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The first enantiospecific total synthesis of (+)-seychellene

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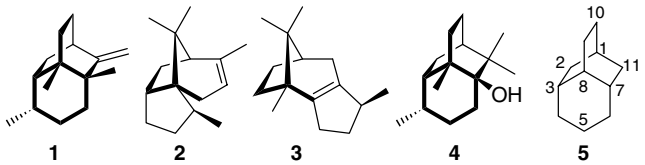
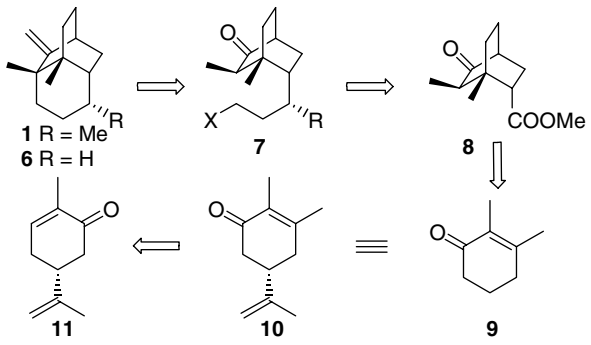
Abstract—The first enantiospecific total synthesis of the tricyclic sesquiterpene (+)-seychellene, starting from (*R*)-carvone via (*S*)-3-methylcarvone, has been accomplished employing a combination of an intermolecular Michael addition–intramolecular Michael addition sequence and an intramolecular alkylation reaction for the generation of the two vicinal quaternary carbon atoms.

The tricyclic sesquiterpene (−)-seychellene **1** was 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-patchoulenes **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 the elegant work of Ourisson and Wolff.[1] The novel structure containing a homoisotwistane carbon framework (tricyclo[5.3.1.$0^{3,8}$]undecane **5**) incorporating two vicinal quaternary carbon atoms, which is structurally and biogenetically closely related to patchouli alcohol **4**, attracted the attention of synthetic chemists, and a number of reports appeared on the synthesis of seychellene **1** in its racemic form.[2] However, so far, there is no report on the enantioselective synthesis of seychellene **1**. In continuation of our interest in the enantiospecific synthesis of tricyclic sesquiterpenes, such as neopupukeananes, pupukeananes, valeriananoids, and patchouli alcohol,[3] starting from the readily available monoterpene (*R*)-carvone, herein, we report an efficient methodology for the enantiospecific synthesis of norseychellene **6** and its extension to the first enantiospecific synthesis of (+)-seychellene **1**.



An intramolecular alkylation reaction of the bicyclic ketone **7** was contemplated for the construction of the tricyclic system containing the two requisite vicinal quaternary carbon atoms, Scheme 1. An intermolecular Michael addition followed by intramolecular addition of the dienolate derived from 2,3-dimethylcyclohexenone **9** to methyl acrylate was conceived for the generation of the bicyclic ester **8**, which could be further elaborated into **7**. Since enone **9** is achiral, 3-methylcarvone **10**, which is readily available from carvone **11**,[4] was identified as a chiral equivalent of enone **9**, with the isopropenyl group serving as a disposable chiral directing group.

Initially, the synthesis of norseychellene **6** was addressed, Scheme 2. Thus, generation of the kinetic lithium dienolate of 3-methylcarvone **10** with 1.1 equiv of lithium hexamethyldisilazide in hexane followed by treatment with 1 equiv of methyl acrylate generated the bicyclic ketoester **12**, $[\alpha]_D^{23}$ +82.3 (*c* 9, $CHCl_3$), via



Scheme 1.

