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Total Synthesis of (±)- Cis -5-Hydroxycalamenene

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Total Synthesis of (±)-*Cis*-5-Hydroxycalamenene

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Abstract: A total synthesis of (±)-*cis*-5-hydroxycalamenene **1** has been achieved from tetralone **5**, which in turn was prepared from 5-methoxy-α-tetralone **3**. Grignard reaction of compound **5** with isopropylmagnesium chloride, followed by dehydration and aromatization, provided the substituted naphthalene **7** whose conversion to (±)-cis-5-hydroxycalamenene **1** was accomplished by demethylation, formylation, and hydrogenation.

Keywords: (±)-*cis*-5-hydroxycalamenene; Grignard reaction; 5-methoxy-α-tetralone; Terpene

INTRODUCTION

(±)-*Cis*-5-hydroxycalamenene **1** is a phenolic sesquiterpene, isolated[1,2] from the essential oil of European liverwort *Bazzonia tricrenta* and *trilobata*, for which the *cis*-structure was assigned on the basis of comprehensive spectral studies. The ^{1}H NMR spectrum of the *trans* isomer, prepared by the acid-catalyzed cyclization[3] of the phenolic sesquiterpene Xanthorrihal **2**,[4] was distinctly different from that of natural product 5-hydroxycalamenene **1**. Furthermore, the (±)-*cis*-5-hydroxycalamenene **1** has also been detected as a principal component in the essential oil of *Myrica rubra var*. tree,[5] and the stereostructure of **1** was revised to be (1*R*, 4*R*)-*cis*-5-hydroxycalamenene by X-ray crystallographic analysis of its *p*-bromobenzoate derivative.[6]

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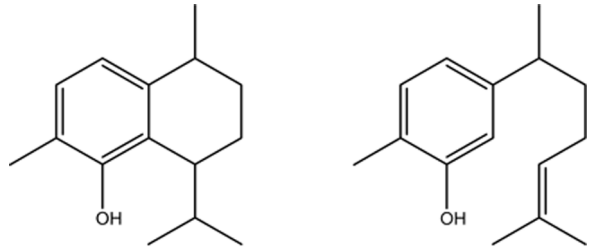

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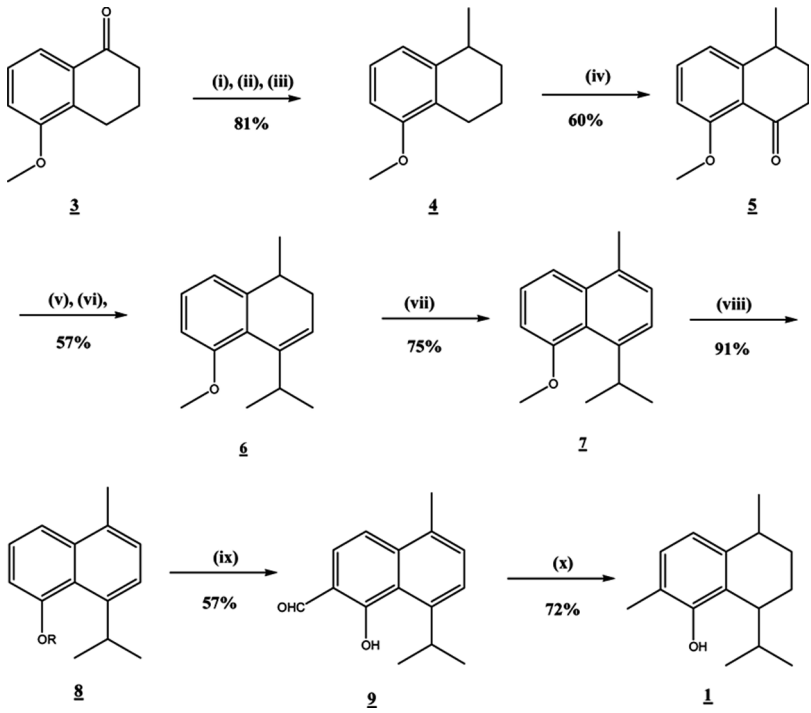
Recently, the antioxidant and antimicrobial activities[5,7] of the essential oils from leaves, bark, and root of *Myrica rubra*, which result from the large content of 5-hydroxycalamenene, have been reported. In



3 4 5 6 7 8 9 1

Scheme 1. (i) CH_3MgBr, $(CH_3CH_2)_2O$; (ii) HCl 6 N; (iii) H_2, Pd/C 5%; (iv) $NaClO_2$, t-BuOOH, CH_3CN, H_2O; (v) i-PrMgCl, THF; (vi) HCl 6 N; DDQ, CH_2Cl_2; (viii) HBr 48%, CH_3COOH; (ix) $(CH_2O)_n$, $MgCl_2$, $(CH_3CH_2)_3N$, THF; (x) H_2, Pd/C 10%, 500 psi.

