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First total synthesis of heterocurvistone

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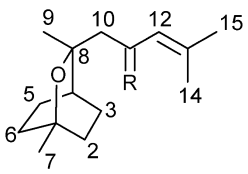
Abstract—The sesquiterpene ketone (±)-heterocurvistone was synthesized in eight steps and 12% overall yield from known methyl *R*-(+)-3-(4-methyl-3-cyclohexen-1-yl)-3-butenoate, readily available from *R*-(+)-limonene. The key synthetic step is an oxymercuration-induced cyclization. © 2003 Published by Elsevier Science Ltd.

1. Introduction

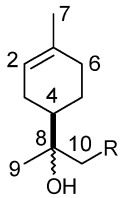
Sesquicineole (**1**), the parent molecule of a scarce series of sesquiterpenes, has been isolated from *Senecio subrubriflorus*,[1] *Anthemis alpestris*,[2] *Aydendron barbeyana*[3] and *Boronia megastigma*,[4] while its 2,3-dehydroderivative is the main constituent of the *Artemisia sieberi* essential oil, from which also 15-hydroxy-2,3-dehydrosesquicineole and several simple esters thereof were isolated as trace constituents.[5] Furthermore, α-bisabolol oxide C (2-hydroxy-sesquicineole) was isolated from *Matricaria chamomilla*,[6] while the only known ketone derivative based on this skeleton is (−)-heterocurvistone (**2**), which was isolated from *Heterotropa curvistigma* in 1981.[7] Two syntheses of racemic sesquicineole (**1**) are reported, the first using *R*-(+)-limonene as the starting material, which gave **1** in very low overall yield (ca. 0.12%)[8] and the second one, executed in six steps from methyl vinyl ketone and hydroquinone,[9] afforded **1** in almost 24% overall yield. In contrast, there is no published synthesis of **2**, and therefore, in the present work we report the first total synthesis of racemic heterocurvistone (**2**), in eight steps and 12% overall yield, starting from known[10] methyl *R*-(+)-3-(4-methyl-3-cyclohexen-1-yl)-3-butenoate (**7**), which in turn is readily available from *R*-(+)-limonene. The key reaction step is a high yield cyclization induced by mercuric acetate in anhydrous THF.

2. Results and discussion

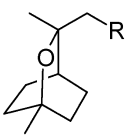
The oxymercuration–demercuration reaction of nonconjugated dienes in aqueous THF has been developed as a valuable method for the construction, in low to moderate yields (30%), of tetrahydropyran rings.[11] When applied to limonene or α-terpineol, it provided 1,8-cineole,[12] while in



1 R = H_2
2 R = O



3 R = OH
4 R = $CH_2CH_2C(OH)Me_2$



5 R = OH
6 R = $CH_2CH_2C(OH)Me_2$

Keywords: heterocurvistone; isoheterocurvistone; heterocurvistol; isoheterocurvistol; sesquicineole derivatives; synthesis.

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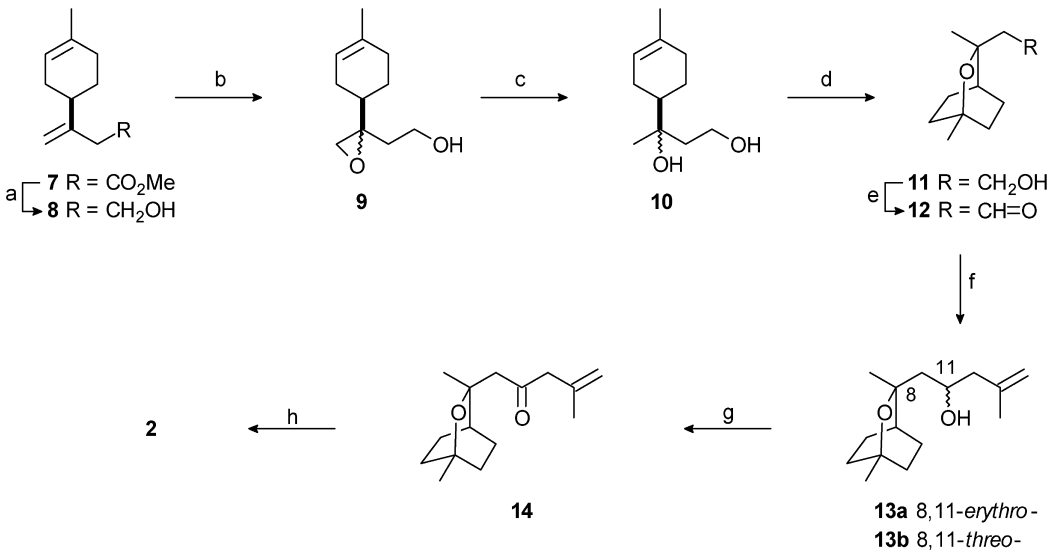

