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TETRAHEDRON: *ASYMMETRY*

Total asymmetric synthesis of (7*S*,9*R*)-(+)-bisacumol

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Abstract—A facile stereoselective synthetic route to (7*S*,9*R*)-(+)-bisacumol **1** has been achieved. This novel approach derives its asymmetry by employing asymmetric dihydroxylation and CBS reduction processes. The resulting sesquiterpene **1** was produced with highly enantio- and diastereoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

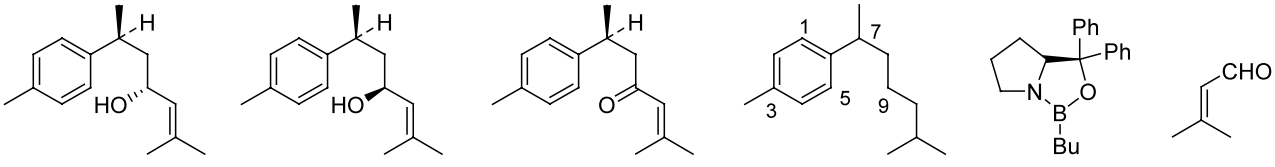
1. Introduction

(+)-Bisacumol **1** (Fig. 1), a member of the aromatic bisabolane sesquiterpene family, was isolated from the rhizome of *Curcuma Xanthorrhiza* and its absolute configuration was determined to be 7*S*,9*R*.[1] As a result of the wide distribution of this class of natural products and their high biological activities,[2] many methods have been developed to synthesize the compounds in racemic form,[3] however, only a few stereoselective syntheses were reported due to the difficulty of introducing a stereogenic center in the benzylic position.[4] To the best of our knowledge, no total asymmetric synthesis of the title compound has been reported. Herein, we describe a short, efficient asymmetric synthesis of (7*S*,9*R*)-(+)-bisacumol **1** along with its epimer (7*S*,9*S*)-(+)-bisacumol, *epi*-**1**, and (+)-*ar*-turmerone **2**, which was isolated from the essential oil from the rhizome of turmeric curcuma *Curcuma Longa Linn*.[5] and is known to have 9*S* configuration.

Inspired by the synthesis of *trans*-2-phenylcyclohexanol,[6] we aimed to prepare the chiral 2-phenyl alcohol **5** using the Sharpless AD reaction[7] and from this versatile chiral synthon, (*S*)-(+)-*ar*-turmerone **2**, which in turn could be subjected to CBS reduction[8] to furnish the title chiral allylic alcohol **1**. Our synthetic strategy is shown in full in Scheme 1.

2. Results and discussion

Treatment of the styrene derivative **3** with AD-mix-α at 0°C afforded the (*S*)-(+)-diol **4** in 96% yield. Stereoselective reduction of the benzylic alcohol **4** with Raney nickel in refluxing ethanol furnished the 2-phenylpropanol **5** (>93% e.e.) in 89% yield, in which retention of the configuration was observed.[9] The corresponding alcohol was treated with PPh_3 (1.2 equiv.) and CBr_4 (1.1 equiv.) in CH_2Cl_2 at room temperature to afford the bromide **6** in 99% yield. Due to the low reactivity of



(7*S*,9*R*)-**1** bisacumol | (7*S*,9*S*)-epi-**1** | (*S*)-**2** *ar*-turmerone | aromatic bisabolane | **8** | **7**

Figure 1.

