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An enantiospecific total synthesis of (−)-patchouli alcohol

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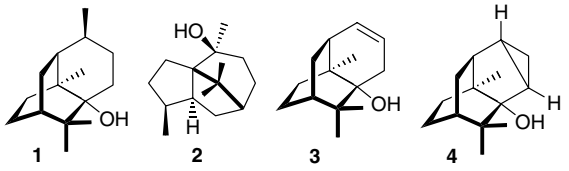
Abstract—An enantiospecific total synthesis of patchouli alcohol, starting from the readily available monoterpene (*R*)-carvone, has been accomplished. A tandem double Michael reaction–alkylation sequence and single electron mediated 6-*endo* trig cyclisation reaction have been employed as key steps.

1. Introduction

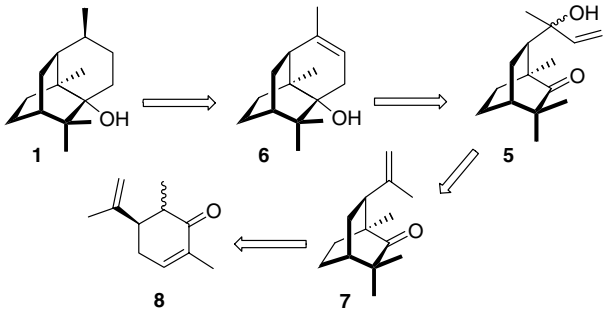
Patchouli oil is an important material in the perfume industry. Several species of the Labiatae family with patchouli-like odour grow in the tropics, but only the *Pogostemon patchouli* pellet is utilised for the commercial distillation of the oil. The scent of the essential oil is partly due to patchouli alcohol **1**, first isolated in its crystalline form by Gal in 1869[1] and formulated as $C_{15}H_{26}O$ by Montgolfier. Early structural investigations[2] established that patchouli alcohol is a saturated tricyclic tertiary alcohol. Initially, structure **2** was proposed for patchouli alcohol by Buchi et al.[3] on the basis of degradative studies, and later it was found to be incorrect. Finally, the structure of the patchouli alcohol **1** was established by single crystal X-ray diffraction analysis of patchouli alcohol diester of chromic acid.[4] Isolation and structure elucidation of norpatchouli alcohol **3**,[5] which also has the odour of patchouli oil, was reported by Teisseire et al. It is generally believed that the odour of the patchouli oil is mainly due to norpatchouli alcohol **3** and a closely related norsesquiterpene alcohol **4**.[6]



The presence of an interesting tricyclic carbon framework incorporating three contiguous quaternary carbon atoms and five stereogenic centres, coupled with its commercial importance and potential biological properties have made patchouli alcohol **1** an interesting and challenging synthetic target. Contrary to the several approaches reported[7] for the synthesis of racemic patchouli alcohol (±)-**1**, there are only two reports[8] in the literature on the enantiospecific total synthesis of **1**. In continuation of our work on the synthesis of sesquiterpenes containing tricyclic carbon framework,[9] we herein report an enantiospecific total synthesis of (−)-patchouli alcohol **1**.

2. Results and discussion

The retrosynthetic analysis of patchouli alcohol **1** is depicted in Scheme 1. On the basis of the methodology used by Bertrand et al.[7c] in their synthesis of racemic



Scheme 1.