Scheme 1. Synthetic strategy for the obtention of heterocurvistone (**2**). (a) $LiAlH_4$, 74%. (b) *tert*-BuOOH/$VO(acac)_2$, 84%. (c) $LiAlH_4$, 77%. (d) $Hg(OAc)_2$/THF, $NaBH_4$/NaOH–H_2O, 68%. (e) CrO_3/Py, 83%. (f) $BrMgCH_2C(Me)=CH_2$, 77%. (g) CrO_3/AcOH, 77%. (h) $KHCO_3$, 75%.

the case of the bisabolene derivative **4**, the sesquicineole derivative **6**[8] was formed. Alternatively, 10-hydroxycineole (**5**) was produced in 65% yield when this procedure was applied to uroterpenol (**3**) in anhydrous THF.[13] The above results suggest that the 8-hydroxyl group in the substrates, and the water used as co-solvent, act as competitive nucleophiles to attack the double bond during the oxymercuration process, and that anhydrous THF should be preferred when an intramolecular attack of the hydroxyl group is desired. Based on the above considerations, 10-hydroxycineole (**5**) could be rationalized as an intermediate for the synthesis of **2**, although the neopentylic nature of its hydroxyl group suggested that the construction of the side chain would be problematic. Therefore, homouroterpenol (**10**) was selected as the key intermediate.

The almost equimolecular mixture of homouroterpenol stereoisomers **10** was prepared in a linear three step sequence, for which the starting ester **7** was obtained from *R*-(+)-limonene following a known procedure.[10] Reduction of **7** with lithium aluminum hydride gave the optically active alcohol **8**, $[\alpha]_D$=+95.5, CH_2OH ^{13}C NMR signal at 60.7 ppm, in 74% yield. The homoallylic nature of the propylidene double bond allowed the regioselective epoxidation[14–16] of **8** with *tert*-butyl hydroperoxide and a catalytic amount of vanadyl acetylacetonate to afford, according to the NMR data given in Section 3, a 57:43 diastereoisomeric mixture of epoxides **9** in 84% yield. Since this mixture could not be separated by column chromatography, it was reduced with lithium aluminum hydride to give an almost equimolecular diastereoisomeric mixture of homouroterpenols **10** in 77% yield.

Compound **10**, the key synthetic intermediate, smoothly underwent ring closure when treated with mercuric acetate in anhydrous THF, followed by demercuration using sodium borohydride in the presence of sodium hydroxide, to provide racemic alcohol **11** in 68% yield, since the sole chiral center of *R*-(+)-limonene is lost. During this transformation the vinylic methyl group of **10** shifted from 1.63 to 1.03 ppm in **11**, while the C-9 methyl group of **10**, which appears at 1.16 and 1.14 ppm in the stereoisomeric mixture **10**, is shifted to 1.29 ppm in **11**. The oxidation of the primary alcohol **11** to afford aldehyde **12** was performed under Collins reaction conditions, as evidenced by the aldehyde carbonyl IR absorption at 1750 cm^{-1} and the aldehyde hydrogen signal, which appeared as a double doublet (J=3.8, 2.0 Hz) at 9.83 ppm in the NMR spectrum.

Since it is well known that vinylic Grignard reagents have no straightforward behavior, placement of the remaining atoms to complete construction of the carbon scaffold was accomplished by addition of 2-methyl-2-propenylmagnesium bromide to aldehyde **12**. The reaction yielded racemic mixtures of the two diastereoisomeric sesquiterpene alcohols **13a** and **13b**, that we name *erythro*- and *threo*-isoheterocurvistol, in 64% overall yield. Since TLC analysis of the reaction outcome showed two well differentiated spots (R_f 0.58 and 0.42, hexane/EtOAc, 4:1), the two racemates were separated by column chromatography and characterized in detail. In fact, the large difference in the chromatographic behavior seems to be associated to the preferred conformation of these molecules in solution.

