Synthesis and natural occurrence of (*Z*/*E*)-β-and γ-curcumen-12-ol

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Dedicated to Professor Atta-ur-Rahman on the occasion of his 65th birthday

Abstract:
(*Z*/*E*)-β-Curcumen-12-ol (*Z*/*E*)-(**1**) was synthesized via Birch reduction of acid **6** starting from α-curcumene (**5**). An olefin isomerization of **1** is the key step in the synthesis of (*Z*/*E*)-γ-curcumen-12-ol (*Z*/*E*)-(**2**). Sesquiterpene alcohol (*E*)-**1** was found for the first time in nature as a minor constituent of different *Santalum* species by using the synthetic sample as reference.

Keywords: β-/γ-Curcumen-12-ol, monocyclic sesquiterpenes, isomerization, Wittig olefination

Introduction

β- and γ-Curcumen-12-ol (**1**)/(**2**) are rare sesquiterpene alcohols, probably due to their highly reactive diene ring systems and may be considered therefore as biogenetic precursors for more complex sesquiterpene skeletons, e.g. tricyclic helifolenals **3** or italicenols **4.**[1] Although, the enzymes involved have not been identified, it can be speculated that either a step-wise ionic mechanism or a concerted intramolecular cycloaddition is responsible for the formation of such terpenes.[1,2]

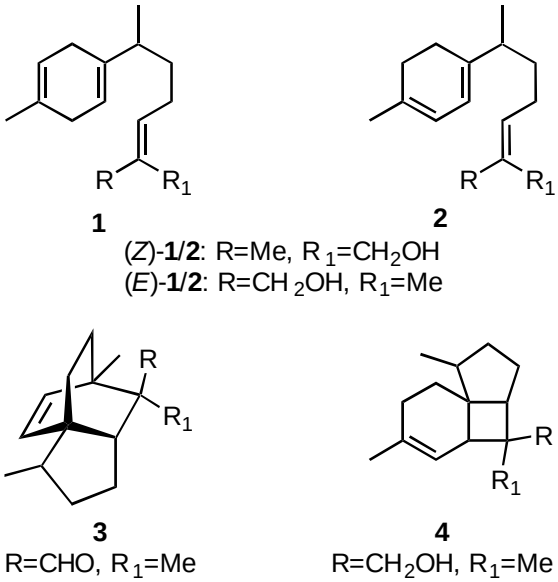


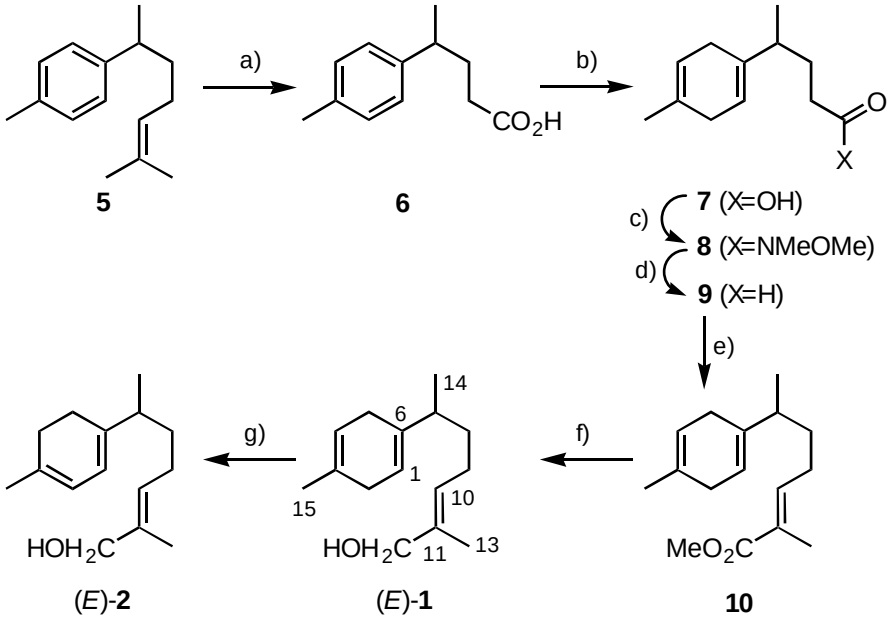
Figure 1. Structures of β- and γ-curcumen-12-ol (**1**)/(**2**), helifolenals **3** and italicenols **4**.