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bromide **6**, its reaction with magnesium powder to form the alkylmagnesium bromide is sluggish. Thus, CH_3I (1.2 equiv.) was used, and by metal-halogen exchange in refluxing ether, the desired Grignard reagent derived from **6** can be obtained. After the addition of 3-methyl crotonaldehyde **7** at −20°C, a pair of diastereoisomers **1** and *epi*-**1** (~1:1 ratio) were obtained in 68% overall yield and which were separable using column chromatography. Oxidation of the diastereoisomers with MnO_2 in CCl_4 at 60°C afforded (+)-*ar*-turmerone **2** in 94% yield, the CBS reduction[8] of compound **2** was carried out with oxazaboralidine **8** (0.1 mol/mol of ketone) and catecholborane (2 equiv.) at −78°C in toluene for 15 h to provide the title compound (7*S*,9*R*)-(+)-bisacumol **1** in 89% yield (d.e. >91%). The corresponding ^1H and ^{13}C NMR spectrum of this pair of diastereoisomers have evident differences. Compared with the spectroscopic data for the natural product (7*S*, 9*R*)-(+)-bisacumol, the absolute configuration of compound **1** and *epi*-**1** can be confirmed as (7*S*,9*R*) and (7*S*,9*S*), respectively. The other spectroscopic data also agreed with that of the natural product.[1]

In summary, we have successfully synthesized the natural (7*S*,9*R*)-(+)-bisacumol **1** in 48% overall yield from the readily available 4-(1-methenylethyl)toluene, the synthesis only required six separate chemical operations and was highly enantio- and diastereoselective. Sharpless AD reaction and Raney nickel reduction induced the stereogenicity in the formation of the benzylic center, and CBS reduction furnished the chiral allylic alcohol. Our strategy thus provides a general and efficient access to aromatic enantiomerially enriched bisabolane sesquiterpenoids, and is expected to find more applications in the synthesis of other related natural products, for example, heliannuol A-E.[10]

3. Experimental

3.1. General

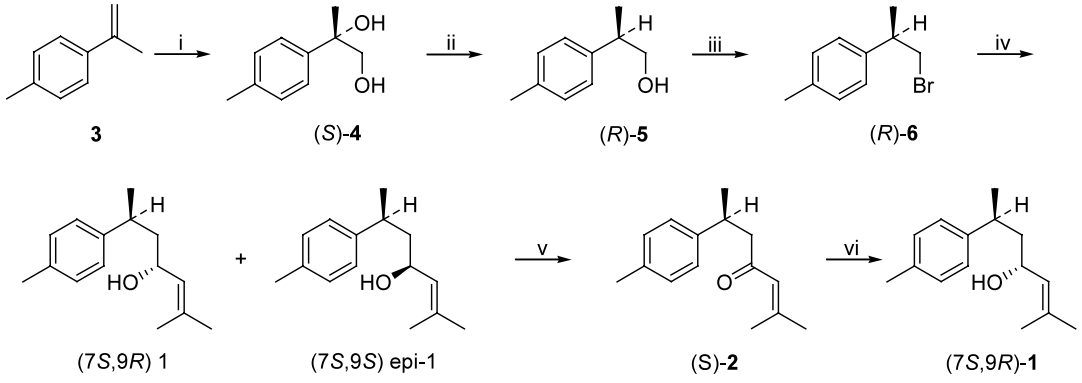
The ^1H and ^{13}C NMR data were recorded in $CDCl_3$ solution with Bruker AM-200 or AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or $CDCl_3$. Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube. Mass spectra were recorded on a ZAB-HS mass spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyser. Chiral analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150×4.6 mm D) with hexane/isopropyl alcohol as eluant. Column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether:ethyl acetate.

3.2. (*S*)-(+)-diol, 4

A 250 mL round-bottom flask, equipped with a magnetic stirrer, was charged with *tert*-butyl alcohol (75 mL), water (75 mL), and AD-mix-α (21 g). Stirring at rt produced two clear phases, the lower aqueous phase being bright yellow. The mixture was cooled to 0°C whereupon some of the dissolved salts precipitated. 4-(1-Methenyl ethyl) toluene **3** (2 g, 15 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 0°C for 18 h. While the mixture was stirred at 0°C, solid sodium sulfite (22.5 g) was added and the mixture was allowed to warm to rt and stirred for 30 min, ethyl acetate 80 mL was added to the reaction mixture, and after separation of the layer, the aqueous phase was further extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to give the diol. This crude product was purified by column chromatography to afford the diol **4** (2.4 g, 96%) ($[\alpha]_D^{20}$ +15.1 (*c* 7.2, $CHCl_3$, e.e.>95%). ^1H NMR δ 1.479 (s, 3H), 2.361 (S, 3H), 3.525 (d, 1H, $J=11.4$ Hz), 3.671 (d, 1H, $J=11.4$ Hz), 7.163 (d, 2H, $J=8.2$ Hz), 7.309 (d, 2H, $J=8.2$ Hz). MS (EI): *m*/*z* 166, 151, 149 and 135.

