesylate **7** (Scheme 1) followed by the degradation of the isopropylidene group. A one step reduction of the olefin as well as the ester group in the α,β -unsaturated ester **8** using lithium in liquid ammonia conditions was employed for the creation of the secondary methyl group. Since the stereoselectivity in the lithium–liquid ammonia reaction was not good, an alternative strategy via the catalytic hydrogenation of the olefin in **8** was explored and herein, we describe a stereoselective synthesis of (–)-seychellene **1**.



Scheme 1. Earlier route to (+)-seychellene.

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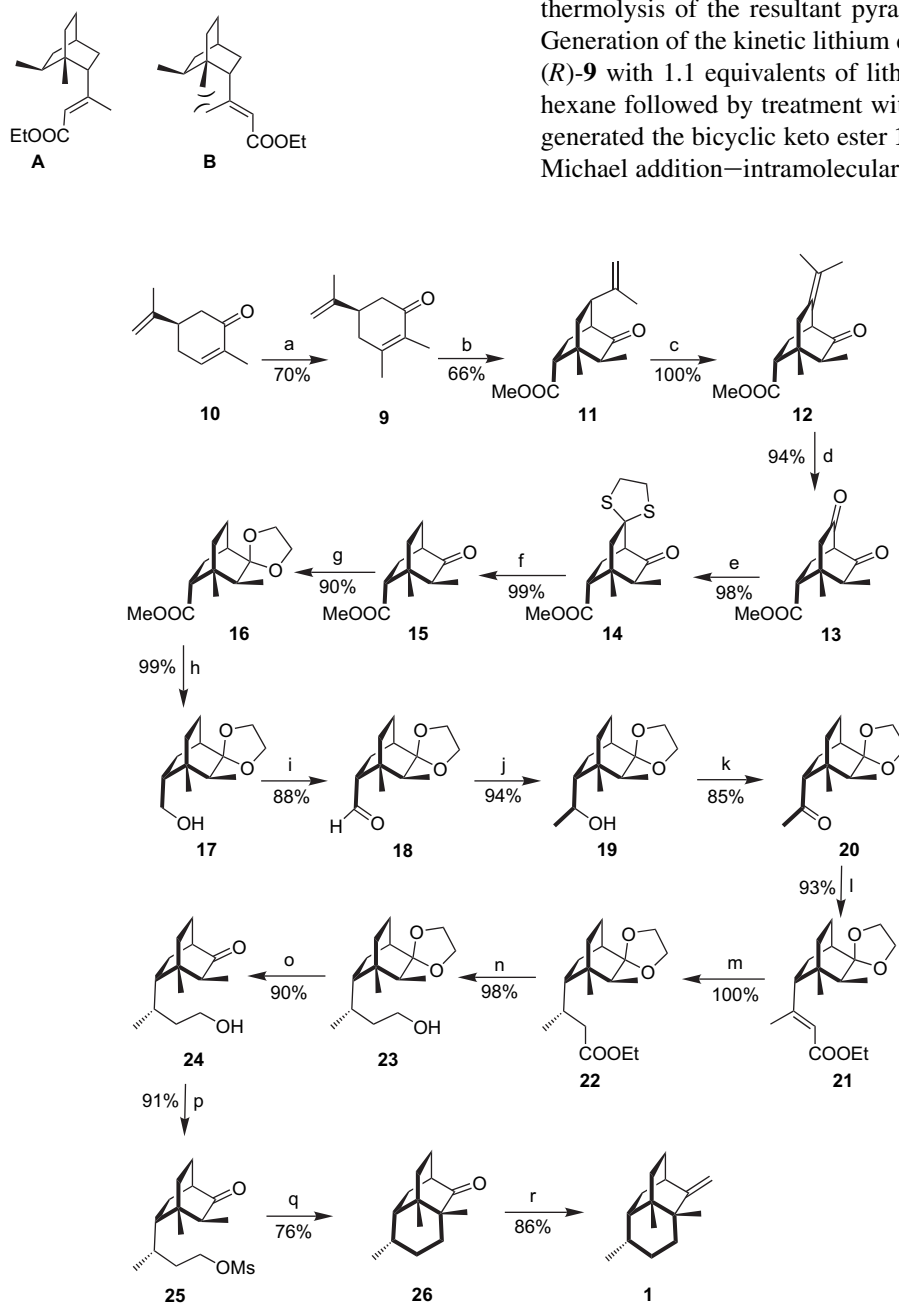
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2. Results and discussion

It was contemplated that among the two rotamers **A** and **B** (considering that the methyl group of the crotonyl side chain prefers to occupy outside the bicyclo[2.2.2]octane framework and hydrogen adds from the less hindered face of the molecule), although molecular mechanics calculations indicated that both rotamers are energetically very similar, in rotamer **B** hydrogenation takes place preferably from the α -face of the molecule due to the steric crowding of the bridgehead methyl (located on the β -face of the molecule), whereas in rotamer **A** it takes

place from the β -face of the molecule as the α -face is blocked by the bicyclic system, leading to the required isomer in a stereoselective manner.