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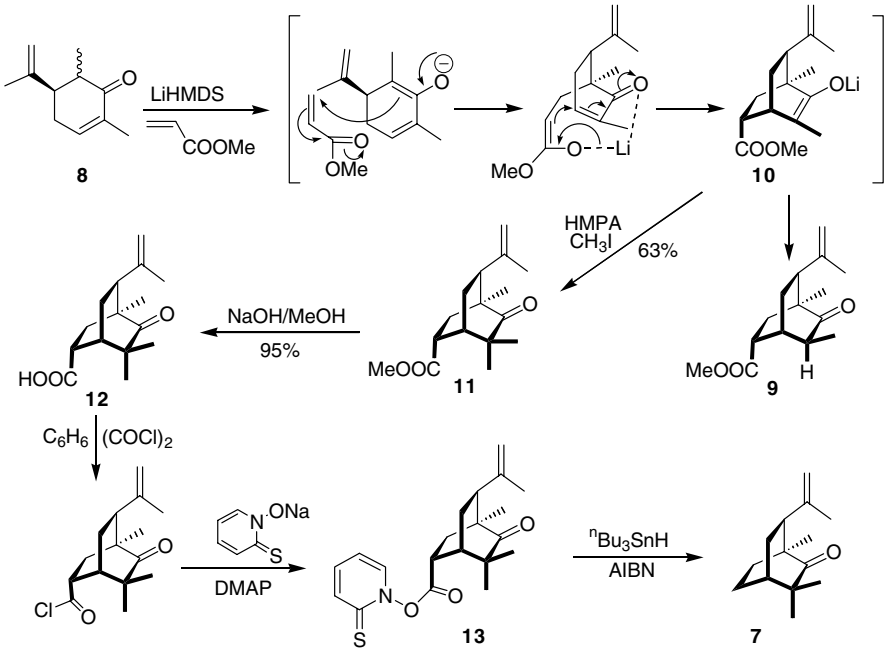
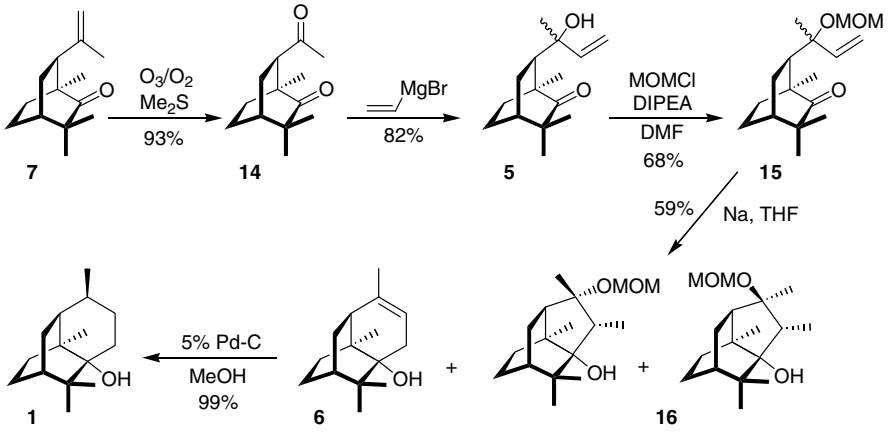
patchouli alcohol (±)-**1**, a single electron transfer mediated cyclisation of the tertiary allyl alcohol **5** (or its derivative) was chosen for the generation of tricyclic tertiary alcohol **6**. The isopropenyl group in the bicyclo[2.2.2]octanone **7** was considered the equivalent of an acetyl group. For the generation of the bicyclo-[2.2.2]octanone **7** containing a methyl group at the C-1 position and two methyl groups at the C-3 position and isopropenyl group with proper stereochemistry, it was contemplated that an intermolecular Michael addition followed by intramolecular Michael addition of 6-methylcarvone **8** with methyl acrylate could be explored,[9,10] followed by reductive decarboxylation of the resultant ester.

The synthetic sequence starting from 6-methylcarvone[11] **8** is depicted in Schemes 2 and 3. It was reasoned that in the tandem[12] intermolecular Michael addition followed by intramolecular Michael addition reaction of 6-methylcarvone **8** with methyl acrylate (**8**→**9**), instead of protonation to quench the final enolate **10**, methylation would lead directly to the trimethyl compound **11**. Thus, the reaction of 6-methylcarvone **8** with LiHMDS in hexane at −10 °C, followed by treatment of the resultant kinetic dienolate with 1.1 equivalents of methyl acrylate generated the lithium enolate **10** of 5-oxobicyclo-[2.2.2]octanoate **9** via intermolecular Michael addition followed by intramolecular Michael addition, which on alkylation with methyl iodide in HMPA at ice temperature for twelve hours, furnished bicyclic ketoester **11** in 63% yield. The structure of adduct **11** was established from its spectral data. The stereochemistry of the ester group in ketoester **11** was assigned on the basis of the expected interaction of the lithium cation with the ester enolate and the enone moieties during the intramolecular Michael reaction. Before addressing the construction of



Scheme 2.