(*Z*)- and (*E*)-γ-Curcumen-12-ole (*Z*/*E*)-(**2**) were first characterized by Weyerstahl et al. in the essential oil of *Pulicaria gnaphalodes* (Vent.) Boiss.[1,3] Isomer (*E*)-**2** is also a constituent in Brazilian lantana oil (*Lantana camara* L.).[4] The isomeric 1,4-diene (*Z*)-β-curcumen-12-ol (*Z*)-(**1**) was recently isolated for the first time in Western Australian sandalwood oil (*Santalum spicatum* (R.Br.) A. DC.) together with the corresponding 1,3-diene (*Z*)-**2**.[5] Both sesquiterpene alcohols (*Z*)-**1** and (*Z*)-**2** were also detected in East Indian (*S. album* L.)[6] and New Caledonian sandalwood oil (*S. austrocaledonicum* Vieill. var. *austrocaledonicum*)[7].

However, it is interesting to note that in contrast to **2**, isomer (*E*)-**1** has not been found in nature and neither a synthesis of terpene alcohol **1** nor of **2** has been described in literature so far. Here, we report a short synthesis of β-and γ-curcumenol (**1**)/(**2**) and the identification of (*E*)-**1** in various sandalwood oils.

Results and Discussion

The synthesis of (*Z*/*E*)-β-curcumen-12-ol (*Z*/*E*)-(**1**) commenced from acid **6**, which was obtained from α-curcumene = ar-curcumene (**5**), a main constituent of curcuma oil (*Curcuma xanthorrhiza* Roxb., Zingiberaceae), following a procedure of Weinreb et al.[8]



Scheme 1. (a) cat. OsO_4, Jones reagent, 84% [8b]; (b) Li, liquid NH_3, 92%; (c) BOP, NEt_3, NHMeOMe x HCl, DMF, 96%; (d) $LiAlH_4$, Et_2O; (e) $Ph_3P^+CHMeCO_2MeBr^-$, NEt_3, CH_2Cl_2, 53% (over 2 steps); (f) $LiAlH_4$, Et_2O, 83%; (g) KO*t*Bu-toluene, microwave, 100°C, 64%.

Benzene derivative **6** was reduced under Birch conditions (Li in liquid NH_3/THF)[9] to form 1,4-cyclohexadiene **7** in 92% yield. Acid **7** was then transformed into the corresponding Weinreb amide **8** (96%)[10] using BOP in DMF as coupling agent[11]. Reduction of **8** with $LiAlH_4$ in Et_2O gave aldehyde **9**, which was reacted without further purification with phosphonium salt [$Ph_3P^+CHMeCO_2MeBr^-$] to obtain α,β-unsaturated ester (*E*)-**10** (53% for two steps, ratio: *E*/*Z* = 95:5). Consecutive reduction of ester (*E*)-**12** with $LiAlH_4$ yielded 83% of alcohol (*E*)-**1**. Its (*E*)-geometry at the C-10/C-11 π bond was confirmed by ^{1}H-NMR: irradiation at δ = 5.4 ppm (olefinic H's) gave a NOE signal at δ = 4.0 ppm (C*H*$_2$OH).

The corresponding *(Z)*-**1** can be analogously prepared from aldehyde **9** by a (*Z*)-selective Wittig type olefination.[12] Synthetic alcohol (*Z*)-**1** was identical in all respects (^{1}H, ^{13}C-NMR, GC-MS, RI) to the natural product (*Z*)-**1** described by Braun et al. from Western Australian sandalwood oil.[5] Enantiomerically pure β-curcumenol (**1**) may be prepared starting from enantiopure aldehyde **9** following the protocol of Ogasawara et al.[13]

With the synthetic sample of (*E*)-**1** in hand, we reinvestigated various commercially available sandalwood oils and were able to detect this so far unknown isomer for the first time as a new minor constituent in nature. GC-MS and retention indices (RI) on two different columns [RI = 2513 (DB-Wax) and RI = 1745 (DB-1)] of synthetic and natural (*E*)-**1** fully matched. However, in all three *Santalum* species (*Z*)-**1**[5-7] is the predominant isomer compared to (*E*)-**1**: *S. spicatum* (7.2%/1.6%), *S. album* (2.0%/1.4%) and in *S. austrocaledonicum* Vieill. var. *austrocaledonicum* (1.1%/0.12%).