Since the selective hydrogenation of the trisubstituted double bond in the presence of tetrasubstituted double bond in the α,β -unsaturated ester **8** was found to be unsuccessful, it was decided to degrade the isopropylidene group prior to the elaboration of the side chain. As (*S*)-3-methylcarvone (*S*)-**9** resulted in *ent*-seychellene (+)-**1**, for generating (–)-seychellene **1**, the sequence was started with (*R*)-3-methylcarvone (*R*)-**9**, which was prepared using an earlier developed method⁵ via a 1,3-dipolar cycloaddition of diazomethane to (*R*)-carvone **10** followed by thermolysis of the resultant pyrazoline derivative, **Scheme 2**. Generation of the kinetic lithium dienolate of 3-methylcarvone (*R*)-**9** with 1.1 equivalents of lithium hexamethyldisilazide in hexane followed by treatment with 1 equiv of methyl acrylate generated the bicyclic keto ester **11** via tandem intermolecular Michael addition–intramolecular Michael addition sequence.⁶



Scheme 2. Reagents: (a) (i) CH_2N_2 , Et_2O ; (ii) 190°C , $(\text{CH}_2\text{OH})_2$; (b) LiHMDS , hexane, $\text{CH}_2=\text{CHCOOMe}$; (c) PTSA , C_6H_6 ; (d) (i) O_3-O_2 , $\text{MeOH}-\text{CH}_2\text{Cl}_2$; (ii) Me_2S ; (e) $(\text{CH}_2\text{SH})_2$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 ; (f) Raney Ni , EtOH ; (g) $(\text{CH}_2\text{OH})_2$, PTSA , C_6H_6 ; (h) LAH , Et_2O ; (i) PDC , CH_2Cl_2 ; (j) MeMgI , Et_2O ; (k) PCC , NaOAc , CH_2Cl_2 ; (l) $(\text{EtO})_2\text{P(O)CH}_2\text{COOEt}$, NaH , THF ; (m) 10% $\text{Pd}-\text{C}$, H_2 (1 atm), hexane; (n) LAH , Et_2O ; (o) $\text{H}_2\text{O}-\text{AcOH}$ (1:1); (p) MsCl , Py , CH_2Cl_2 ; (q) NaH , THF ; (r) Mg , TiCl_4 , CH_2Cl_2 , THF .

Isomerization of the olefinic bond of the isopropenyl group in the keto ester **11** with a catalytic amount of *p*-toluenesulfonic acid (PTSA) in refluxing benzene furnished the ester **12** in 100% yield. Ozonolysis followed by reductive work-up with dimethyl sulfide transformed keto olefin **12** into dione **13** in 94% yield. In diketone **13**, the C-5 ketone is sterically more crowded than the C-8 ketone, which has been exploited for the selective reductive removal of the C-8 ketone. Thus, reaction of the diketone **13** with 1,2-ethanedithiol and a catalytic amount of boron trifluoride diethyl etherate in methylene chloride furnished the thioketal **14** in 98% yield, which on desulfurization with Raney nickel in refluxing ethanol quantitatively furnished the keto ester **15**. To avoid regiochemical problems, the ketone group in the keto ester **15** was protected as its ketal by reacting with 1,2-ethanediol and *p*-toluenesulfonic acid in refluxing benzene using a Dean–Stark apparatus to furnish the ketal ester **16**. The ester in **16** was then modified into a methyl ketone. Accordingly, reduction of the ester **16** with lithium aluminum hydride (LAH) in diethyl ether furnished the primary alcohol **17**, which on oxidation with pyridinium dichromate (PDC) in methylene chloride generated the aldehyde **18**. Grignard reaction of the aldehyde **18** with methylmagnesium iodide followed by oxidation of the resultant secondary alcohol **19** with pyridinium chlorochromate (PCC) and sodium acetate in methylene chloride furnished the methyl ketone **20**. Horner–Wadsworth–Emmons reaction of the ketone **20** with triethyl phosphonoacetate and sodium hydride in refluxing THF furnished the unsaturated ester **21**. As anticipated, hydrogenation of the α,β -unsaturated ester **21** with 10% palladium over carbon as the catalyst in hexane furnished the saturated ester **22** in a highly stereoselective manner (>95%). Reduction of the ester **22** with LAH furnished the hydroxy ketal **23**, which was transformed into (–)-seychellene employing an intramolecular alkylation strategy. Thus, hydrolysis of the ketal moiety in the hydroxy ketal **23** with aqueous acetic acid followed by mesylation of the resultant hydroxy ketone **24** with methanesulfonyl chloride and pyridine in methylene chloride generated the ketomesylate **25** in 91% yield.

Intramolecular alkylation reaction of the ketomesylate **25** with sodium hydride in refluxing THF furnished norseychellene **26**, whose structure was established by comparing the spectral data with that of the racemic compound reported in the literature. Finally, methylenation of the ketone **26** with methylene chloride–magnesium–titanium chloride⁷ in THF furnished (–)-seychellene **1**, which exhibited ¹H and ¹³C NMR spectral data identical to that reported in the literature^{2c} for the racemic compound.

3. Conclusions

In summary, we have developed an efficient enantiospecific methodology for the stereoselective synthesis of (–)-seychellene **1** starting from (*R*)-carvone **10** via (*R*)-3-methylcarvone **9**. A combination of intermolecular Michael addition–intramolecular Michael addition sequence, a stereoselective hydrogenation, and an intramolecular alkylation reaction was strategically employed for the generation of the tricyclic system containing two vicinal quaternary carbon atoms.