addition, 5-hydroxycalamenene exhibit strong antifungal activity against *P. oryzae*.[8]

Because of their notable biological activities, two groups have attempted synthetic studies of the (±)-*cis*-5-hydroxycalamenene **1**. In 1982, Sangaiah and Rao[9] first reported the total synthesis of 5-hydroxycalamenene in which the relative stereochemistry of the isopropyl and methyl group remained unspecified. Tanaka and Adachi[10] reported the synthesis of (±)-*cis*-5-hydroxycalamenene **1** and confirmed the stereochemistry of the naturally occurring compound **1**. The synthetic routes of the published procedures are lengthy.

In a continuation of our earlier work[11] on terpene compounds, we set out to develop a simple and concise route for the synthesis of (±)-*cis*-5-hydroxycalamenene **1** (Scheme 1).

RESULTS AND DISCUSSIONS

Tetralene **4**, prepared[11] from tetralone **3**, was oxidizedwith sodium chlorite and *tert*-butyl hydroperoxide[12] to obtain tetralone **5** in 60%. This method afforded the most satisfactory result compared to the other reagents such as CrO_3-MeCOOH,[13] pyridinium chlorochromate,[14] and pyridinium dichromate[15] because of the difficult workup of the environmentally hazardous chromium residues. Tetralone **5** was treated with isopropyl magnesium chloride in tetrahydrofuran to obtain the compound **6**.

This supposedly straightforward transformation proved to be much more complicated than we had anticipated. Considerable difficulty was encountered in finding proper conditions to effect the **5**→**6** conversion. The best result was obtained by treatment of tetralone **5** with isopropyl magnesium chloride in tetrahydrofuran (3 equivalents). The difficulty encountered in the Grignard reaction may be due to the 5-methoxy group which hindered attack of the bulky Grignard reagent on the carbonyl group to afford the alcohol in high yield. The resulting alcohol was treated with hydrochloric acid (6 N) to afford product **6**. Dehydrogenation with 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) gave the compound **7**, which on demethylation with hydrobromic acid and acetic acid furnished the naphthalene **8**. Its conversion into the aldehyde **9** in 80% yield was achieved by heating with paraformaldehyde, magnesium chloride, and triethylamine.[16] To complete the synthesis of hydroxycalamenene, all that was required the conversion of the formyl group to a methyl and partial hydrogenation of the aromatic ring containing the isopropyl group. These were effectively accomplished by carrying out the catalytic hydrogenation of compound **9** with Pd/C (10%) under

high pressure (500 psi) at room temperature. The resulting compound was identified as (±)-cis-5-hydroxycalamenene **1**, whose spectroscopic properties (NMR ^1H and ^{13}C) were identical with those reported.[2,10]

CONCLUSIONS

In conclusion, an efficient synthesis of (±)-cis-hydroxycalamenene has been developed from 5-methoxy-α-tetralone. The present method has two merits compared with the published synthesis[9,10]: (a) our procedure involves 10 steps, while the reported method requires 16 steps and (b) the overall yield of our procedure is higher (8%) if compared with published yield (5.5%). The present synthetic route proceeds via intermediates, which can be utilized for the synthesis of other representative members of this group (calamenenes) of natural products.

EXPERIMENTAL

Unless otherwise stated, IR spectra were taken on Nicolet FT instrument. ^1H NMR and ^{13}C NMR spectra were recorded on Brucker AM 300-Hz instrument in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Mass spectra were run on gas chromatograph Hewlett Packard 5890 Quadrupolar 5972 Series S. Column chromatography was performed on silica gel (Merck grade 60, 70–230 mesh). All organic extracts were washed with brine, dried ($MgS0_4$), and evaporated under reduced pressure. The spectral and analytical data of all new compounds have been reported in the Experimental section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas.

3,4-Dihydro-8-methoxy-4-methylnaphtha len-1(2H)-one 5

To a stirred solution of compound **4** (0.10 g, 0.56 mmol) in CH_3CN/H_2O (3:1, v/v) (8 ml), *tert*-butyl hydroperoxide (0.4 ml/2.8 mmol, 70% aqueous solution) and sodium chlorite (0.076 g, 0.67 mmol) were added. The reaction mixture was heated at 50°C for 12 h, then diluted with sodium sulfite solution (10%), and extracted with dichloromethane. The organic extracts were washed with water and saturated aqueous $NaHCO_3$, dried, and chromatographed (hexane/ether 1:1) to obtain the tetralone **5**, a colorless liquid (0.063 g, 60%). ν_{max} (KBr) 1676.08 cm^{-1} (CO); m/z: 191 ($M^+ + 1$), 190 (M^+), 161 (M^+-COH), 133 (M^+-COH-C_2H_4); NMR ^1H δ: 1.32 (d, 3H, CH_3, $J = 7.1$ Hz), 1.8–1.9 (m, 1H), 2.1–2.2 (m, 1H), 2.6–2.7 (m, 2H), 3.0–3.1 (m, 1H),