The key step for the synthesis of (*Z*/*E*)-γ-curcumenol (*Z*/*E*)-(**2**) is a microwave-assisted[14] olefin isomerization[15] of (*Z*/*E*)-**1** under basic conditions (KOtBu/toluene). As a model compound we used 1,4-diene **7**, which was rearranged into the corresponding 1,3-diene in 62% yield (31% of diene **7** recovered). In contrast (*E*)-**1** led to a 4:1 mixture of (*E*)-**2** and (*E*)-**1** together with a minor amount of aromatized product [(*E*)-Nuciferol]. For further separation the crude product can be transformed into the corresponding acetates under standard conditions (Ac_2O, NEt_3, DMAP, CH_2Cl_2) and separated by column chromatography using $AgNO_3$ impregnated silica gel.[16] However, (*Z*/*E*)-**2** is chemically much more sensitive to decomposition and/or air-oxidation compared to (*Z*/*E*)-**1** as described before.[1,5]

In summary, we have demonstrated a short total synthesis (6 steps, 33% over all yield) of (*Z*/*E*)-β-curcumen-12-ol (*Z*/*E*)-(**1**) and its transformation into (*Z*/*E*)-γ-curcumen-12-ol (*Z*/*E*)-(**2**) by microwave assisted olefin isomerization. Furthermore, we have shown (*E*)-β-curcumen-12-ol (*E*)-(**1**) being a new natural product present in different sandalwood oils. This is a further example, that natural product synthesis and structure elucidation are closely connected.[17]

Experimental Section

General Procedures

All reagents were commercial products (*Fluka*, *Aldrich* or *Lancaster*) and were used as received. THF and Et_2O were freshly distilled from Na/benzophenone. All other solvents were distilled prior to use. Reactions involving air and/or moisture sensitive reagents were conducted under an argon atmosphere, and the glassware was oven dried (140°C) and purged with argon. All reactions were monitored by analytical TLC (silica gel 60 F_{254}), Merck, Darmstadt, Germany. Preparative column chromatography: silica gel 60 (63-200 μm), Macherey & Nagel, Düren, Germany. NMR: Unity INOVA Varian 300 spectrometer (^{1}H: 300 MHz; ^{13}C: 75.48 MHz) in $CDCl_3$ if not otherwise stated with TMS as internal standard; chemical shifts (δ in ppm and coupling constants (*J*) in Hz. IR: Perkin-Elmer Paragon 1000 FT-IR spectrometer; wave number (ν) in cm^{-1}. MS: Finnigan MAT 8200 in EI mode (70 eV); data in m/z (%). GC-MS: Hewlett Packard 5973N; columns: DB-Wax or DB-1 (20m x 0.18mm x 0.18μm film thickness, carrier gas: He) programmed from 60°C to 220°C at 9°C/min, mass spectrometer operating at 70 eV ionization energy (EI mode).

4-(4-Methyl-phenyl)pentanoic acid (6). Prepared according to literature, starting from α-curcumene = ar-curcumene (**5**)[8b] [isolated from curcuma oil (*Curcuma xanthorrhiza* Roxb., Zingiberaceae) (15-18%) or ginger oil (*Zingiber officinale* Roscoe, Zingiberaceae) (9-13%)]. Concentration of **5** can be increased in ginger oil by aromatization of zingiberene (>25%) and sesquiphellandrene (11-15%) prior to oxidative cleavage.[8b] IR (neat): 2959 (br), 1702. ^{1}H NMR: 10.8 (br, 1H), 7.12-7.04 (m, 4H), 2.76-2.62 (m, 1H), 2.32 (s, 3H), 2.26-2.20 (m, 2H), 1.95-1.83

(m, 2H), 1.30 (d, *J* = 7 Hz, 3H). ^{13}C NMR: 180.4 (s, C-10), 143.3 (s), 136.0 (s), 129.5 (d), 127.1 (d), 39.1 (d, C-7), 33.2, 32.6 (t, C-8, C-9), 22.5 (q, Me), 21.3 (q, Me).