4. Experimental section

4.1. General

Melting points were recorded using a Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Perkin–Elmer 781 and Jasco FTIR 410 spectrophotometers. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were recorded on JNM λ -300 spectrometer. The chemical shifts (δ , parts per million) and coupling constants (hertz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ¹H) or the central line (77.0 ppm) of CDCl₃ (for ¹³C). In the ¹³C NMR, the nature of carbons (C, CH, CH₂, CH₃) was determined by recording the DEPT-135 spectra and is given in parentheses. High-resolution mass spectra were recorded using 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 cm² g^{–1}. Ozonolysis experiment was carried out using Fischer 502 ozone generator. Hydrogenation reaction at 1 atm pressure was carried out using a balloon filled with hydrogen. Thin-layer chromatographies (TLC) were performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Acme's silica gel G containing 13% calcium sulfate as binder and various combinations of ethyl acetate, methylene chloride, and hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapor or anisaldehyde–H₂SO₄ or MeOH–H₂SO₄ spray followed by heating. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

4.2. Methyl (1*R*,2*R*,4*S*,6*S*,8*R*)-8-(1-methylethenyl)-1,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (**11**)

To a cold (–70 °C) magnetically stirred solution of hexamethyldisilazane (3.3 mL, 15.8 mmol) in dry hexane (40 mL) was slowly added a solution of *n*-BuLi (2.5 M in hexane, 5.8 mL, 14.6 mmol) and the reaction mixture was stirred for 15 min at the same temperature. To LiHMDS thus formed was added drop wise a solution of (*R*)-3-methylcarvone **9**⁵ (2.0 g, 12.2 mmol) in dry hexane (16 mL) and the reaction mixture was stirred for 45 min at the same temperature. Methyl acrylate (1.21 mL, 13.4 mmol) was added to the reaction mixture and stirred for 3 h at rt. It was then filtered through a small silica gel column using ethyl acetate–hexane (1:3) as eluent. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the bicyclic adduct **11** (2.0 g, 66%) as oil. $[\alpha]_D^{21}$ –76.8 (c 7.3, CHCl₃); IR (neat): $\nu_{\max}$ /cm^{–1} 3087, 2949, 1740, 1720, 1647, 1458, 1437, 1369, 1217, 1163, 1043, 1024, 897, 848, 760; ¹H NMR (300 MHz, CDCl₃): δ 4.72 (2H, s), 3.69 (3H, s), 2.77 (1H, qd, *J* 7.5 and 1.8 Hz), 2.67 (1H, t, *J* 9.0 Hz), 2.60–2.40 (2H, m), 2.07 (2H, dd, *J* 9.0 and 3.0 Hz), 1.82–1.45 (2H, m), 1.68 (3H, s), 0.99 (3H, d, *J* 7.2 Hz), 0.94 (3H, s); ¹³C NMR (75 MHz, CDCl₃): δ 216.3 (C), 175.1 (C), 146.6 (C), 110.5 (CH₂), 51.5 (CH₃), 46.1 (CH), 45.6 (CH), 45.1 (CH), 43.7

(CH), 37.9 (C), 35.3 (CH₂), 27.9 (CH₂), 22.2 (CH₃), 21.7 (CH₃), 8.5 (CH₃). HRMS, *m/z* calcd for C₁₅H₂₂O₃Na (M+Na): 273.1467; found: 273.1455.

4.3. Methyl (1*R*,2*R*,4*S*,6*S*)-8-(1-methylethylidene)-1,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (12**)**

To a magnetically stirred solution of the keto ester **11** (1.0 g, 4.0 mmol) in benzene (10 mL) was added PTSA (153 mg, 0.8 mmol) and the reaction mixture was refluxed for 1 h. It was then filtered through a short silica gel column using CH₂Cl₂ as eluent. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the keto ester **12** (1.0 g, 100%) as colorless oil. $[\alpha]_D^{21}$ –40.0 (*c* 0.6, CHCl₃); IR (neat): $\nu_{\max}/\text{cm}^{-1}$ 2954, 2936, 2878, 1727, 1453, 1435, 1366, 1302, 1263, 1195, 1163, 1023, 907; ¹H NMR (300 MHz, CDCl₃): δ 3.68 (3H, s), 3.26 (1H, t, *J* 2.7 Hz), 2.69 (1H, qd, *J* 7.5 and 1.8 Hz), 2.52 (1H, dd, *J* 10.5 and 6.9 Hz), 2.29 (1H, d, *J* 16.8 Hz), 2.12 (1H, ddd, *J* 13.5, 7.2, and 2.1 Hz), 2.05–1.85 (2H, m), 1.68 (3H, s), 1.61 (3H, s), 1.01 (3H, s), 0.99 (3H, d, *J* 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 212.9 (C), 174.9 (C), 127.1 (C), 125.2 (C), 51.4 (CH₃), 47.6 (CH), 47.5 (CH), 44.7 (CH), 38.5 (C), 37.5 (CH₂), 27.2 (CH₂), 22.5 (CH₃), 20.3 (CH₃), 19.8 (CH₃), 9.9 (CH₃). HRMS, *m/z* calcd for C₁₅H₂₂O₃Na (M+Na): 273.1467; found: 273.1462.