Scheme 3.

the third ring of patchouli alcohol **1**, the ester group in the bicyclic ketoester **11** was degraded. For the reductive removal of the ester moiety in ketoester **11**, Barton's decarboxylation methodology[13] was chosen. Accordingly, the hydrolysis of ester **11** with sodium hydroxide in refluxing aqueous methanol furnished acid **12**. Reaction of acid **12** with oxalyl chloride in dry benzene at room temperature for 2 h, followed by treatment of the resultant acid chloride with sodium salt of 1-hydroxypyridine-2-thione and a catalytic amount of DMAP in refluxing dry benzene for one hour generated ester **13**. Treatment of the ester **13** with tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing benzene for 5 h furnished the bicyclic ketone **7**.

Oxidative cleavage of the isopropenyl group with ozone in methanol–methylene chloride followed by reductive work up with dimethyl sulfide generated dione **14** in 93% yield. Dione **14** was then transformed into patchouli alcohol (−)-**1** by employing the same procedure, which was used[7c] for the synthesis of racemic (±)-**1**. Thus, the reaction of dione **14** with vinylmagnesium bromide at ice temperature for one hour furnished a 3:2 epimeric mixture of the tertiary allyl alcohol **5** in a highly regioselective manner, in 82% yield. Reaction of the tertiary allyl alcohol **5** with methoxymethyl chloride and diisopropylethylamine (DIPEA) in DMF at ice temperature for sixteen hours gave the MOM ether **15** in 68% yield. Treatment of MOM ether **15** with sodium in refluxing THF for sixteen hours furnished a ≈1:1:1 mixture of the tricyclic alcohol **6** and two diastereomeric isotwistanols **16**, whose structures were established from their spectral data.[14] Isotwistanols **16** were obviously formed via 5-*exo* trig cyclisation of the radical anion formed by electron transfer to the ketone in **5**. Finally, stereocontrolled hydrogenation of the trisubstituted olefin in **5** with 10% palladium on activated charcoal as the catalyst in methanol at room temperature for 12 h furnished patchouli alcohol **1** in 99% yield, in a highly stereoselective manner, which exhibited the ^{1}H and ^{13}C NMR spectral data identical to that of the authentic sample reported[15] by Takeya and Itakawa. The specific rotation of the synthetic sample, $[\alpha]_D^{25} = -121.8$ (*c* 2.3, $CHCl_3$) [lit.[15] −118.1 (*c* 1.88, $CHCl_3$)], was in good agreement with that of the natural compound.

3. Conclusion

In conclusion, we have accomplished an enantiospecific total synthesis of the natural enantiomer of patchouli alcohol **1**. A tandem intermolecular Michael reaction-intramolecular Michael reaction–alkylation sequence and a 6-*endo* trig cyclisation initiated by a single electron transfer has been employed as key steps.

Experimental

Melting points were recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Jasco FT-IR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on JNM λ-300 spectrometer. Chemical shifts (δ ppm) and coupling constants (hertz) 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). Samples were prepared in a 1:1 mixture of $CDCl_3$ and CCl_4. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 spectrum and is given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GC–MS 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 ionisation mode. Microanalyses were carried out on a Carlo Erba 1106 CHN analyser. 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. For generating dry ozone, oxygen gas was passed through a cold (−70 °C) trap prior to passing into ozonator. Hydrogenation reactions at one atmospheric pressure were carried out using a balloon filled with hydrogen. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). All small-scale dry reactions were carried out using standard syringe-septum technique.