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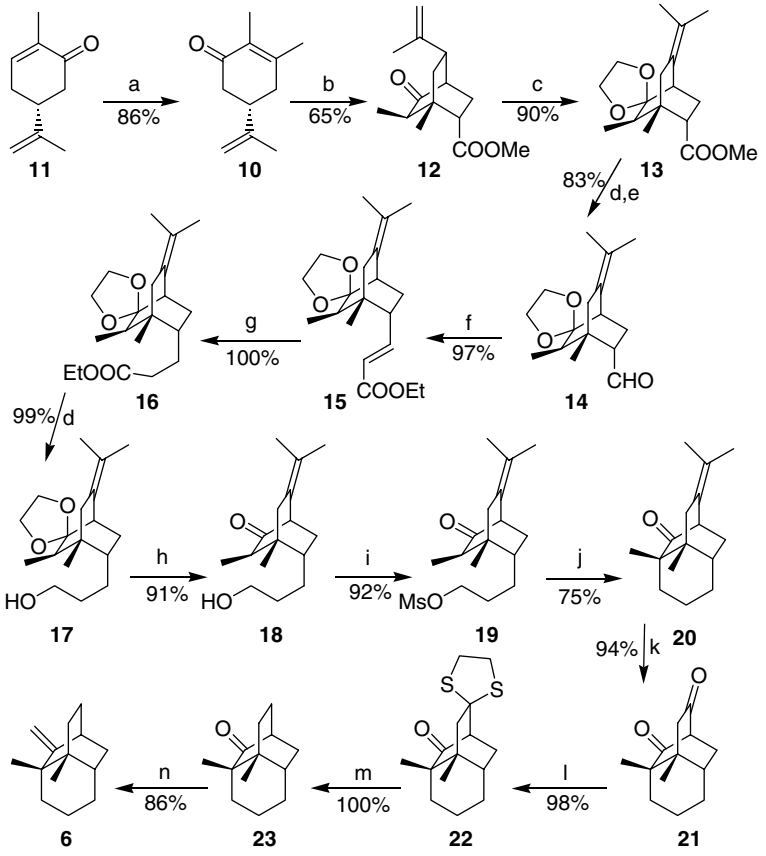
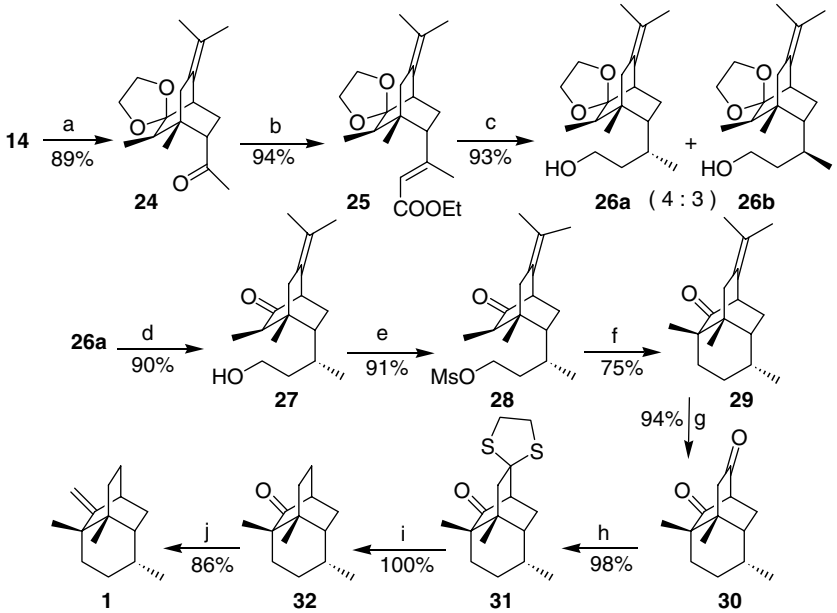
a tandem intermolecular Michael addition–intramolecular Michael addition sequence.[5] Simultaneous protection of the ketone and isomerisation of the olefin bond of the isopropenyl group in keto ester **12** with 1,2-ethanediol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) in refluxing benzene under Dean-Stark conditions furnished ketal ester **13** in 90% yield. Ester **13** was then converted into aldehyde **14** employing a reduction–oxidation protocol in 83% yield. Horner–Wadsworth–Emmons reaction of aldehyde **14** with triethyl phosphonoacetate and sodium hydride in THF furnished α,β-unsaturated ester **15**, in 97% yield, $[\alpha]_D^{24}$ +62.5 (*c* 13.5, $CHCl_3$). Regioselective hydrogenation of the disubstituted olefin in **15** using 10% palladium on charcoal as the catalyst generated ester **16**, which on reduction with lithium aluminium hydride (LAH) furnished primary alcohol **17**, in 99% yield. Next, attention was turned towards the construction of the third ring via an intramolecular alkylation reaction. Hydrolysis of the ketal in **17** with aqueous acetic acid followed by treatment of the resultant hydroxyketone **18** with methanesulfonyl chloride and pyridine in methylene chloride furnished ketomesylate **19** in 84% yield (2 steps). Intramolecular alkylation of ketomesylate **19** with sodium hydride in refluxing THF furnished the tricyclic ketone† **20**, in 75% yield, whose structure was established from its spectral data. Ozonolysis followed by reductive work-up with dimethyl sulfide transformed ketoolefin **20** into dione **21** in 94% yield. In diketone **21**, the C-2 ketone is more sterically crowded than the C-10 ketone, and this property was exploited for the selective reductive removal of the C-10 ketone. Thus, reaction of diketone **21** with 1,2-ethanedithiol and a catalytic amount of boron trifluoride diethyl etherate in methylene chloride furnished thioketal **22** in 98% yield, which on desulfurisation with Raney nickel in refluxing ethanol quantitatively furnished bis-norseychellenone **23**. Since the conventional Wittig reaction was unsuccessful, methylenation was carried out employing the conditions developed by Yan and co-workers.[6] Accordingly, reaction of ketone **23** with methylene chloride–magnesium–titanium chloride in THF gave norseychellene† **6** in 86% yield, whose structure was established from its spectral data.