4.4. Methyl (1*R*,2*R*,4*S*,6*S*)-1,6-dimethyl-5,8-dioxobicyclo[2.2.2]octane-2-carboxylate (13**)**

A pre-cooled (–70 °C) mixture of ozone in oxygen was passed through a cold (–70 °C) solution of the keto olefin **12** (1.0 g, 4.0 mmol) and a catalytic amount of NaHCO₃ in methanol (3 mL) and CH₂Cl₂ (12 mL) until it turns blue (ca. 16 min). The reaction mixture was flushed off with oxygen. Dimethyl sulfide (0.44 mL, 6 mmol) was added to the reaction mixture, then slowly warmed up to rt and magnetically stirred for 5 h. The reaction mixture was diluted with water (8 mL) and extracted with CH₂Cl₂ (3×7 mL). The combined organic layer was washed with brine (8 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the diketone **13** (850 mg, 94%) as a colorless solid, which was recrystallized from a 1:1 mixture of CH₂Cl₂ and hexane. Mp: 86–88 °C; $[\alpha]_D^{20}$ –30.8 (*c* 5.2, CHCl₃); IR (thin film): $\nu_{\max}/\text{cm}^{-1}$ 2971, 2883, 1731, 1455, 1406, 1372, 1304, 1016, 908, 854; ¹H NMR (300 MHz, CDCl₃): δ 3.73 (3H, s), 3.11 (1H, t, *J* 3.3 Hz), 2.87 (1H, qd, *J* 7.5 and 2.4 Hz), 2.77 (1H, dd, *J* 10.5 and 7.2 Hz), 2.42 (1H, d, *J* 19.2 Hz), 2.40–2.20 (2H, m), 2.12 (1H, dd, *J* 19.2 and 2.7 Hz), 1.17 (3H, s), 1.07 (3H, d, *J* 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 206.9 (C), 204.3 (C), 173.5 (C), 62.3 (CH), 51.6 (CH₃), 46.4 (2C, CH and CH₂), 44.9 (CH), 38.7 (C), 25.5 (CH₂), 21.4 (CH₃), 10.1 (CH₃). HRMS, *m/z* calcd for C₁₂H₁₆O₄Na (M+Na): 247.0946; found: 247.0935. Anal. Calcd for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.23%.

4.5. Methyl (1*R*,2*R*,4*R*,6*S*)-1,6-dimethyl-5-oxobicyclo[2.2.2]octane-spiro[8.2']-1,3-dithiolane-2-carboxylate (14**)**

To a cold (0 °C) magnetically stirred solution of the diketone **13** (750 mg, 3.3 mmol) and 1,2-ethanedithiol (0.56 mL, 6.7 mmol) in dry CH₂Cl₂ (5 mL) was added a catalytic amount of BF₃·Et₂O and stirred for 2 h at rt. Aqueous NaOH solution (5%, 2 mL) was added to the reaction mixture and extracted with CH₂Cl₂ (3×6 mL). The combined organic layer was washed with brine (8 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the thioketal **14** (920 mg, 98%) as colorless oil. $[\alpha]_D^{21}$ –75.3 (*c* 9.5, CHCl₃); IR (neat): $\nu_{\max}/\text{cm}^{-1}$ 2932, 1724, 1452, 1435, 1368, 1270, 1222, 1200, 1166, 1030, 1012, 906, 846; ¹H NMR (300 MHz, CDCl₃): δ 3.68 (3H, s), 3.50–3.20 (4H, m), 2.70–2.35 (5H, m), 2.20–2.00 (2H, m), 1.05 (3H, d, *J* 7.5 Hz), 0.93 (3H, s); ¹³C NMR (75 MHz, CDCl₃): δ 211.9 (C), 174.3 (C), 64.7 (C), 55.4 (CH), 51.4 (CH₃), 47.3 (CH₂), 45.6 (CH), 43.8 (CH), 39.6 (2C, CH₂), 38.6 (C), 25.7 (CH₂), 21.7 (CH₃), 10.1 (CH₃). HRMS, *m/z* calcd for C₁₄H₂₀O₃S₂Na (M+Na): 323.0752; found: 323.0760.

4.6. Methyl (1*R*,2*R*,4*R*,6*S*)-1,6-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (15**)**

To a magnetically stirred solution of the thioketal **14** (750 mg, 2.5 mmol) in dry ethanol (5 mL) was added excess of Raney nickel (500 mg) and refluxed for 2 h. The reaction mixture was 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 (1:19) as eluent furnished the keto ester **15** (520 mg, 99%) as colorless oil. $[\alpha]_D^{22}$ –51.1 (*c* 20.0, CHCl₃); IR (neat): $\nu_{\max}/\text{cm}^{-1}$ 2951, 2873, 1724, 1452, 1367, 1212, 1190, 1166, 1044, 1017, 925; ¹H NMR (300 MHz, CDCl₃): δ 3.68 (3H, s), 2.71 (1H, qd, *J* 7.5 and 1.8 Hz), 2.63 (1H, dd, *J* 10.5 and 7.5 Hz), 2.35–2.25 (1H, m), 2.15–1.90 (2H, m), 1.88–1.60 (3H, m), 1.40–1.25 (1H, m), 1.02 (3H, d, *J* 7.5 Hz), 0.93 (3H, s); ¹³C NMR (75 MHz, CDCl₃): δ 217.2 (C), 175.1 (C), 51.4 (CH₃), 46.9 (CH), 45.3 (CH), 41.3 (CH), 38.1 (C), 28.7 (CH₂), 26.7 (CH₂), 24.1 (CH₂), 22.5 (CH₃), 9.1 (CH₃). HRMS, *m/z* calcd for C₁₂H₁₈O₃Na (M+Na): 233.1149; found: 233.1154.