4.1. (−)-(1*S*,2*R*,4*S*,8*S*)-8-Isopropenyl-4,6,6-trimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid methyl ester 11

To a cold (−10 °C) magnetically stirred solution of hexamethyldisilazane (0.82 ml, 3.96 mmol) in dry hexane (12 ml) was slowly added a solution of ^{n}BuLi (1.85 M in hexane, 1.98 ml, 3.6 mmol) and the reaction mixture stirred for 15 min. To the LiHMDS thus formed was added dropwise, a solution of 6-methylcarvone[11] **8** (500 mg, 3.05 mmol) in dry hexane (2 ml) and the reaction mixture stirred for 45 min at the same temperature. The enolate was treated with methyl acrylate (0.30 ml, 3.35 mmol) and stirred for 4 h at room temperature. It was then recooled to 0 °C and HMPA (0.95 ml) added, followed by methyl iodide (0.95 ml, 15.24 mmol) and stirred for 12 h at room temperature. The reaction mixture was diluted with water (10 ml) and 3 M aqueous HCl (10 ml), and extracted with ether (3 × 10 ml). The organic layer was washed with brine and dried over Na_2SO_4. 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** (507 mg, 63%) as oil. $[\alpha]_D^{23} = -96.6$ (*c* 3.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1731, 1715, 1642, 895. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.71 (1H, s) and 4.65 (1H, s) [C=CH_2], 3.69 (3H, s, OCH_3), 2.78 (1H, t, *J* 9.9 Hz), 2.46 (1H, t, *J* 9.6 Hz), 2.40 (1H, br s), 2.14 (1H, dd, *J* 14.6 and 9.0 Hz), 2.00–1.75 (3H, m), 1.49 (3H, s, olefinic CH_3), 1.16 (3H, s), 0.98 (3H, s) and 0.90 (3H, s) [3 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 219.8 (C, C-2), 174.9 (C, OC=O), 145.9 (C, *C*=CH_2), 114.1 (CH_2, C=*C*H_2), 51.8 (CH_3, OCH_3), 51.0 (CH), 46.5 (C), 46.0 (C), 41.0 (CH), 40.9 (CH), 35.4 (CH_2), 30.4 (CH_2), 25.8 (CH_3), 23.7 (CH_3),

19.6 (CH_3), 18.2 (CH_3). Mass: *m*/*z* 264 (M^+, 50%), 177 (28), 163 (70), 135 (55), 133 (88), 123 (60), 121 (75), 109 (75), 107 (100), 96 (70), 93 (72), 91 (65). HRMS: *m*/*z* Calcd for $C_{16}H_{24}O_3Na$ (M+Na): 287.1623. Found: 287.1622.

4.2. (−)-(1*S*,4*R*,6*S*)-6-Isopropenyl-1,3,3-trimethylbicyclo-[2.2.2]octan-2-one 7

A magnetically stirred solution of the keto ester **11** (59 mg, 0.22 mmol) in methanol (2 ml) and 10% aqueous NaOH (2 ml) was refluxed for 8 h. The reaction mixture was cooled to room temperature and washed with CH_2Cl_2 (10 ml). Then, the aqueous layer was acidified with 3 M HCl and extracted with CH_2Cl_2 (3 × 3 ml). The CH_2Cl_2 extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent furnished acid **12** (52 mg, 93%) as oil.