The relative configuration of isoheterocurvistols (**13a** and **13b**) follows from careful evaluation of NMR data, including COSY, NOESY, gHSQC and gHMBC two-dimensional measurements, which provided definitive signal assignments. The hydrogen geminal to the hydroxyl group appeared, in the case of the less polar compound **13a**, as a double triplet of doublets (J=11.0, 6.7, 1.4 Hz) at 4.26 ppm, while in the more polar compound **13b** it appeared as an almost first order quintet (J=6.0 Hz) at 3.95 ppm. Similarly, in the less polar molecule, the hydrogen atoms attached to C-10 (dd, J=14.3, 11.0 Hz at 1.94 ppm and dd, J=14.3, 1.4 Hz at 1.23 ppm) and to C-12 (dd, J=13.5, 6.7 Hz at 2.32 ppm and dd, J=13.5, 6.7 Hz at 2.06 ppm) show highly diastereotopic chemical shifts, while in the more polar stereoisomer they appear as two almost first order doublets (J=6.0 Hz) at 1.72 and 2.20 ppm, for

C-10 and C-12, respectively. These spectral facts suggest that the less polar compound has a preferred conformation due to the existence of a relative stable intramolecular hydrogen bond involving the hydroxyl group proton and the ether bridge, while in the more polar compound the side chain has a significant level of conformational freedom. These results, combined with the inspection of Dreiding models, allowed to assign the less polar compound as *erythro*-isohererocurvistol (**13a**). The relative stereochemistry assignment is further in line with the strong correlation observed between CH_3-9 and H-11 in the NOESY contour plot of **13a**, and by shielding of 2.7, 3.5 and 1.0 ppm for C-9, C-10 and C-12, respectively, when the NMR carbon chemical shifts are compared to those of *threo*-isoheterocurvistol (**13b**). The higher field carbon chemical shift values found in **13a** are due to steric compression.

Each isoheterocurvistol **13** was oxidized with chromium trioxide in acetic acid to give isoheterocurvistone (**14**) in 75% yield, as evidenced by the carbonyl absorption at 1706 cm^{-1} in the IR spectrum. To complete the synthesis of heterocurvistone (**2**), the isomerization of the double bond, to provide the α,β-unsaturated ketone, followed in 74% yield after treatment of **14** with potassium bicarbonate. The spectroscopic properties of the synthetic material, excepting the optical activity, were identical to those reported[7] for the natural product. It has however to be noted that the published ^{13}C NMR assignments for C-9 and C-14 have to be reversed to the values given in Section 3, as evidenced from gHSQC and gHMQC measurements. All NMR assignments were secured after performing two-dimensional measurements.

3. Experimental

3.1. General experimental procedures

IR spectra in $CHCl_3$, were recorded in a Perkin–Elmer 16F PC spectrophotometer and the optical rotation was measured on a Perkin–Elmer 241 polarimeter. ^1H, ^{13}C, COSY, NOESY, gHMBC and gHSQC NMR measurements were performed on Varian XL-300GS and Mercury 300 spectrometers at 300 (^1H) and 75.4 (^{13}C) MHz in $CDCl_3$ solutions containing TMS as internal standard. LREIMS were obtained on a Hewlett–Packard 5989A spectrometer at 20 eV or on a Varian Saturn 2000 spectrometer at 70 eV, while HREIMS were measured on a VG 7070 high resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside. Merck Silica gel (230–400 mesh, ASTM) was used for column chromatography.