4.7. Methyl (1*R*,2*R*,4*R*,6*S*)-1,6-dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane-2-carboxylate (16**)**

To a magnetically stirred solution of the keto ester **15** (680 mg, 3.6 mmol) in benzene (10 mL) were added 1,2-ethanedithiol (0.4 mL, 7.3 mmol) and PTSA (50 mg, 0.26 mmol) and the reaction mixture was refluxed for 7 h by using Dean–Stark water trap. Satd aq NaHCO₃ solution (4 mL) was added to the reaction mixture and extracted with ether (3×8 mL). The ether extract was washed with brine (8 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the ketal ester **16** (740 mg, 90%) as colorless oil.

$[\alpha]_D^{24}$ –56.7 (*c* 15.8, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 2875, 1732, 1462, 1434, 1381, 1364, 1220, 1194, 1161, 1143, 1052, 951, 927; ^1H NMR (300 MHz, CDCl_3): δ 4.00–3.73 (4H, m), 3.64 (3H, s), 2.48 (1H, qd, *J* 7.2 and 2.7 Hz), 2.34 (1H, t, *J* 9.3 Hz), 2.15–1.50 (5H, m), 1.40–1.25 (1H, m), 1.05–0.92 (1H, m), 0.75 (3H, s), 0.74 (3H, d, *J* 7.2 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 175.4 (C), 112.2 (C), 65.3 (CH_2), 63.2 (CH_2), 50.9 (CH_3), 47.1 (CH), 38.8 (CH), 35.5 (C), 33.0 (CH), 28.0 (CH_2), 26.0 (CH_2), 22.2 (CH_3), 21.7 (CH_2), 7.3 (CH_3). HRMS, *m/z* calcd for $\text{C}_{14}\text{H}_{22}\text{O}_4\text{Na}$ (*M*+*Na*): 277.1416; found: 277.1416.

4.8. (1*S*,2*R*,4*R*,6*S*)-1,6-Dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane-2-methanol (**17**)

To a cold (0 °C) magnetically stirred solution of the ester **16** (510 mg, 2.01 mmol) in dry ether (3 mL) was added LAH (153 mg, 2.0 mmol) and stirred for 30 min at rt. Ethyl acetate (0.5 mL) was added to the reaction mixture to consume the excess LAH. The reaction mixture was then quenched with water (10 mL) and extracted with ether (3×5 mL). The ether extract was washed with brine (3 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the alcohol **17** (450 mg, 99%) as colorless oil. $[\alpha]_D^{22}$ –45.8 (*c* 15.4, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3412, 2934, 2872, 1463, 1380, 1356, 1168, 1148, 1097, 1058, 1039, 949; ^1H NMR (300 MHz, CDCl_3): δ 4.00–3.65 (5H, m), 3.52 (1H, dd, *J* 10.2 and 7.2 Hz), 1.93 (1H, qd, *J* 7.5 and 1.8 Hz), 1.80–1.30 (8H, m), 1.10–0.95 (1H, m), 0.78 (3H, s), 0.77 (3H, d, *J* 7.5 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 112.6 (C), 64.9 (CH_2), 63.6 (CH_2), 62.9 (CH_2), 43.1 (CH), 40.2 (CH), 34.0 (C), 33.2 (CH), 28.8 (CH_2), 26.7 (CH_2), 22.4 (CH_3), 21.7 (CH_2), 7.8 (CH_3). HRMS, *m/z* calcd for $\text{C}_{13}\text{H}_{22}\text{O}_3\text{Na}$ (*M*+*Na*): 249.1467; found: 249.1465.

4.9. (1*S*,2*R*,4*R*,6*S*)-1,6-Dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane-2-carboxaldehyde (**18**)

To a magnetically stirred solution of the primary alcohol **17** (454 mg, 2.0 mmol) in dry CH_2Cl_2 (2 mL) was added PDC (1.5 g, 4.0 mmol) and stirred for 6 h 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 on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the aldehyde **18** (395 mg, 88%) as colorless oil. $[\alpha]_D^{23}$ –54.7 (*c* 2.9, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 2874, 2726, 1717, 1461, 1382, 1355, 1167, 1148, 1101, 1056, 946; ^1H NMR (300 MHz, CDCl_3): δ 9.49 (1H, d, *J* 3.3 Hz), 3.70–3.45 (4H, m), 2.00–1.80 (2H, m), 1.71 (1H, qd, *J* 7.5 and 1.8 Hz), 1.60–1.40 (2H, m), 1.35–1.20 (2H, m), 1.20–1.06 (1H, m), 0.85–0.74 (1H, m), 0.66 (3H, s), 0.54 (3H, d, *J* 6.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 204.5 (CH), 111.8 (C), 65.3 (CH_2), 63.4 (CH_2), 54.2 (CH), 42.2 (CH), 36.1 (C), 32.8 (CH), 28.2 (CH_2), 23.0 (CH_3), 22.0 (CH_2), 21.7 (CH_2), 8.1 (CH_3). HRMS, *m/z* calcd for $\text{C}_{13}\text{H}_{21}\text{O}_3$ (*M*+*H*): 225.1485; found: 225.1495.