To a magnetically stirred solution of acid **12** (52 mg, 0.21 mmol) in dry benzene (2 ml) at 0 °C was added oxalyl chloride (0.09 ml, 1.04 mmol) and stirred for 2 h at room temperature. Evaporation of the solvent and excess oxalyl chloride under reduced pressure afforded the acid chloride, which was taken in dry benzene (2 ml) and added to a benzene (2 ml) solution of 2-thiopyridine-1-oxide sodium salt (46 mg, 0.31 mmol) and a catalytic amount of DMAP and the reaction mixture was refluxed for 1 h. To the thus formed ester **13** was added dropwise a solution of tributyltin hydride (0.33 ml, 1.25 mmol) and a catalytic amount of AIBN in dry benzene (3 ml) over a period of 5 min and the reaction mixture was then refluxed for 5 h. A solution of 1% aqueous ammonia solution was added to the reaction mixture and extracted with ether (3 × 5 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:30) as eluent furnished the bicyclic ketone **7** (20 mg, 47%) as oil. $[\alpha]_D^{24} = -51.2$ (*c* 4.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1713, 1641, 892. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.67 (1H, s) and 4.61 (1H, s) [C=CH_2], 2.47 (1H, dd, *J* 10.8 and 8.4 Hz), 2.05–1.88 (1H, m), 1.90–1.48 (6H, m), 1.51 (3H, s, olefinic CH_3), 1.15 (3H, s), 1.14 (3H, s) and 0.84 (3H, s) [3 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 221.6 (C, C=O), 146.8 (C, *C*=CH_2), 113.3 (CH_2, C=*C*H_2), 51.4 (CH, C-6), 46.2 (C), 45.6 (C), 38.3 (CH, C-4), 33.5 (CH_2), 29.9 (CH_2), 26.0 (CH_3), 23.4 (CH_3), 22.3 (CH_2), 19.9 (CH_3), 18.5 (CH_3). Mass: *m*/*z* 206 (M^+, 74%), 191 (24), 181 (16), 163 (23), 149 (16), 135 (65), 134 (60), 121 (52), 119 (47), 110 (88), 107 (100), 96 (88), 95 (80), 93 (93), 91 (57). HRMS: *m*/*z* Calcd for $C_{14}H_{22}ONa$ (M+Na): 229.1568. Found: 229.1577.

4.3. (−)-(1*S*,4*R*,6*R*)-6-Acetyl-1,3,3-trimethylbicyclo-[2.2.2]octan-2-one 14

Dry ozone in oxygen was passed through a cold (−70 °C) solution of enone **7** (100 mg, 0.48 mmol) and a catalytic amount of $NaHCO_3$ in methanol (2 ml) and CH_2Cl_2 (8 ml) until the solution became blue (ca. 4 min). The reaction mixture was flushed off with oxygen and dimethyl sulfide (0.17 ml, 2.43 mmol) was added to the reaction mixture. It was then slowly warmed up to rt and magnetically stirred at room temperature for 10 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the diketone **14** (94 mg, 93%), which was recrystallised from a mixture of CH_2Cl_2 and hexane. Mp: 77–79 °C [lit. 74–75 °C]. $[\alpha]_D^{23} = -44.0$ (*c* 5.2, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1718. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.92 (1H, dd, *J* 10.8 and 7.5 Hz, H-6), 2.09 (3H, s, CH_3C=O), 1.99 (1H, br s), 1.90–1.80 (2H, m), 1.75–1.45 (4H, m), 1.13 (3H, s), 1.10 (3H, s) and 0.87 (3H, s) [3 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 217.7 (C, C=O), 209.4 (C=O), 54.7 (CH, C-6), 45.7 (C), 44.2 (C), 38.2 (CH, C-4), 31.9 (CH_2), 31.1 (CH_3), 27.4 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.5 (CH_2), 18.8 (CH_3). Mass: *m*/*z* 208 (M^+, 30%), 165 (48), 149 (32), 137 (95), 123 (45), 121 (52), 109 (53), 108 (50), 107 (45), 95 (100), 93 (85). HRMS: *m*/*z* Calcd for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361. Found: 231.1367. Anal. for $C_{13}H_{20}O_2$ Calcd: C, 74.60; H, 9.68. Found: C, 74.50; H, 9.52.

4.4. (1*S*,4*R*,6*R*)-6-(2-Hydroxybut-3-en-2-yl)-1,3,3-trimethylbicyclo[2.2.2]octan-2-one 5

