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Synthesis of (±)-*ar*-Macrocarpene

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Abstract: An efficient first synthesis of the sesquiterpene *ar*-macrocarpene, an irregular sesquiterpene isolated from *Cupressus macrocarpa* foliage, starting from 3-methylcyclohexenone has been described, which confirmed the structures of macrocarpenes.

Keywords: cuparenes, macrocarpenes, sesquiterpenes, terpene synthesis

Cupressus macrocarpa Hartw. ex Gord. (Moneterey cypress) is a large and picturesque tree and is the best known and most widely planted conifer in California. A number of sesquiterpenes were ubiquitous in *C. macrocarpa* foliage, such as α-cubebene, β-funebrene, caryophyllene, germacrenes, and cedrol. Recently, Cool has reported the isolation of a number of new sesquiterpenes from *C. macrocarpa* foliage;[1] of particular interest are the five irregular sesquiterpenes containing unprecedented carbon framework, named macrocarpenes. Four of them are dienes **1**–**4** and one is aromatic **5**, which is referred as *ar*-macrocarpene. Structures of all the macrocarpenes **1**–**5** were established from their spectral data and their conversion into a single saturated compound by hydrogenation. The absolute configuration of *ar*-macrocarpene **5** has been assigned tentatively, on the basis of the optical rotation and correlation with the related natural products in the literature. The aromatic sesquiterpene cuparene **6**, containing a 1-(aryl)-1,2,2-trimethylcyclopentane carbon framework, has been known for the past five decades[2] and has been present in a variety of essential oils. Cuparenoids also attracted significant attention from synthetic chemists and a large number of methods

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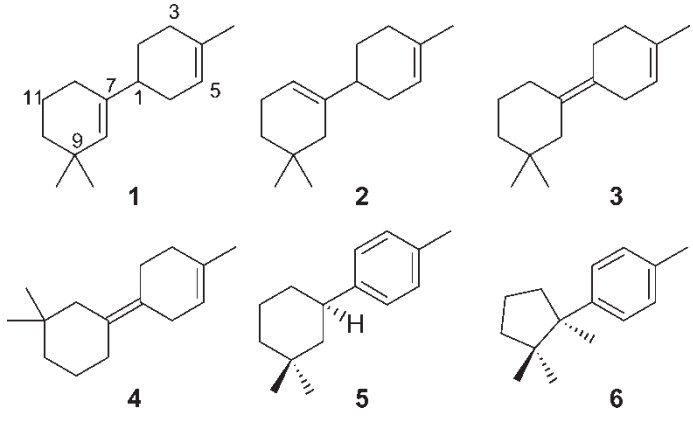
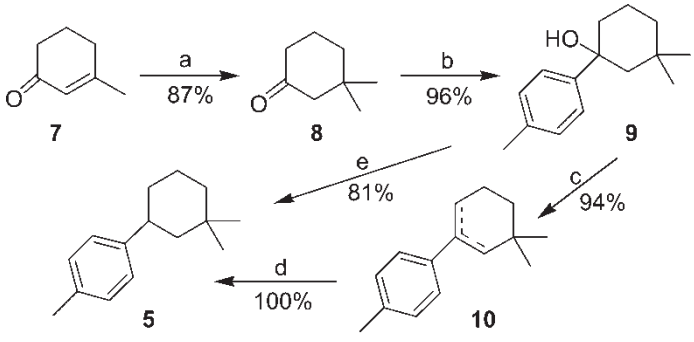
have been developed for the construction of the aryltrimethylcyclopentane carbon framework of cuparenoids.[3,4] Cool reported that *S*-cuparene **6** is also present in *C. macrocarpa* as a minor constituent.[1] Structures of a macrocarpenes **1**–**5** are very close to cuparene **6** (i.e., presence of a six-membered ring in place of a five-membered ring by incorporation of the methyl carbon on benzylic carbon of cuparene into the ring). In continuation of our interest in the synthesis of cuparenoid natural products,[4] and because macrocarpenes **1**–**6** have an unprecedented sesquiterpene carbon framework, we contemplated confirming the structures by synthesis of *ar*-macrocarpene **5**, which is the subject of this communication.