4.10. (1*S*,2*R*,4*R*,6*S*)-2-(1-Hydroxyethyl)-1,6-dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane (**19**)

To an ice cold magnetically stirred solution of the aldehyde **18** (520 mg, 2.32 mmol) in anhydrous ether (2 mL) was added a solution of methylmagnesium iodide [freshly prepared from magnesium (111 mg, 4.64 mmol) and methyl iodide (0.4 mL, 6.96 mmol)] in dry ether (5 mL) and stirred for 45 min at the same temperature. The reaction was then quenched with satd aq NH_4Cl solution (2 mL) and extracted with ether (3×7 mL). The combined ether layer was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the secondary alcohol **19** (525 mg, 94%) as oil. $[\alpha]_D^{21}$ –43.8 (*c* 1.5, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3460, 2958, 2931, 2872, 1465, 1378, 1360, 1265, 1148, 1103, 1049, 1062, 946, 742; ^1H NMR (300 MHz, CDCl_3): δ 4.16–4.12 (1H, m), 4.00–3.70 (4H, m), 2.55–2.50 (1H, m), 2.23 (1H, br s), 1.90–1.16 (8H, m), 1.12 (3H, d, *J* 6.6 Hz), 0.85 (3H, s), 0.77 (3H, d, *J* 6.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 112.8 (C), 66.7 (CH), 65.0 (CH_2), 63.0 (CH_2), 46.5 (CH), 40.3 (CH), 35.0 (C), 33.9 (CH), 29.5 (CH_2), 22.8 (CH_3), 22.3 (CH_3), 21.9 (CH_2), 21.3 (CH_2), 8.2 (CH_3). HRMS, *m/z* calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3\text{Na}$ (*M*+*Na*): 263.1623; found: 263.1624.

4.11. 1-[(1*S*,2*R*,4*R*,6*S*)-1,6-Dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolan-2-yl]ethanone (**20**)

To a magnetically stirred suspension of PCC (715 mg, 3.32 mmol) and NaOAc (430 mg, 4.99 mmol) in anhydrous CH_2Cl_2 (3 mL) was added a solution of the secondary alcohol **19** (400 mg, 1.66 mmol) in anhydrous CH_2Cl_2 (2 mL) and stirred vigorously for 3 h at rt. The reaction mixture was then filtered through a small silica gel column and the column was eluted with more CH_2Cl_2 . Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the ketone **20** (337 mg, 85%) as oil. $[\alpha]_D^{20}$ –84.0 (*c* 9.0, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 2873, 1706, 1460, 1358, 1143, 1103, 1064, 947; ^1H NMR (300 MHz, CDCl_3): δ 4.08–3.70 (4H, m), 2.55 (1H, t, *J* 9.3 Hz), 2.46 (1H, q, *J* 7.5 Hz), 2.15 (3H, s), 2.00–1.46 (4H, m), 1.40–1.26 (1H, m), 1.10–0.80 (2H, m), 0.82 (3H, s), 0.73 (3H, d, *J* 7.2 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 211.1 (C), 112.2 (C), 65.3 (CH_2), 63.2 (CH_2), 53.3 (CH), 38.6 (CH), 35.7 (C), 33.3 (CH), 32.4 (CH_3), 28.5 (CH_2), 26.1 (CH_2), 22.4 (CH_3), 21.9 (CH_2), 7.4 (CH_3). HRMS, *m/z* calcd for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{Na}$ (*M*+*Na*): 261.1467; found: 261.1468.

4.12. Ethyl *E*-3-[(1*S*,2*S*,4*R*,6*S*)-1,6-dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane-2-yl]but-2-enoate (**21**)

A suspension of sodium hydride (460 mg, 60% dispersion in oil, 11.5 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in dry THF (2 mL) and cooled in an ice bath. Triethyl phosphonoacetate (2.4 mL, 12.0 mmol) was added drop wise and the reaction mixture was

stirred for 30 min at rt. A solution of ketone **20** (550 mg, 2.31 mmol) in dry THF (2 mL) was added drop wise to the reaction mixture and refluxed for 48 h. The reaction was then quenched by careful addition of satd aq NH_4Cl solution (3 mL) and extracted with ether (3×6 mL). The ether extract was washed with brine (6 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the α,β -unsaturated ester **21** (660 mg, 93%) as oil. $[\alpha]_D^{23}$ –40.2 (*c* 5.0, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2958, 2938, 2874, 1713, 1634, 1461, 1227, 1210, 1143, 1102, 1049, 949, 865; ^1H NMR (300 MHz, CDCl_3): δ 5.75 (1H, s), 4.13 (2H, q, *J* 6.9 Hz), 4.00–3.70 (4H, m), 2.23 (3H, s), 2.30–2.10 (1H, m), 2.00–1.50 (5H, m), 1.44–1.26 (2H, m), 1.29 (3H, t, *J* 6.9 Hz), 1.00–0.90 (1H, m), 0.76 (3H, d, *J* 7.5 Hz), 0.69 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 166.5 (C), 162.1 (C), 118.4 (CH), 112.4 (C), 65.4 (CH_2), 63.3 (CH_2), 59.3 (CH_2), 52.7 (CH), 39.9 (CH), 36.5 (C), 33.8 (CH), 29.6 (CH_2), 27.9 (CH_2), 22.5 (CH_3), 21.9 (CH_2), 19.7 (CH_3), 14.5 (CH_3), 7.9 (CH_3). HRMS, *m/z* calcd for $\text{C}_{18}\text{H}_{28}\text{O}_4\text{Na}$ (*M*+*Na*): 331.1885; found: 331.1881.