3.86 (s, 3H, OCH_3), 6.81 (d, 1H, $J = 8.4$ Hz), 6.85 (dd, 1H, ArH, $J = 7.8$ Hz, $J = 8.0$ Hz), 7.39 (dd, 1H, ArH, $J = 7.9$ Hz, $J = 7.2$ Hz) ppm; NMR ^{13}C δ: 20.97, 29.56, 33.62, 37.45, 55.93, 109.88, 119.41, 121.58, 134.02, 151.59, 160.00, 197.64 ppm. Anal. calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.01; H, 7.56.

1,2-Dihydro-4-isopropyl-5-methoxy-1-methylnaphthalene 6

To the isopropylmagnesium chloride (2 M, 0.65 ml, 1.26 mmol) in dry tetrhydrofuran (5 ml), tetralone **5** (0.16 g, 0.84 mmol) was added dropwise and stirred over 48 h at room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with diethyl ether. To the resulting organic extract, hydrochloric acid (6 N, 8 ml) was added and stirred for 3 h at room temperature. The aqueous phase was extracted with ether, and the combined extracts were dried and concentrated. The residue on chromatographic purification (hexane/ether 9:1) yielded the olefin **6** as a light yellow liquid (0.11 g, 57%). ν_{max} (KBr) 1676.08 cm^{-1} (CO); m/z: 216 ($C_{15}H_{20}O$, M^+), 173 (M^+-C_3H_7), 158 (M^+-C_4H_9); NMR ^1H δ: 1.05 (2d, 6H, -$CH(CH_3)_2$, $J = 6.7$ Hz), 1.16 (d, 3H, CH_3, $J = 7.0$ Hz), 1.9–2.0 (m, 1H), 2.2–2.3 (m, 1H), 2.70 (sept., 1H, -$CH(CH_3)_2$, $J = 6.8$ Hz), 3.80 (s, 3H, OCH_3), 5.85 (t, 1H, $J = 4.7$ Hz), 6.72 (d, 1H, $J = 8.2$ Hz), 6.82 (d, 1H, $J = 7.5$ Hz), 7.12 (t, 1H, ArH, $J = 7.9$ Hz) ppm; NMR ^{13}C δ: 18.74, 22.40, 22.82, 29.88, 30.46, 33.65, 55.40, 110.07, 118.90, 120.54, 123.90, 127.21, 143.15, 145.32, 156.25 ppm. Anal. calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.55; H, 9.48.

8-Isopropyl-5-methylnaphtalen-1-ol 8

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.30 g, 1.33 mmol) was added to a solution of compound **6** (0.24 g, 1.11 mmol) in dichloromethane (6 ml) at 0–5°C. The mixture was stirred at room temperature for 1 h, concentrated, and chromatographed rapidly (hexane) to provide the oily naphthalene **7** (0.20 g, 75%); m/z: 214 ($C_{15}H_{18}O$, M^+), 199 (M^+-CH_3), 184 (M^+-CH_2O); NMR ^1H δ 1.31 (2d, 6H, -$CH(CH_3)_2$, $J = 6.7$ Hz), 2.62 (s, 3H, C_5-CH_3), 3.95 (s, 3H, OCH_3), 4.46 (sept. 1H, $J = 7.1$ Hz), 6.88 (d, 1H, ArH, $J = 7.6$ Hz), 7.25 (d, 1H, ArH, $J = 7.4$ Hz), 7.34 (d, 1H, ArH, $J = 7.4$ Hz), 7.39 (t, 1H, ArH, $J = 8.1$ Hz), Hz), 7.58 (dd, 1H, ArH, $J = 8.4$ Hz, $J = 1.0$ Hz) ppm; NMR ^{13}C δ: 20.40, 24.83, 30.87, 55.34, 105.73, 117.53, 122.37, 124.15, 125.06, 127.04, 131.57, 135.22, 144.55, 158.19 ppm.