To a cold (0 °C) magnetically stirred solution of diketone **14** (140 mg, 0.67 mmol) in dry THF (1 ml) was added a solution of vinylmagnesium bromide [prepared from Mg (81 mg, 3.36 mmol) and vinyl bromide (0.38 ml, 5.38 mmol) in dry THF (4 ml)] and stirred for 1 h at the same temperature. The reaction was quenched with aqueous NH_4Cl solution and extracted with ether (3 × 4 ml). The organic layer was washed with 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 (1:10) as eluent furnished a ~1:2 epimeric mixture of the tertiary allyl alcohol **5** (130 mg, 82%) as oil. $[\alpha]_D^{23} = -65.8$ (*c* 3.6, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3489, 1712, 918. ^1H NMR (300 MHz, $CDCl_3$+CCl_4, 1:2 mixture of diastereomers): δ 5.92 and 5.80 (1H, dd, *J* 17.1 and 10.8 Hz, C*H*=CH_2), 5.19 and 5.14 (1H, d, *J* 10.8 Hz), 5.05 and 4.98 (1H, d, *J* 17.1 Hz) [CH=CH_2], 2.05–1.85 (2H, m), 1.83–1.40 (7H, m), 1.24 and 1.15 (3H, s), 1.14 and 1.03 (3H, s), 1.10 (3H, s) and 1.08 (3H, s) [4 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, 1:2 mixture of diastereomers): δ 222.4 and 221.4 (C, C=O), 146.7 and 142.8 (CH, *C*H=CH_2), 113.7 and 111.2 (CH_2, CH=*C*H_2), 76.4 and 76.3 (C, C–OH), 51.5 (CH), 46.7 (C), 45.8 and 45.7 (C), 38.0 and 37.9 (CH), 35.0 and 34.6 (CH_2), 28.1 and 27.5 (CH_2), 26.7 and 26.6 (CH_3), 26.0 and 25.7 (CH_3), 23.4 (CH_3), 22.0 and 21.9 (CH_2), 21.6 and 20.9 (CH_3). HRMS: *m*/*z* Calcd for $C_{15}H_{24}O_2Na$ (M+Na): 259.1674. Found: 259.1677.

4.5. (1*S*,4*R*,6*R*)-6-[2-(Methoxymethyloxy)but-3-en-2-yl]-1,3,3-trimethylbicyclo[2.2.2]octan-2-one 15

To a cold (0 °C) magnetically stirred solution of the tertiary allyl alcohol **5** (148 mg, 0.63 mmol) in dry DMF

(1.5 ml), methoxymethyl chloride (0.33 ml, 4.39 mmol) and a catalytic amount of DMAP was added slowly DIPEA (0.75 ml, 4.39 mmol). The reaction mixture was stirred for 16 h at room temperature. It was then diluted with water and extracted with CH_2Cl_2 (3×5 ml). The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished an epimeric mixture of the ether **15** (120 mg, 68%) as oil. $[\alpha]_D^{23} = -74.9$ (*c* 5.5, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1714, 921. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.71 (dd, *J* 17.7 and 11.1 Hz) and 5.66 (dd, *J* 17.4 and 10.8 Hz) [1H, C*H*=CH_2], 5.25 (dd, *J* 10.8 and 1.2 Hz) and 5.16 (dd, *J* 11.1 and 1.2 Hz) [1H, CH=C*H*$_2$], 5.14 (dd, *J* 17.4 and 1.2 Hz) and 5.06 (dd, *J* 17.7 and 1.2 Hz) [1H, CH=C*H*$_2$], 4.62 and 4.60 (1H, d, *J* 6.9 Hz) and 4.45 and 4.30 (1H, d, *J* 6.9 Hz) [OCH_2O], 3.33 and 3.31 (3H, s, OCH_3), 2.23–1.95 (1H, m), 1.95–1.85 (1H, m), 1.77–1.34 (6H, m), 1.23 and 1.14 (3H, s), 1.13 and 1.10 (3H, s), 1.09 and 1.08 (3H, s), 1.07 and 1.05 (3H, s) [$4 \times$ *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 221.4 and 221.1 (C, C=O), 142.9 and 140.2 (CH, *C*H=CH_2), 117.8 and 115.1 (CH_2, CH=*C*H_2), 91.7 and 91.3 (CH_2, OCH_2O), 82.7 and 82.3 (C, C–O), 56.0 and 55.5 (CH_3, OCH_3), 51.6 and 50.8 (CH), 46.8 and 46.7 (C), 45.7 (C), 37.9 and 37.8 (CH), 35.2 and 35.1 (CH_2), 28.2 and 27.6 (CH_2), 26.1 (CH_3), 26.0 (CH_3), 23.4 and 23.3 (CH_3), 22.0 and 21.9 (CH_2), 21.1 and 21.0 (CH_3). Mass: *m*/*z* 219 (M^+−OCH_2OMe, 10%), 178 (10), 165 (12), 137 (100), 115 (82), 107 (10), 91 (10). HRMS: *m*/*z* Calcd for $C_{17}H_{28}O_3Na$ (M+Na): 303.1936. Found: 303.1937.