4.13. Ethyl (3*S*)-3-[(1*S*,2*S*,4*R*,6*S*)-1,6-dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolan-2-yl]butanoate (22**)**

To a solution of the unsaturated ester **21** (46 mg, 0.14 mmol) in hexane (1 mL) was added activated 10% Pd–C (25 mg) and the reaction mixture was stirred at 1 atm pressure hydrogen atmosphere, created by evacuative displacement of air (balloon), for 4 h. The reaction mixture was passed 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 (1:19) as eluent furnished the saturated ester **22** (46 mg, 100%) as oil. $[\alpha]_D^{23}$ –57.9 (*c* 9.4, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2937, 2873, 1734, 1462, 1381, 1271, 1173, 1151, 1064, 1034, 948; ^1H NMR (300 MHz, CDCl_3): δ 4.11 (2H, q, *J* 7.2 Hz), 4.00–3.70 (4H, m), 2.49 (1H, dd, *J* 13.5 and 3.6 Hz), 2.45–2.25 (1H, m), 2.16 (1H, dd, *J* 13.5 and 11.4 Hz), 2.00 (1H, qd, *J* 7.2 and 1.5 Hz), 1.80–1.30 (7H, m), 1.26 (3H, t, *J* 7.2 Hz), 1.05–0.94 (1H, m), 0.92 (3H, d, *J* 6.6 Hz), 0.84 (3H, s), 0.75 (3H, d, *J* 6.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 173.3 (C), 112.8 (C), 65.4 (CH_2), 63.1 (CH_2), 59.9 (CH_2), 45.4 (CH), 40.5 (CH), 37.2 (CH_2), 35.3 (C), 33.9 (CH), 30.7 (2C, CH and CH_2), 23.6 (CH_2), 21.8 (CH_3), 21.7 (CH_2), 19.4 (CH_3), 14.4 (CH_3), 7.6 (CH_3). HRMS, *m/z* calcd for $\text{C}_{18}\text{H}_{30}\text{O}_4\text{Na}$ (*M*+*Na*): 291.1936; found: 291.1927.

4.14. (3*S*)-3-[(1*S*,2*S*,4*R*,6*S*)-1,6-Dimethylbicyclo[2.2.2]octane-spiro[5.2']-1,3-dioxolane-2-yl]butanol (23**)**

To a cold (0 °C) magnetically stirred solution of the saturated ester **22** (46 mg, 0.14 mmol) in dry ether (1 mL) was added LAH (32 mg, 0.87 mmol) and stirred for 1 h at rt. Ethyl acetate (0.5 mL) was added to the reaction mixture to consume the excess LAH. The reaction was then quenched with water (1 mL) and extracted with ether (3×5 mL). The ether extract was

washed with brine (3 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:3) as eluent furnished the alcohol **23** (38 mg, 98%) as oil. $[\alpha]_D^{22}$ –69.8 (*c* 4.1, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3397, 2929, 2871, 1462, 1265, 1151, 1102, 1056, 947; ^1H NMR (300 MHz, CDCl_3): δ 4.00–3.50 (6H, m), 2.05–1.20 (13H, m), 0.89 (3H, d, *J* 7.2 Hz), 0.81 (3H, s), 0.74 (3H, d, *J* 7.2 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 113.1 (C), 65.3 (CH_2), 63.1 (CH_2), 61.6 (CH_2), 46.1 (CH), 40.6 (CH), 35.4 (C), 34.3 (CH_2), 34.0 (CH), 30.8 (CH_2), 29.9 (CH), 23.4 (CH_2), 21.8 (CH_2), 21.7 (CH_3), 18.8 (CH_3), 7.6 (CH_3). HRMS, *m/z* calcd for $\text{C}_{16}\text{H}_{28}\text{O}_3\text{Na}$ (*M*+*Na*): 333.2042; found: 333.2042.

4.15. (1*R*,3*S*,4*S*,5*S*)-5-[(1*S*)-3-Hydroxy-1-methylpropyl]-3,4-dimethylbicyclo[2.2.2]octan-2-one (24**)**

A solution of the ketal **23** (22 mg, 0.08 mmol) in acetic acid (0.5 mL) and water (0.5 mL) was heated at 60 °C for 1 h. It was then cooled, diluted with 3 N HCl (2 mL), and extracted with CH_2Cl_2 (3×3 mL). The combined organic phase was washed with aq NaHCO_3 (3 mL) and brine (6 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:3) as eluent furnished the keto alcohol **24** (16 mg, 90%) as oil. $[\alpha]_D^{21}$ –27.5 (*c* 0.4, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 3408, 2931, 2871, 1716, 1513, 1462, 1387, 1216, 1053, 829; ^1H NMR (300 MHz, CDCl_3): δ 3.75–3.50 (2H, m), 2.44 (1H, qd, *J* 7.2 and 1.8 Hz), 2.29 (1H, br s), 2.18–2.00 (1H, m), 2.00–1.50 (7H, m), 1.40–1.05 (3H, m), 1.01 (3H, d, *J* 7.2 Hz), 0.97 (3H, s), 0.93 (3H, d, *J* 6.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 219.3 (C), 60.9 (CH_2), 46.6 (CH), 46.4 (CH), 42.6 (CH), 37.9 (C), 34.4 (CH_2), 31.5 (CH_2), 29.7 (CH), 24.7 (CH_2), 23.9 (CH_2), 21.9 (CH_3), 19.2 (CH_3), 9.5 (CH_3). HRMS, *m/z* calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{Na}$ (*M*+*Na*): 247.1674; found: 247.1672.