3.2. Preparation of new compounds

3.2.1. (*R*)-(+)-3-(4-Methyl-3-cyclohexen-1-yl)-3-buten-1-ol (8). To a cooled (0°C) and vigorously stirred solution of **7**[10] (1.15 g, 5.93 mmol) in anhydrous THF (120 mL), were added 1.15 g of $LiAlH_4$ in small portions. The suspension was stirred at room temperature for 1 h, and further refluxed for additional 3 h. The mixture was cooled and treated dropwise, under stirring, successively with EtOAc (20 mL), MeOH (20 mL) and H_2O (100 mL), and stirring continued for additional 2 h. The white precipitate that formed was collected by suction filtration and thoroughly washed with EtOAc (200 mL). The organic layer was decanted, washed with water (2×20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (93:7 to 17:3 hexane/EtOAc) to give **8** (728 mg, 74%) as a colorless oil; $[\alpha]_D$=+95.9, $[\alpha]_{578}$=+100.0, $[\alpha]_{546}$=+114.6, $[\alpha]_{436}$=+196.3, $[\alpha]_{365}$=+314.4 (*c* 4.66, $CHCl_3$); IR ν_{max} 3624, 3082, 3014, 1638, 1226, 1048, 900, 800 cm^{-1}; ^1H NMR δ 5.40 (1H, br signal, H-2), 4.90 (1H, br s, H-9a), 4.83 (1H, br q, *J*=1.1 Hz, H-9b), 3.72 (2H, t, *J*=6.5 Hz, H-11), 2.34 (2H, td, *J*=6.5, 1.1 Hz, H-10), 1.65 (3H, br s, H-7); ^{13}C NMR δ 150.5 (C-8), 133.6 (C-1), 120.4 (C-2), 109.6 (C-9), 60.7 (C-11), 39.4 (C-4), 37.8 (C-10), 31.2 (C-3), 30.5 (C-6), 28.1 (C-5), 23.3 (C-7); EIMS 20 eV *m/z* (rel. int.): 166 (M^+, 42), 165 (13), 149 (74), 148 (66), 135 (26), 133 (49), 122 (52), 121 (100), 105 (76), 93 (77), 81 (74), 67 (60); HREIMS *m/z* 166.1356 $[M]^+$ (calcd for $C_{11}H_{18}O$ 166.1358).

3.2.2. 3,4-Epoxy-3-(4-methyl-3-cyclohexen-1-yl)-butan-1-ol (9). A solution of 0.42 mL (2.3 mmol) of 5.5 M *tert*-butylhydroperoxide in decane, quantified by iodometric titration, was added dropwise to a stirred solution of **8** (300 mg, 1.81 mmol) and $VO(acac)_2$ (3.1 mg, 0.011 mmol) in anhydrous benzene (5 mL). The resulting light orange solution was stirred at room temperature for 18 h, diluted with ether and washed twice with a 10% aqueous sodium sulfite solution. The organic phase was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (9:1 to 41:9 hexane/EtOAc) to yield the epimeric mixture **9** (ratio 57:43) as a colorless oil (276 mg, 84%); IR ν_{max} 3524, 3028, 3018, 3012, 1260, 1060, 918 cm^{-1}; ^1H NMR δ 5.36 (1H, br signal, H-2), 3.65 (2H, m, H-11), 2.87, 2.71 (1H each, d, *J*=4.1 Hz, H-9a), 2.81, 2.69 (1H each, d, *J*=4.1 Hz, H-9b), 1.64 (3H, br s, H-7); ^{13}C NMR δ 134.0 (C-1), 119.7 (C-2), 61.6, 61.4 (C-8), 58.6 (C-11), 50.3, 49.5 (C-9), 39.4, 38.6 (C-4), 32.8, 32.0 (C-10), 30.1, 29.9 (C-6), 27.5, 26.7 (C-3), 24.8, 23.8 (C-5), 23.4, 23.3 (C-7); EIMS 20 eV *m/z*(rel. int.): 182 (M^+, 7), 167 (4), 165 (73), 164 (24), 152 (11), 151 (11), 147 (25), 137 (22), 131 (42), 121 (31), 119 (59), 107 (31), 105 (100), 96 (38), 95 (57), 94 (76), 81 (38), 79 (34), 67 (36), 53 (22); HREIMS *m/z* 182.1311 $[M]^+$ (calcd for $C_{11}H_{18}O_2$ 182.1307).