To confirm the structures of macrocarpenes, a rapid synthesis of *ar*-macrocarpene has been undertaken. The synthetic sequence starting from 3-methylcyclohexenone[5] **7** is depicted in Scheme 1. Conjugate addition of methylmagnesium iodide in the presence of copper iodide transformed the enone **7** into 3,3-dimethylcyclohexanone **8** in 87% yield. Reaction of the cyclohexanone **8** with 4-methylphenylmagnesium bromide at ice temperature



Scheme 1. (a) MeMgI, CuI, Et_2O; (b) 4-MeC_6H_4MgBr, THF; (c) $POCl_3$, py, CH_2Cl_2; (d) H_2, 10% Pd-C, hexane; (e) Li, liq. NH_3, THF.

generated the tertiary alcohol **9** in 96% yield. Dehydration of the tertiary alcohol **9** with phosphorousoxy chloride and pyridine in methylene chloride generated a 3 : 1 mixture of the olefines **10** in 94% yield, which on catalytic hydrogenation in hexane with 10% palladium on charcoal as the catalyst generated quantitatively (±)-*ar*-macrocarpene **5**. Alternatively, the tertiary alcohol **9** on reaction with lithium in liquid ammonia directly generated (±)-*ar*-macrocarpene **5** in 81% yield. Synthetic *ar*-macrocarpene (±)-**5** exhibited ^{1}H and ^{13}C NMR spectral data (in C_6D_6) identical to that reported for the natural product.

In conclusion, we have accomplished a rapid and efficient synthesis of *ar*-macrocarpene (±)-**5** starting from 3-methylcyclohexenone **7** in four steps with an overall yield of 79%. The present sequence confirms the structures of macrocarpenes **1**–**5**.

EXPERIMENTAL

IR spectra were recorded on Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. A 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for preparing the NMR samples. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). 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 spectra and is given in parentheses. High-resolution mass spectra were recorded using a Micromass Q-TOF micromass spectrometer using electrospray ionization.

3,3-Dimethylcyclohexanone 8

To a cold (−30°C) magnetically stirred solution of CuI (8.66 g, 45.5 mmol) in dry ether (10 ml), a solution of methylmagnesium iodide [prepared from Mg (3.3 g, 136.4 mmol) and MeI (8.5 ml, 136.4 mmol) in ether (17 ml)] was added, and the reaction mixture was stirred for 15 min at the same temperature. The resultant yellow solution was added to a solution of the enone **7** (1.0 g, 9.1 mmol) in dry ether (3 ml) at −30°C over a period of 15 min. The reaction mixture was stirred at the same temperature for 1 h and then at rt for 1 h. It was quenched with saturated aq. NH_4Cl (10 ml) and extracted with ether (3 × 5 ml). The combined organic layer was washed with brine (10 ml) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using methylene chloride–hexane (1:10) as eluent furnished the cyclohexanone **8** as a colorless oil (995 mg, 87%). IR (neat): ν_{max}/cm^{-1} 1712. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.19 (2H, t, *J* 6.9 Hz, H-6), 2.07 (2H, s, H-2), 1.90–1.75 (2H, m),

1.60–1.48 (2H, m), 0.94 (6H, s, 2 × *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 210.3 (C, C═O), 54.9 (CH_2, C-2), 40.7 (CH_2), 38.1 (CH_2), 35.9 (C, C-3), 28.6 (2C, CH_3, 2 × CH_3), 22.5 (CH_2, C-5). HRMS: m/z calcd. for $C_8H_{15}O$ (M + H): 127.1123; found: 127.1125.

1-(4-Methylphenyl)-3,3-dimethylcyclohexan-1-ol 9

To an ice-cold magnetically stirred solution of the cyclohexanone **8** (200 mg, 1.59 mmol) in ether (3 ml), a solution of 4-methylphenylmagnesium bromide [prepared from 4-bromotoluene (0.9 ml, 7.95 mmol) and Mg (309 mg, 12.7 mmol) in ether (5 ml)] was added and stirred for 30 min at the same temperature. The reaction was quenched with saturated aq. NH_4Cl (5 ml) and extracted with ether (3 × 5 ml). The combined organic layer was washed with brine (5 ml) and dried (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 alcohol **9** as a colorless oil (333 mg, 96%). IR (neat): ν_{max}/cm^{-1} 3556, 3456, 1512, 814. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.31 (2H, d, *J* 8.1 Hz) and 7.07 (2H, d, *J* 8.1 Hz) [Ar-H], 2.30 (3H, s, Ar-CH_3), 2.00–1.15 (9H, m), 1.16 (3H, s) and 0.86 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 147.3 (C), 135.8 (C), 128.8 (2C, CH), 124.5 (2C, CH), 74.2 (C, C-OH), 51.2 (CH_2, C-2), 39.2 (CH_2), 38.9 (CH_2), 34.3 (CH_3), 31.3 (C, C-3), 27.5 (CH_3), 21.0 (CH_3), 19.0 (CH_2). HRMS: m/z calcd. for $C_{15}H_{22}ONa$ (M + Na): 241.1568; found: 241.1576.