4.6. (+)-(1*R*,3*R*,7*S*,8*S*)-2,2,6,8-Tetramethyltricyclo-[5.3.1.0^{3,8}]undec-5-en-3-ol 6

To a magnetically stirred solution of methoxymethyl ether **15** (115 mg, 0.06 mmol) in dry THF (3 ml) was added freshly cut sodium metal (151 mg, 6.57 mmol) and the reaction mixture refluxed for 16 h. It was then cooled to room temperature and the excess sodium metal quenched carefully with ethanol, diluted with water and extracted with ether (3×5 ml). The organic layer was washed with brine and dried over 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 furnished the tricyclic alcohol **6** (17 mg, 19%) as a colourless solid, which was recrystallised from a mixture of CH_2Cl_2 and hexane. Mp: 44–46 °C. $[\alpha]_D^{24} = +42.3$ (*c* 1.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3509. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.14 (1H, br s, C=C*H*), 2.34 (1H, dd, *J* 17.4 and 4.4 Hz), 2.10–1.70 (4H, m), 1.67 (3H, s, olefinic–CH_3), 1.75–1.50 (3H, m), 1.40–1.25 (1H, m), 1.20–1.00 (2H, m), 1.09 (6H, s) and 0.79 (3H, s) [$3 \times$ *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 139.0 (C), 118.3 (CH, *C*H=C), 75.0 (C, C–OH), 45.0 (CH), 39.5 (C), 39.2 (CH), 35.9 (CH_2), 35.4 (C), 30.1 (CH_2), 27.1 (CH_2), 26.6 (CH_3), 25.6 (CH_3), 23.5 (CH_2), 22.1 (CH_3), 21.1 (CH_3). Mass: *m*/*z* 220 (M^+, 64%), 205 (36), 149 (18), 137 (72), 121 (100), 107 (30). HRMS: *m*/*z* Calcd for $C_{15}H_{23}$ (M^+−OH): 203.1800. Found: 203.1801. Anal. for $C_{15}H_{24}O$, Calcd: C, 81.76; H, 10.98. Found: C, 81.63; H, 11.13.

Further elution of the column using ethyl acetate–hexane (1:25) as eluent furnished the first diastereomer of isotwistane **16a** (16 mg, 16%) as a colourless solid, which was recrystallised from a mixture of CH_2Cl_2 and hexane. Mp: 111–114 °C. $[\alpha]_D^{24} = -17.2$ (*c* 1.1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3574. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.74 (1H, d, *J* 6.6 Hz) and 4.47 (1H, d, *J* 6.6 Hz) [OCH_2O], 3.31 (3H, s, OCH_3), 2.32 (1H, q, *J* 7.8 Hz), 1.95–1.80 (1H, m), 1.84 (1H, dd, *J* 10.8 and 2.4 Hz), 1.72–1.55 (2H, m), 1.60–1.35 (2H, m), 1.34 (3H, s, *tert*-CH_3), 1.20 (1H, br s, OH), 1.20-1.00 (2H, m), 1.08 (3H, s, *tert*-CH_3), 0.97 (3H, d, *J* 7.8 Hz, *sec*-CH_3), 0.97 (3H, s) and 0.90 (3H, s) [$2 \times$ *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 91.5 (CH_2, OCH_2O), 84.1 (C, *C*–OCH_2), 82.2 (C, C–OH), 55.3 (CH_3, OCH_3), 49.3 (CH), 46.7 (CH), 44.8 (C), 41.6 (C), 38.0 (CH), 27.9 (2C, CH_2), 26.9 (CH_3), 25.4 (CH_2), 25.3 (CH_3), 23.7 (CH_3), 22.8 (CH_3), 11.7 (CH_3). Mass: *m*/*z* 222 (M^+−OCH_2OMe, 11%), 221 (100), 220 (17), 149 (10), 137 (24), 124 (30), 123 (20), 121 (22), 109 (14), 95 (21). HRMS: *m*/*z* Calcd for $C_{17}H_{30}O_3Na$ (M+Na): 305.2093. Found: 305.2086. Anal. for $C_{17}H_{30}O_3$, Calcd: C, 72.30; H, 10.71. Found: C, 72.54; H, 10.70.