A solution of hydrobromic acid 48% (11 ml) was added slowly to a stirred solution of naphthalene **7** (0.13 g, 0.61 mmol) in acetic acid (2 ml) at room temperature and then was refluxed for 1 h. The reaction mixture was diluted with water and extracted with ether. The extracts were washed with water and $NaHCO_3$ (5%), dried, evaporated, and chromatograhed (hexane) to yield **8** (0.11 g, 91%) as a colorless oil. m/z: 200 ($C_{14}H_{16}O$, M^+), 185 (M^+-CH_3), 157 (M^+-C_3H_7); NMR ^1H δ: 1.34 (d, 6H, -$CH(CH_3)_2$, $J = 6.9$ Hz), 2.67 (s, 3H, CH_3), 3.05 (sept., 1H, -$CH(CH_3)_2$, $J = 6.9$ Hz), 5.37 (s, 1H, OH), 6.80 (d, 1H, ArH, $J = 7.4$ Hz), 7.25 (d, 1H, ArH, $J = 7.4$ Hz), 7.28 (dd, 1H, ArH, $J = 7.4$ Hz, $J = 8.3$ Hz), 7.53 (d, 1H, ArH, $J = 8.5$ Hz), 7.86 (s, 1H, ArH) ppm; NMR ^{13}C δ: 19.91, 23.97, 34.43, 108.62, 115.81, 116.86, 124.52, 124.74, 127.15, 132.69, 134.14, 145.47, 151.53 ppm. Anal. calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.18; H, 8.17.

1-Hydroxy-8-isopropyl-5-methylnaphtalene-2-carbaldehyde 9

To napthol **8** (0.08 g, 0.4 mmol) dissolved in dry tetrahydrofuran (15 ml) under nitrogen, magnesium chloride (0.076 g, 0.8 mmol), triethylamine (0.12 ml, 0.8 mmol), and paraformaldehyde (0.036 g, 1.2 mmol) were added and heated under reflux for 4 h. The reaction mixture was cooled to room temperature, acidified with hydrochloric acid (1 N), and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ (5%), dried, concentrated, and chromatographed (hexane) to obtain aldehyde **9**, pale yellow oil(0.06 g, 65%). ν_{max} (KBr) 1643.28 cm^{-1} (CO); m/z: 228 ($C_{15}H_{16}O_2$, M^+), 213 (M^+-CH_3), 185 (M^+-C_3H_7), 170 (M^+-2COH); NMR ^1H δ: 1.33 (d, 6H, -$CH(CH_3)_2$, $J = 6.9$ Hz), 2.65 (s, 3H, CH_3), 3.05 [sept. 1H, -$CH(CH_3)_2$, $J = 6.9$ Hz], 7.40 (s, 1H, ArH), 7.44 (d, 1H, ArH, $J = 8.7$ Hz), 7.47 (d, 1H, ArH, $J = 8.0$ Hz), 8.12 (s, 1H, ArH), 9.95 (s, 1H, CHO), 12.58 (s, 1H, OH) ppm; NMR ^{13}C δ: 19.68, 23.84, 34.25, 114.10, 115.65, 118.58, 124.74, 125.50, 131.38, 134.20, 135.33, 146.55, 161.87, 196.41 ppm. Anal. calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.18; H, 7.21.

(±)-Cis-5-hydroxycalamenene 1

A solution of the aldehyde **9** (0.06 g, 0.26 mmol) in ethyl acetate (25 ml) was stirred overnight with palladium-charcoal (10%, 0.03 g) under hydrogen at 500 psi. Removal of catalyst by filtration and evaporation of the solvent gave a residue, which was chromatographed (hexane/ether ether 9:1) to obtain (±)-*cis*-hydroxycalamenene **1** as viscous liquid (0.04 g, 72%). ν_{max} (KBr) 3450 cm^{-1} (OH); m/z: 218 ($C_{15}H_{22}O$, M^+),

203 (M^+-CH_3), 175 [M^+-$CH(CH_3)_2$], 147 [M^+-$CH(CH_3)_2$-CO]; NMR ^1H δ: 0.97 (2d, 6H, -$CH(CH_3)_2$, $J = 6.7$ Hz), 1.28 (d, 3H, CH_3, $J = 6.8$ Hz), 1.5–1.7 (m. 4H), 1.8–1.9 [m, 1H, -$CH(CH_3)_2$], 2.20 (s, 3H, CH_3), 2.7–2.8 (m, 2H), 4.60 (s, 1H, OH), 6.81 (d, 1H, C_8-H, $J = 7.9$ Hz), 6.92 (d, 1H, C_7-H, $J = 7.9$ Hz) ppm; [lit.[1,10] 0.91 (d, 3H), 0.94 (d, 3H), 1.29 (d, 3H), 1.6 (m, 2H), 1.8 (m, 2H), 1.97 (m, 1H), 2.18 (s, 3H), 2.8 (m, 2H), 4.59 (s, 1H, OH), 6.72 (1H, $J_{AB} = 8$ Hz), 6.92 (d, 1H, $J_{AB} = 8$ Hz) ppm]; NMR ^{13}C δ: 15.59, 19.51, 19.61, 21.71, 27.30, 32.66, 33.77, 36.26, 40.11, 118.41, 119.60, 122.84, 127.60, 141.18, 151.37 ppm. Anal. calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.73; H, 10.31.

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