4.16. (3*S*)-3-[(1*S*,2*S*,4*R*,6*S*)-1,6-Dimethyl-5-oxobicyclo[2.2.2]octan-2-yl]but-1-yl methanesulfonate (25**)**

To an ice cold (0 °C) magnetically stirred solution of the keto alcohol **24** (9 mg, 0.04 mmol) in pyridine (1 mL) and CH_2Cl_2 (0.5 mL) was added methanesulfonyl chloride (0.03 mL, 0.4 mmol) and the reaction mixture was stirred for 45 min at rt. It was then diluted with 2 mL of water and extracted with CH_2Cl_2 (3×2 mL). The organic layer was washed with 3 N HCl (2 mL), satd aq NaHCO_3 solution (2 mL), and brine (5 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:3) as eluent furnished the ketomesylate **25** (11 mg, 91%) as oil. $[\alpha]_D^{21}$ –42.4 (*c* 2.0, CHCl_3); IR (neat): $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 2941, 2874, 1716, 1471, 1354, 1174, 976, 949, 892; ^1H NMR (300 MHz, CDCl_3): δ 4.30–4.10 (2H, m), 2.94 (3H, s), 2.31 (1H, qd, *J* 7.2 and 1.8 Hz), 2.27 (1H, br s), 2.20–2.00 (1H, m), 2.00–1.35 (8H, m), 1.30–1.10 (1H, m), 0.99 (3H, d, *J* 7.5 Hz), 0.95 (3H, d, *J* 7.2 Hz), 0.94 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 218.2 (C), 67.8 (CH_2), 46.7 (CH), 46.3 (CH), 42.6 (CH), 38.0 (C), 37.5 (CH), 31.7 (CH_2),

31.1 (CH₂), 29.8 (CH₃), 24.8 (CH₂), 23.9 (CH₂), 21.9 (CH₃), 18.8 (CH₃), 9.6 (CH₃). HRMS, *m/z* calcd for C₁₅H₂₆O₄Na (M+Na): 325.1450; found: 325.1437.

4.17. (1*R*,3*R*,6*S*,7*S*,8*S*)-3,6,8-Trimethyltricyclo[5.3.1.0^{3,8}]-undecan-2-one (norseychellenone **26**)

A suspension of sodium hydride (20 mg, 60% dispersion in oil, 0.5 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in dry THF (0.5 mL) and cooled in an ice bath. A solution of ketomesylate **25** (15 mg, 0.05 mmol) in THF (1 mL) was added drop wise to the reaction mixture and then it was refluxed for 7 h. The reaction was then quenched by careful addition of satd aq NH₄Cl solution (3 mL) and extracted with ether (3 × 2 mL). The combined ether layer was washed with brine (5 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished norseychellenone **26** (8 mg, 76%) as oil. [α]_D²³ –57.3 (c 1.1, CHCl₃); IR (neat): ν_{max} /cm^{–1} 2952, 2929, 2870, 1718, 1465, 1381, 1366, 1270, 1244, 1152, 1029, 997, 828; ¹H NMR (300 MHz, CDCl₃): δ 2.21 (1H, br s), 2.05–1.85 (1H, m), 1.85–1.51 (8H, m), 1.45–1.23 (3H, m), 0.96 (3H, s), 0.94 (3H, s), 0.80 (3H, d, *J* 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 222.7 (C), 49.1 (C), 43.9 (CH), 42.9 (CH), 37.4 (C), 33.4 (CH₂), 30.6 (CH₂), 29.9 (CH), 26.7 (CH₂), 24.0 (CH₂), 22.8 (CH₂), 20.2 (CH₃), 19.4 (CH₃), 18.6 (CH₃). HRMS, *m/z* calcd for C₁₄H₂₂ONa (M+Na): 229.1568; found: 229.1563.

4.18. (1*R*,3*S*,6*S*,7*S*,8*S*)-3,6,8-Trimethyl-2-methylenetricyclo[5.3.1.0^{3,8}]undecane (seychellene **1**)

To an ice cold suspension of Mg (97 mg, 4.03 mmol) and TiCl₄ (0.11 mL, 1.01 mmol) in CH₂Cl₂ (2 mL) was added drop wise a solution of the ketone **26** (28 mg, 0.13 mmol) in CH₂Cl₂ (1.5 mL) and THF (1 mL), and stirred for 30 min at 0 °C and for 20 min at rt. The reaction mixture was recooled to 0 °C, satd aq potassium carbonate solution (4 mL) was added, and extracted with ether (3 × 4 mL). The ether extract was washed with brine (5 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished (–)-seychellene **1** (21 mg, 86%) as oil. [α]_D²² –70.0 (c 0.3, CHCl₃) {lit.¹ [α]_D –72 (c 0.4, CHCl₃)}; IR (neat): ν_{max} /cm^{–1} 3067, 2954, 2925,

2860, 1642, 1462, 1379, 1366, 883; ¹H NMR (300 MHz, CDCl₃): δ 4.79 (1H, d, *J* 1.5 Hz), 4.58 (1H, d, *J* 1.5 Hz), 2.20 (1H, s), 1.95–1.75 (1H, m), 1.70–1.10 (11H, m), 0.96 (3H, s), 0.83 (3H, s), 0.75 (3H, d, *J* 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 162.4 (C), 103.4 (CH₂), 44.7 (CH), 39.8 (C), 37.6 (CH), 37.2 (CH₂), 35.1 (C), 31.6 (CH₂), 29.9 (CH), 27.7 (CH₂), 26.5 (CH₂), 26.4 (CH₂), 24.9 (CH₃), 20.7 (CH₃), 18.7 (CH₃).

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