3.2.3. 3-(4-Methyl-3-cyclohexen-1-yl)-1,3-butanediol, homouroterpenol (10). Compound **9** (1.05 g, 5.78 mmol) was treated with $LiAlH_4$ (1.05 g) following the same procedure as is described above for the preparation of **8**. After workup and purification by column chromatography (17:3 to 19:6 $CHCl_3$/EtOAc) the stereoisomeric mixture **10** (approximate ratio 1:1) was obtained as a colorless oil (820 mg, 77%); IR ν_{max} 3614, 3496, 3014, 1224, 1212, 1098, 1068 cm^{-1}; ^1H NMR δ 5.39, 5.35 (1H, br s, H-2), 3.87 (2H, m, H-11), 1.78, 1.67 (1H, m, H-10a), 1.83, 1.59 (1H, m, H-10b), 1.63 (3H, br s, Me-7), 1.16, 1.14 (3H, s, Me-9); ^{13}C NMR δ 134.2, 133.9 (C-1), 120.5, 120.2 (C-2), 75.6, 75.5 (C-8), 59.7, 59.6 (C-11), 44.4, 43.8 (C-4), 39.7, 38.6 (C-10), 31.0, 30.9 (C-6), 27.0, 26.0 (C-3), 24.1, 23.1 (C-5), 23.6, 22.7 (C-9), 23.3, 23.2 (C-7); EIMS 20 eV

m/z(rel. int.): 185 (2), 184 (M^+, 1), 166 (55), 149 (30), 133 (25), 121 (49), 105 (20), 93 (32), 81 (19), 71 (36), 43 (100); HREIMS *m/z* 185.1548 $[M+H]^+$ (calcd for $C_{11}H_{21}O_2$ 185.1542).

3.2.4. 11-Hydroxyhomocineole (11). A solution of **10** (750 mg, 4.08 mmol) in anhydrous THF (25 mL) was treated with mercuric acetate (3 g, 9.42 mmol) and the resulting suspension was stirred at 55°C for 30 h. A solution of NaOH (10 mL, 5 M), followed by a solution of $NaBH_4$ (270 mg) in NaOH (10 mL, 5 M) were added, and stirring continued for 1 h. The suspension was concentrated, diluted with EtOAc (50 mL) and saturated with NaCl. The organic layer was decanted, washed with brine (3×5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (9:1 to 41:9 hexane/EtOAc) to give **11** (510 mg, 68%) as a colorless oil. IR ν_{max} 3440, 2970, 1380, 1220, 1210, 1080, 1050, 980, 950 cm^{-1}; ^1H NMR δ 4.04 (1H, td, *J*=11.0, 3.5 Hz, H-11a), 3.71 (1H, dt, *J*=11.0, 4.5 Hz, H-11b), 2.25 (1H, ddd, *J*=14.0, 11.0, 4.5 Hz, H-10a), 1.34 (1H, ddd, *J*=14.0, 4.5, 3.5 Hz, H-10b), 2.09, 1.53 (2H, m, H-3a,b), 2.06, 1.51 (2H, m, H-5a,b), 1.71, 1.53 (2H, m, H-2a,b), 1.68, 1.51 (2H, m, H-6a,b), 1.41 (1H, m, H-4), 1.29 (3H, br s, Me-9), 1.03 (3H, s, Me-7); ^{13}C NMR δ 77.2 (C-8), 70.3 (C-1), 60.2 (C-11), 40.2 (C-10), 32.5 (C-4), 31.4 (C-6), 31.2 (C-2), 27.4 (C-7), 24.6 (C-9), 22.7 (C-5), 22.3 (C-3); EIMS 20 eV *m/z* (rel. int.): 185 (16), 184 (M^+, 4), 167 (15), 149 (21), 139 (100), 108 (22), 95 (15), 81 (13), 67 (10), 43 (33); HREIMS *m/z* 185.1547 $[M+H]^+$ (calcd for $C_{11}H_{21}O_2$ 185.1542).

3.2.5. Aldehyde 12. To a solution of chromium trioxide (652 mg, 6.52 mmol) in pyridine (1.1 mL) and dichloromethane (16 mL) was added dropwise a solution of **11** (197 mg, 1.07 mmol) in dichloromethane (1.2 mL), the resulting suspension stirred for 5 min and then filtered through a short pad of silica gel, using dichloromethane as the eluting solvent. The organic layer was washed successively with 10% HCl (10 mL), brine (15 mL), a saturated solution of $NaHCO_3$ (10 mL), and brine (15 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (19:1 to 8:1 hexane/Et_2O) to give **12** (162 mg, 83%) as a colorless oil. IR ν_{max} 2928, 2700, 1750, 1716, 1048, 968 cm^{-1}; ^1H NMR δ 9.83 (1H, dd, *J*=3.8, 2.0 Hz, H-11), 2.74 (1H, dd, *J*=14.9, 2.0 Hz, H-10a), 2.54 (1H, dd, *J*=14.9, 3.8 Hz, H-10b), 1.38 (3H, s, Me-9), 1.07 (3H, s, Me-7); ^{13}C NMR δ 202.8 (C-11), 74.7 (C-8), 70.0 (C-1), 55.0 (C-10), 31.6 (C-6), 31.5 (C-4), 31.3 (C-2), 27.2 (C-7), 27.1 (C-9), 22.6 (C-5), 22.2 (C-3); EIMS 20 eV *m/z* (rel. int.): 182 (M^+, 2), 181 (M^+-1, 1), 165 (4), 147 (6), 139 (100), 136 (23), 121 (19), 111 (10), 107 (18), 95 (28), 94 (19), 93 (36), 81 (16), 67 (13), 43 (50); HREIMS *m/z* 181.1228 $[M-1]^+$ (calcd for $C_{11}H_{17}O_2$ 181.1229).