Further elution of the column using ethyl acetate–hexane (1:20) as eluent furnished the second diastereomer of isotwistane **16b** (26 mg, 26%) as a colourless solid, which was recrystallised from a mixture of CH_2Cl_2 and hexane. Mp: 58–60 °C. $[\alpha]_D^{24} = -122.5$ (*c* 2.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3626, 3532. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.62 and 4.56 (2H, $2 \times$ d, *J* 7.0 Hz, OCH_2O), 3.36 (3H, s, OCH_3), 2.51 (1H, q, *J* 7.8 Hz), 2.30 (1H, m of d, *J* 14.4 Hz), 1.95–1.80 (1H, m), 1.74 (1H, dd, *J* 10.4 and 1.8 Hz), 1.60 (1H, ddd, *J* 14.4, 11.4 and 6.6 Hz), 1.40 (3H, s, *tert*-CH_3), 1.35–1.05 (5H, m), 1.06 (3H, s, *tert*-CH_3), 1.01 (3H, d, *J* 7.8 Hz, *sec*-CH_3), 0.97 (3H, s) and 0.86 (3H, s) [$2 \times$ *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 92.1 (CH_2, OCH_2O), 84.0 (C, *C*OCH_2O), 82.1 (C, C–OH), 55.7 (CH_3, OCH_3), 51.2 (CH), 47.0 (CH), 43.7 (C), 42.2 (C), 37.6 (CH), 28.0 (CH_2), 27.1 (CH_3), 25.9 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 23.8 (CH_3), 14.4 (CH_3). Mass: *m*/*z* 267 (M^+−OCH_2-OMe, 18%), 237 (17), 222 (10), 221 (100), 220 (29), 205 (11), 149 (13), 137 (32), 124 (45), 109 (26), 95 (32), 93 (25), 91 (9). HRMS: *m*/*z* Calcd for $C_{17}H_{30}O_3Na$ (M+Na): 305.2093. Found: 305.2102. Anal. for $C_{17}H_{30}O_3$, Calcd: C, 72.30; H, 10.71. Found: C, 72.23; H, 10.70.

4.7. (−)-(1*R*,3*R*,6*S*,7*S*,8*S*)-2,2,6,8-Tetramethyltricyclo-[5.3.1.0^{3,8}]undecan-3-ol (patchouli alcohol) 1

To a solution of the dehydropatchouli alcohol **6** (10 mg, 0.04 mmol) in dry methanol (2 ml) was added 5% Pd–C (20 mg) and the reaction stirred at room temperature in a hydrogen atmosphere, created by evacuative displacement of air (balloon), for 12 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 (1:20) as eluent furnished patchouli alcohol **1** (10 mg, 99%) as a colourless solid. $[\alpha]_D^{25} = -121.3$ (*c* 2.3, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3505. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.00–1.80 (3H, m), 1.75–1.55 (1H, m), 1.55–1.15 (9H, m), 1.16 (1H, br s, OH), 1.06 (3H, s), 1.04 (3H, s) and 0.82 (3H, s) [3 × *tert*-CH_3], 0.78 (3H, d, *J* 6.6 Hz, *sec*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 75.2 (C, C–OH), 43.7 (CH), 40.1 (C), 39.1 (CH), 37.6 (C), 32.8 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.1 (CH), 26.9 (CH_3), 24.6 (2C, CH_2), 24.4 (CH_3), 20.7 (CH_3), 18.7 (CH_3). Mass: *m*/*z* 222 (M^+, 70%), 207 (25), 161 (41), 138 (100), 125 (70), 98 (97).

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