After successfully accomplishing the enantiospecific synthesis of norseychellene **6** (obtained from *R*-carvone in 16 steps with an average yield of 91% in each step), the methodology was extended to the first enantiospecific total synthesis of (+)-seychellene **1** employing aldehyde **14** as the starting material, Scheme 3. The requisite methyl group was introduced by converting aldehyde **14** into ketone **24**, $[\alpha]_D^{24}$ +120.2 (*c* 11.4, $CHCl_3$), in 89% yield, employing a Grignard reaction–oxidation protocol. Horner–Wadsworth–Emmons reaction of ketone **24** with triethyl phosphonoacetate and sodium hydride in refluxing THF furnished the unsaturated ester **25**. Since, selective hydrogenation of the olefin in **25** was found to be inefficient, a one step, one electron transfer methodology was adopted for the direct conversion of the unsaturated ester **25** into the primary alcohol **26**. Accordingly, treatment of the unsaturated ester **25** with lithium in liquid ammonia furnished a 4:3 diastereomeric mixture of the primary alcohols **26a**, $[\alpha]_D^{24}$ +65.5 (*c* 14, $CHCl_3$), and **26b**, $[\alpha]_D^{24}$ +68.5 (*c* 2.7, $CHCl_3$), which were separated by column chromatography on silica gel. On the basis of thermodynamic considerations, the *R*-configuration was assigned tentatively to the newly created chiral centre in the major isomer **26a**, which was later confirmed by its conversion to seychellene **1**. The same sequence, as that used for norseychellene **6**, was continued with the major isomer **26a**. Thus, hydrolysis of the ketal moiety in hydroxyketal **26a** with aqueous acetic acid followed by mesylation of the resultant hydroxyketone **27** with methanesulfonyl chloride and pyridine in methylene chloride generated ketomesylate **28**, $[\alpha]_D^{23}$ +54.7 (*c* 3.6, $CHCl_3$), in 91% yield. Intramolecular alkylation reaction of ketomesylate **28** with sodium hydride in refluxing THF furnished the tricyclic ketone† **29** in 75% yield, which on ozonolysis gave dione **30** in 94% yield. Regioselective thioketalisation of dione **30**, followed by Raney nickel mediated desulfurisation of thioketal **31** in refluxing ethanol furnished norseychellenone† **32**, whose structure was established by comparing the spectral data with that of the racemic compound reported in the literature. Finally, methylenation of ketone **32** with methylene chloride–magnesium–titanium chloride in THF furnished (+)-seychellene **1**, $[\alpha]_D^{23}$ +27.6 (*c* 1.7, $CHCl_3$), which exhibited ^1H and ^{13}C NMR spectral data virtually identical to that reported in the literature[2e] for the racemic compound.

† Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and HRMS) consistent with their structures. Selected spectral data for tricyclic ketone **20**: $[\alpha]_D^{21}$ +52 (*c* 3, $CHCl_3$); IR (neat): ν_{max} 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 3.15 (1H, s), 2.32 (1H, d, *J* 17.1 Hz), 1.90–1.81 (2H, m), 1.61 (3H, s), 1.54 (3H, s), 1.73–1.47 (4H, m), 1.40–1.13 (4H, m), 0.95 (3H, s), 0.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 218.2 (C), 126.1 (C), 125.7 (C), 49.5 (C), 49.2 (CH), 39.1 (CH_2), 37.2 (C), 37.1 (CH), 32.4 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 20.2 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.6 (CH_3), 18.4 (CH_2); HRMS: *m/z* calcd for $C_{16}H_{24}ONa$ (M+Na): 255.1725; found: 255.1722. For norseychellene **6**: $[\alpha]_D^{25}$ +20.9 (*c* 2.1, $CHCl_3$); IR (neat): ν_{max} 1639, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.81 and 4.60 (2H, 2 × d, *J* 1.5 Hz), 2.22 (1H, br s), 1.82–1.04 (13H, m), 0.97 (3H, s), 0.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4 (C), 103.5 (CH_2), 40.2 (C), 38.4 (CH), 37.8 (CH), 36.3 (CH_2), 34.1 (C), 32.2 (CH_2), 31.4 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 25.3 (CH_3), 20.4 (CH_3), 18.0 (CH_2). For the tricyclic ketone **29**: $[\alpha]_D^{21}$ +76.0 (*c* 3.5, $CHCl_3$); IR (neat): ν_{max} 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 3.19 (1H, t, *J* 3.0 Hz), 2.38 (1H, d, *J* 17.1 Hz), 2.10–1.88 (2H, m), 1.80–1.50 (5H, m), 1.67 (3H, s), 1.60 (3H, s), 1.40 (1H, dd, *J* 13.8 and 4.5 Hz), 1.35–1.18 (1H, m), 1.02 (3H, s), 0.86 (3H, s), 0.81 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 218.3 (C), 126.0 (C), 125.5 (C), 49.1 (C), 48.9 (CH), 43.4 (CH), 39.3 (CH_2), 38.3 (C), 33.2 (CH_2), 29.9 (CH_3), 26.8 (CH_2), 23.3 (CH_2), 20.1 (2C, CH_3), 19.7 (CH_3), 19.6 (CH_3), 18.9 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{27}O$ (M+H): 247.2062; found: 247.2071. For norseychellenone **32**: $[\alpha]_D^{22}$ +38.1 (*c* 2.7, $CHCl_3$); IR (neat): ν_{max} 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.21 (1H, br s), 2.05–1.85 (1H, m), 1.85–1.50 (8H, m), 1.45–1.23 (3H, m), 0.96 (3H, s), 0.94 (3H, s), 0.80 (3H, d, *J* 6.9 Hz *sec*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 222.7 (C), 49.1 (C), 43.9 (CH), 42.9 (CH), 37.4 (C), 33.4 (CH_2), 30.6 (CH_2), 29.9 (CH), 26.8 (CH_2), 24.0 (CH_2), 22.8 (CH_2), 20.2 (CH_3), 19.4 (CH_3), 18.6 (CH_3); HRMS: *m/z* calcd for $C_{14}H_{22}ONa$ (M+Na): 229.1568; found: 229.1563.



Scheme 2. Reagents and conditions: (a) (i) MeMgI, Et_2O, 0 °C → rt, 45 min; (ii) PCC, silica gel, CH_2Cl_2, 6 h; (b) LiHMDS, hexane, CH_2=CHCOOMe, −70 °C → rt, 3 h; (c) $(CH_2OH)_2$, PTSA, C_6H_6, reflux, 4 h; (d) LAH, Et_2O, 0 °C → rt, 0.5 h; (e) PCC, NaOAc, CH_2Cl_2, rt, 0.5 h; (f) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 0 °C → rt, 0.5 h; (g) 10% Pd–C, H_2 (1 atm), hexane, 4 h; (h) H_2O–AcOH (1:1), 60 °C, 1 h; (i) MsCl, py, CH_2Cl_2, 0 °C → rt, 0.5 h; (j) NaH, THF, reflux, 6 h; (k) (i) O_3/O_2, MeOH:CH_2Cl_2 (1:4), −70 °C; (ii) Me_2S, 6 h; (l) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 1 h; (m) Raney Ni, EtOH, reflux, 2 h; (n) Mg, $TiCl_4$, CH_2Cl_2, THF, 0 °C → rt, 1 h.



Scheme 3. Reagents and conditions: (a) (i) MeMgI, Et_2O, 0 °C → rt, 0.75 h; (ii) PCC, NaOAc, CH_2Cl_2, 0.5 h; (b) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, reflux, 48 h; (c) Li, liq. NH_3, THF, EtOH, −33 °C, 0.5 h; (d) H_2O–AcOH (1:1), 60 °C, 1 h; (e) MsCl, py, CH_2Cl_2, 0 °C → rt, 0.75 h; (f) NaH, THF, reflux, 6 h; (g) (i) O_3/O_2, MeOH:CH_2Cl_2 (1:4), −70 °C; (ii) Me_2S, 6 h; (h) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 1 h; (i) Raney Ni, EtOH, reflux, 2 h; (j) Mg, $TiCl_4$, CH_2Cl_2, THF, 0 °C → rt, 1 h.

In summary, we have developed an efficient enantiospecific methodology for the synthesis of norseychellene (+)-**6**, and extended it to the first enantiospecific total synthesis of *ent*-seychellene (+)-**1** starting from (*R*)-carvone via (*S*)-3-methylcarvone. A combination of an intermolecular Michael addition–intramolecular Michael addition sequence and an intramolecular alkylation reaction was strategically employed for the generation of the tricyclic system containing two vicinal quaternary carbon atoms. Since the conversion of (*R*)-carvone to (*R*)-3-methylcarvone is also known,[4] the present sequence is also applicable to (−)-seychellene.

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