1-(4-Methylphenyl)-3,3-dimethylcyclohexene and 1-(4-Methylphenyl)-5,5-dimethylcyclohexenes 10

To a magnetically stirred ice-cold solution of the alcohol **9** (21 mg, 0.1 mmol) in methylene chloride (3 ml), pyridine (0.12 ml, 1.5 mmol) and $POCl_3$ (0.14 ml, 1.5 mmol) were added sequentially and stirred at the same temperature for 1 h. The reaction was quenched with water (5 ml) and extracted with methylene chloride (3 × 3 ml). The combined organic layer was washed with 3 *N* HCl (3 ml) and brine (3 ml) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using hexane as eluent furnished a ~3:1 mixture of cyclohexenes **10** (18 mg, 94%) as colorless oil. IR (neat): ν_{max}/cm^1 3024, 810. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): (3:1 mixture of regioisomers) δ 7.56 (2H, d, *J* 7.8 Hz) and 7.39 (2H, d, *J* 7.8 Hz) [Ar-H], 6.33 and 6.09 (1H, brs, C═CH), 2.65 (3H, s, Ar-CH_3), 2.70–2.50 (2H, m), 2.50–2.45 (1H, m), 2.15–2.06 and 1.84–1.79 (1H, m), 1.73 (2H, t, *J* 6.6 Hz), 1.32 and 1.39 (6H, s, 2 × *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): (3 : 1 mixture of regioisomers) δ 140.0 and 139.7 (C, *C*═CH), 135.9 (C, Ar-C), 135.5 (C, Ar-C), 122.3 and 134.2 (CH, C═*C*H), 128.8 (2C, CH, 2 × Ar-CH), 125.1 (2C, CH, 2 × Ar-CH), 41.5

and 37.0 (CH_2), 34.9 and 27.6 (CH_2), 29.4 and 32.3 (C, *C*Me_2), 28.5 and 30.2 (2C, CH_3, 2 × *tert*-CH_3), 23.8 and 20.2 (CH_2), 21.1 (CH_3, Ar-CH_3).

1,1-Dimethyl-3-(4-methylphenyl)cyclohexane (*ar*-Macrocarpene 5)

To a solution of the mixture of cyclohexenes **10** (17 mg, 0.09 mmol) in hexane (2 ml), 10% Pd/C (10 mg) was added and stirred at rt in an atmosphere of hydrogen created by evacuative displacement of air (balloon) for 7 h. The reaction mixture was filtered through a small column of silica gel using methylene chloride. Evaporation of the solvent and purification of the residue over a silica-gel column using hexane as eluent furnished *ar*-macrocarpene (±)-**5** as a colorless oil (17 mg, 100%).

Alternative Procedure

To magnetically stirred, freshly distilled (over sodium) ammonia (50 ml) in a two-necked flask equipped with Dewar condenser, freshly cut lithium (35 mg, 5.0 mmol) was added followed by a solution of the alcohol **9** (72 mg, 0.33 mmol) in anhydrous THF (3 ml). The resulting blue solution was stirred at −33°C for 20 min and then quenched with NH_4Cl (solid). After evaporation of ammonia, the residue was taken in water (5 ml) and extracted with ether (3 × 5 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using hexane as eluent furnished *ar*-macrocarpene (±)-**5** (54 mg, 81%) as a colorless oil. IR (neat): ν_{max}/cm^{-1} 1514, 810. ^{1}H NMR (300 MHz, C_6D_6): δ 6.87 (4H, s, Ar-H), 2.33 (1H, tt, *J* 12.3 and 3.6 Hz, H-3), 1.89 (3H, s, Ar-CH_3), 1.54 (1H, m), 1.30–0.74 (7H, m), 0.64 (3H, s) and 0.62 (3H, s) [2 × *tert*-CH_3]. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.04 (4H, s, Ar-H), 2.63 (1H, tt, *J* 12.3 and 6.6 Hz, H-3), 2.30 (3H, s, Ar-CH_3), 1.90–1.79 (1H, m), 1.70–1.10 (7H, m), 0.99 (3H, s) and 0.94 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, C_6D_6): δ 145.0 (C, Ar-C), 135.3 (C, Ar-C), 129.3 (CH, 2 × Ar-CH), 127.2 (CH, 2 × Ar-CH), 48.0 (CH_2), 40.0 (CH), 39.2 (CH_2), 34.6 (CH_2), 33.7 (CH_3, Ar-CH_3), 31.3 (C, *C*Me_2), 30.2 (CH_2), 24.7 (CH_3), 21.1 (CH_2), 21.0 (CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 144.7 (C), 135.0 (C), 129.0 (2C, CH), 126.8 (2C, CH), 47.8 (CH_2), 39.7 (CH), 39.1 (CH_2), 34.3 (CH_2), 33.7 (CH_3), 31.4 (C, C-1), 24.8 (CH_3), 22.9 (CH_2), 21.1 (CH_3).

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