3.2.6. *erythro*- (13a) and *threo*-Isoheterocurvistol (13b). Grignard reagent, prepared from 3-bromo-2-methylpropene (361 mg, 2.67 mmol) and excess Mg turnings (289 mg) in anhydrous Et_2O (1.5 mL) and 1,2-dibromoethane (25 μL), under an argon atmosphere at room temperature, was added dropwise to a cooled (−20°C) and vigorously stirred solution of **12** (98 mg, 0.54 mmol) in THF/Et_2O (1:3, 4 mL) during 5 min and then allowed to reach the room temperature. The reaction was quenched with a saturated NH_4Cl solution (1.5 mL) and diluted with EtOAc (12 mL). The organic layer was decanted, washed with a saturated NH_4Cl solution (2×2.5 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. TLC analysis of the residue showed two spots with R_f 0.58 and 0.42 (hexane/EtOAc, 4:1). Column chromatography (19:1 hexane/EtOAc) of the mixture provided 43 mg of **13a** (34%, R_f 0.58) and 56 mg of **13b** (44%, R_f 0.42) as colorless oils.

Compound **13a** shows IR ν_{max} 3416, 3076, 1648, 1128, 1020 cm^{-1}; ^1H NMR δ 4.79 (1H, br d, *J*=1.6 Hz, H-14a), 4.76 (1H, br d, *J*=1.1 Hz, H-14b), 4.26 (1H, dtd, *J*=11.0, 6.7, 1.4 Hz, H-11), 2.32 (1H, dd, *J*=13.5, 6.7 Hz, H-12a), 2.06 (1H, dd, *J*=13.5, 6.7 Hz, H-12b), 1.94 (1H, dd, *J*=14.3, 11.0 Hz, H-10a), 1.78 (3H, br s, H-15), 1.32 (3H, s, H-9), 1.23 (1H, dd, *J*=14.3, 1.4 Hz, H-10b), 1.03 (3H, s, H-7); ^{13}C NMR δ 143.0 (C-13), 112.3 (C-14), 77.3 (C-8), 70.6 (C-1), 66.9 (C-11), 46.5 (C-12), 44.2 (C-10), 32.8 (C-4), 31.4 (C-6), 31.1 (C-2), 27.2 (C-7), 24.8 (C-9), 22.6 (C-5), 22.6 (C-15), 22.3 (C-3); EIMS 70 eV *m/z* (rel. int.): 239 (20), 238 (M^+, 6), 203 (3), 183 (13), 165 (16), 147 (17), 140 (13), 139 (100), 138 (9), 121 (14), 108 (6), 107 (6), 105 (8), 95 (4), 43 (19); HREIMS *m/z* 239.2006 $[M+H]^+$ (calcd for $C_{15}H_{27}O_2$ 239.2011).