4-(4-Methyl-1,4-cyclohexadienyl)pentanoic acid (7). A solution of **6** (1.5 g, 7.8 mmol) in anhydrous THF (35 mL) was added slowly with stirring to liquid ammonia (100 mL) at -70°C. To the clear solution Li metal (2.5 g, 357 mmol) was added in small pieces. After 30 min EtOH (5 mL) was added to the deep blue mixture and stirring was continued for 1h. The reaction was quenched with EtOH and the ammonia was allowed to distill off over night. The reaction mixture was concentrated in vacuum, the remaining aqueous phase cooled with ice and acidified with 1M HCl and extracted with *tert*. butylmethyl ether (5 x 50 mL). The combined organic phases were washed with water (4 x 30 mL), concentrated and the remaining oil distilled to yield 1.40 g (92%) of **7**. Colorless, viscous oil. Bp (Kugelrohr) 110-120°C/0.01 Torr. IR (film): 2954, 1515. ^{1}H NMR: 5.51 and 5.47 (br s, 2H), 2.8-2.5 (m, 4H), 2.4-2.2 (m, 2H), 1.68 (s, 3H), 1.8-1.6 (m, 2H), 1.04 (d, *J* = 7 Hz, 3H). ^{13}C NMR: 180.4 (s, C-10), 137.8 (s, C-6), 131.5 (s, C-3), 119.3, 118.8 (d, C-1, C-4), 40.4 (d, C-7), 32.4 (t, C-2), 31.8 (t, C-9), 29.6 (t, C-8), 26.5 (t, C-5), 23.2 (q, Me), 19.6 (q, Me). GC-MS: 194 (15) $[M]^+$, 134 (10), 132 (15), 105 (40), 93 (50), 91 (100)77 (45). HRMS m/z 194.1306 $[M]^+$, (calcd. for $C_{12}H_{18}O_2$ 194.1307).

***N*-Methoxy, *N*-methyl 4-(4-methyl-1,4-cyclohexadienyl)pentanoic amide** (**8**): To an ice-cold solution of acid **7** (0.21 g, 1.1 mmol) in DMF (5 mL) and 1 mL NEt_3 was added BOP (0.58 g, 1.3 mmol) under stirring. After 30 min *N,O*-dimethylhydroxylamine hydrochloride (0.20 g, 2 mmol) was added in one portion. The reaction mixture was diluted with H_2O (20 mL) and extracted with petroleum ether (5x30 mL). The combined organic phases were filtered through silica gel (30 g) concentrated and the remaining oil distilled to give 2.50 g (96%) of **8**. Colorless oil. Bp (Kugelrohr) 110-120°C/0.002 Torr. IR (film): 1662. ^{1}H NMR: 5.47-5.43 (br m, 2H, 2- and 5-H), 3.66 (s, 3H, OMe), 3.16 (s, 3H, NMe), 2.57 (br s, 4H, 1- and 4-H), 2.4-2.2 (m, 2H, 9-H), 2.14 (m, 7-H), 1.62 (br s, 5H, 8-H, olefin. Me), 1.04 (d, *J* = 6.9 Hz, 3H, Me); ^{13}C NMR: 175.1 (s, C-10), 138.4 (s, C-6), 131.4 (s, C-3), 118.9, 118.8 (d, C-1, C-4), 61.4 (q, OMe), 40.6 (d, C-7), 32.5 (q, NMe), 31.8 (t, C-2), 30.3 (t, C-9), 29.6 (t, C-8), 26.7 (t, C-5), 23.2 (q, Me), 19.8 (q, Me). GC-MS: 237 (3) $[M]^+$, 236 (5), 222 (5), 206 (2), 188 (7), 175 (35), 159 (33), 158 (15), 157 (19), 144 (19), 143 (13), 134 (32), 119 (59), 105 (56), 103 (48), 93 (29), 91 (100), 79 (33), 77 (47), 73 (28), 61 (26), 58 (26). ESI-HRMS m/z 260.1624 $[M+Na]^+$, (calcd. for $C_{14}H_{23}NO_2$+Na^+ 260.1621; $C_{14}H_{23}NO_2$ 237.1729).

Methyl (*E*)-2-methyl-6-(4-methyl-cyclohexa-1,4-dienyl)hept-2-enoate (10). To a solution of amid **8** (0.54 g, 2.3 mmol) in Et_2O (10 mL) at 5°C was added $LiAlH_4$ (0.20 g, 5.3 mmol) in small portions with stirring. Stirring was continued for 30 min and then ethyl acetate (3 mL) was added followed by 1M HCl (5 mL). The organic phase was separated and the aqueous extracted with Et_2O (3x 25 mL). The combined organic phases were washed with H_2O (2x10 mL), filtered through silica gel (30 g) and the filtrate was concentrated to obtain aldehyde **9**, which was used without further purification for the consecutive Wittig reaction. Crude aldehyde **9** was dissolved in CH_2Cl_2 (20 mL) and $Ph_3P^+CHMeCO_2MeBr^-$ (1.10 g, 2.6 mmol) was added under stirring followed by NEt_3 (0.5 mL). The reaction mixture was concentrated after 18h, the residue