Compound **13b** shows IR ν_{max} 3558, 3486, 3076, 3022, 1644, 1144, 1006, 920 cm^{-1}; ^1H NMR δ 4.87 (1H, br q, *J*=1.3 Hz, H-14a), 4.78 (1H, br q, *J*=1.1 Hz, H-14b), 3.95 (1H, br quintet, *J*=6 Hz, H-11), 2.20 (2H, d, *J*=6 Hz, H-12), 1.76 (3H, br s, H-15), 1.72 (2H, d, *J*=5.6 Hz, H-10), 1.32 (3H, s, H-9), 1.04 (3H, s, H-7); ^{13}C NMR δ 142.8 (C-13), 113.4 (C-14), 75.6 (C-8), 69.8 (C-1), 66.6 (C-11), 47.7 (C-10), 47.5 (C-12), 32.4 (C-4), 31.8 (C-6), 31.6 (C-2), 27.5 (C-9), 27.5 (C-7), 22.8 (C-5), 22.7 (C-3), 22.4 (C-15); EIMS 70 eV *m/z* (rel. int.): 238 (M^+, 0.2), 220 (0.2), 205 (1), 183 (1), 165 (4), 147 (5), 140 (10), 139 (100), 121 (9), 108 (8), 107 (7), 105 (4), 95 (15), 93 (11), 81 (7), 67 (8), 43 (35); HRDCIMS (NH_3) *m/z* 239.2014 $[M+H]^+$ (calcd for $C_{15}H_{27}O_2$ 239.2011).

3.2.7. Isoheterocurvistone (14). A solution of chromium trioxide (34 mg) in water (0.1 mL) was diluted with AcOH (1.5 mL), cooled to 12°C and added dropwise to a stirred solution of **13a** (32 mg, 0.134 mmol) in glacial acetic acid (1.7 mL) at 12°C. The reaction mixture was kept at room temperature during 1 h, diluted with cold brine (6 mL) and extracted with EtOAc (3×12 mL). The organic layer was washed successively with brine (10 mL), a satured solution of $NaHCO_3$ (10 mL) and brine (12 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography (97:3 hexane/EtOAc) to give **14** (26 mg, 82%) as a colorless oil. Compound **13b** (80 mg, 0.336 mmol) was oxidized as above to also give **14** (60 mg, 76%) as a colorless oil. IR ν_{max} 3080, 3026, 3018, 2972, 1706, 1648, 1224, 1050, 968, 900 cm^{-1}; ^1H NMR δ 4.94 (1H, br s, H-15a), 4.82 (1H, br s, H-15b), 3.18 (1H, d, *J*=14.8 Hz, H-12a), 3.16 (1H, d, *J*=14.8 Hz, H-12b), 2.86 (1H, d, *J*=15.4 Hz, H-10a), 2.64 (1H, d, *J*=15.4 Hz, H-10b), 1.74 (3H, br s, Me-14), 1.31 (3H, s, Me-9), 1.06 (3H, s, Me-7); ^{13}C NMR δ 207.9 (C-11), 139.4 (C-13), 115.0 (C-14), 75.2 (C-8), 69.9 (C-1), 53.9 (C-12), 52.7

(C-10), 31.7 (C-6), 31.5 (C-2), 30.6 (C-4), 27.4 (C-7), 26.2 (C-9), 22.9 (C-5), 22.6 (C-15), 22.3 (C-3); EIMS 20 eV *m/z* (rel. int.): 236 (M^+, 0.3), 221 (1), 218 (1), 139 (100), 121 (6), 95 (15), 83 (5), 81 (6), 67 (8), 55 (11), 43 (31); HRDCIMS (NH_3) *m/z* 237.1850 $[M+H]^+$ (calcd for $C_{15}H_{25}O_2$ 237.1856).

3.2.8. Heterocurvistone (2). A solution of $KHCO_3$ (10 mg) in water (0.2 mL) was added to a solution of **14** (20 mg, 11.8 mmol) in MeOH (2 mL) (Scheme 1). The reaction mixture was refluxed for 3 h, concentrated and diluted with Et_2O (10 mL). The organic layer was washed with water (1 mL), dried and evaporated. The residue was purified by column chromatography (97:3 hexane/EtOAc) to give **2** (15 mg, 75%) as a colorless oil. ^{13}C NMR δ 199.7 (C-11), 154.8 (C-13), 125.3 (C-12), 75.6 (C-8), 69.9 (C-1), 55.5 (C-10), 31.8 (C-6), 31.6 (C-2), 30.5 (C-4), 27.8 (C-15), 27.4 (C-7), 26.6 (C-9), 23.0 (C-5), 22.3 (C-3), 20.7 (C-14); HREIMS *m/z* 236.1778 $[M+H]^+$ (calcd for $C_{15}H_{24}O_2$ 236.1776). The IR and ^1H NMR data are in agreement with published values.[7]

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