dissolved in Et_2O (50 mL), the solution decanted from the precipitate and filtered through silica gel (40 g). The filtrate was concentrated and the oily residue distilled to yield 0.30 g (53% for two steps) of **10**. Colorless oil. *E*/*Z* = 95:5. Bp (Kugelrohr) 110-120°C/0.001 Torr. IR (film): 1713, 1261. ^{1}H NMR: 6.76 (q, *J* = 6 Hz, 1H, 10-H), 5.45 (m, 2H), 3.74 (s, 3H, ester Me), 2.59 (br s, 4H), 2.05-2.26 (m, 4H), 1.82 (s, 3H, 13-H), 1.68 (s, 3H, 15-H), 1.6-1.35 (m, H), 1.03 (d, *J* = 7 Hz, 3H, 14-H). ^{13}C NMR: 169.0 (s, C-12), 143.1 (s, C-11), 138.4 (s, C-6), 131.6 (s, C-3), 127.6 (d, C-10), 118.8, 118.7 (d, C1, C-4), 51.9 (OMe), 40.6 (d, C-7), 33.8 (t, C-8), 31.8, 27.0, 26.6 (t, C-2, C-5, C-9) 23.2 (q, C-15), 19.8 (q, C-14), 12.6 (q, C-13). GC-MS: 248 (2) $[M]^+$, 216 (10), 119 (100), 91 (45). HRMS m/z 248.1761 $[M]^+$, (calcd. for $C_{16}H_{24}O_2$ 248.1763).

(*E*)-2-Methyl-6-(4-methyl-cyclohexa-1,4-dienyl)hept-2-en-1-ol = (*E*)-β-curcumen-12-ol (*E*)-(1). To an ice-cold solution of ester **10** (0.30 g, 1.2 mmol) in Et_2O (50 mL) was added $LiAlH_4$ (0.20 g, 5.3 mmol) in small portions with stirring. 0.1M HCl (10 mL) was added after 30 min, the organic phase separated and the aqueous extracted with Et_2O (3x20 mL). The combined organic phases were filtered through silica gel (30 g). The filtrate was concentrated and the oily residue distilled to yield 0.22 g (83%) of alcohol (*E*)-**1**. Colorless oil. Bp (Kugelrohr) 90-100°C/0.03 Torr. *E*/*Z* = 95:5. IR (film): 3327 (br). ^{1}H NMR: 5.4-5.36 (m, 3H), 4.0 (s, 2H), 2.6 (br s, 4H), 2.2-2.0 (m, 1H), 2.0-1.9 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.6-1.2 (m, 4H), 1.05 (d, *J* = 7 Hz, 3H). ^{13}C NMR: 139.0 (s, C-6), 134.8 (s, C-11), 131.6 (s, C-3), 126.9 (d, C-10), 119.0 and 118.2 (d, C-1, C-4), 69.4 (t, C-12), 40.5 (d, C-7), 34.8 (t, C-8), 31.9 and 26.8 (t, C-2, C-5), 25.9 (t, C-9), 23.2 (q, C-15), 19.8 (q, C-14), 13.9 (q, C-13). GC-MS: 220 (0.5) $[M]^+$, 202 (2), 187 (6), 159 (5), 145 (23), 132 (68), 119 (100), 105 (34), 93 (47), 91 (38), 77 (21), 68 (7), 55 (10), 43 (10). HRMS m/z 220.1827 $[M]^+$, (calcd. for $C_{15}H_{24}O$ 220.1827).

(*E*)-2-Methyl-6-(4-methyl-cyclohexa-1,3-dienyl)hept-2-en-1-ol = (*E*)-γ-curcumen-12-ol (*E*)-(2). A mixture of *(E)*-**1** (0.1 g, 0.45 mmol) and KO*t*Bu (0.2 g) in degassed toluene (4 mL) was heated with stirring under Ar atmosphere in a microwave oven at 100°C for 2h. The cooled yellow reaction mixture was diluted with Et_2O (20 mL), the organic phase washed with H_2O (5 mL) and brine (5 mL) and filtered through a pad of silica gel (20 g). The filtrate was concentrated and the remaining oil distilled via Kugelrohr (100°C/0.03 Torr) to yield 0.08 g (80%) of a 4:1 mixture of *(E)*-**2** and *(E)*-**1**. The mixture can be separated after transformation into the corresponding acetates on silica gel/10% $AgNO_3$.[16] (*E*)-**2** is very sensitive to decomposition.

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