3.3. (*R*)-(+)-2-(4-Methylphenyl)propanol, 5

To a stirred solution of diol **4** (2.3 g, 13.8 mmol) in ethanol (50 mL) was added freshly prepared Raney nickel (14 g). The mixture was heated under reflux for 3 h, then the catalyst was filtered off and washed with ethanol, the organic solution was evaporated and the



Scheme 1. *Reagents and conditions*: (i) AD-mix-α, *t*-BuOH/H_2O, 0°C, 18 h; (ii) Raney Ni, EtOH, reflux, 3 h; (iii) PPh_3, CBr_4, CH_2Cl_2, rt, 4 h; (iv) a. Mg powder, CH_3I, Et_2O, reflux, 3 h, b. 3-methyl crotonaldehyde, Et_2O, −20°C; (v) MnO_2, CCl_4, 60°C, 30 min; (vi) oxazaboralidine **8** (0.1 mol/mol of ketone) and catecholborane (2 equiv.), toluene, −78°C, 15 h.

crude product was purified by column chromatography to afford the alcohol **5** (1.85 g, 89%), $[\alpha]_D^{20}$ +14.6, (c = 5.0, $CHCl_3$, e.e.>93%, lit.[11] $[\alpha]_D$ +14.01 (c 1.26, $CHCl_3$). ^{1}H NMR δ 1.208 (d, 3H, J = 7.0 Hz), 2.303 (s, 3H), 2.790–2.894 (m, 1H), 3.565 (d, 2H, J = 7.2 Hz), 7.096 (s, 4H). MS (EI): m/z 150, 119 and 91.

3.4. (*R*)-(+)-1-Bromo-2-(4-methylphenyl)propane, 6

To a solution of alcohol **5** (1.8 g, 12 mmol) together with triphenyl phosphine (3.8 g, 14.5 mmol) in methylene dichloride 40 mL was added in portion carbon tetrabromide (4.1 g, 12.4 mmol). After addition, the solution was stirred at rt for 4 h, then petroleum ether 40 mL was added. The reaction mixture was filtered by suction, and washed with petroleum ether: ethyl acetate (10:1), the organic solution was evaporated and the crude product was purified by column chromatography to give the bromide **6** (2.52 g, 99%), $[\alpha]_D^{20}$ +24.2 (c 9.0, $CHCl_3$). ^{1}H NMR δ 1.450 (d, 3H, J = 6.8 Hz), 2.398 (s, 3H), 3.077–3.250 (m, 1H), 3.469–3.665 (m, 2H), 7.186 (s, 4H). MS (EI): m/z 214, 212, 133, 119 and 91.

3.5. (7*S*,9*R*)-(+)-Bisacumol, 1 and (7*S*,9*S*)-(+)-bisacumol, *epi*-1

Under an atmosphere of Ar, a solution of bromide **6** (2.0 g, 9.4 mmol) together with iodomethane (1.6 g, 11.3 mmol) in dry ethyl ether (30 mL) was added dropwise to magnesium powder (600 mg, 25 mmol) in dry ethyl ether (10 mL). The mixture was stirred under reflux for 3 h, and then cooled to −20°C, 3-methyl crotonaldehyde (2.0 g, 24 mmol) was added slowly, the mixture was stirred at this temperature for 2 h, and rt for another 2 h, then quenched with saturated ammonium chloride. After separation of the organic layer, the aqueous phase was further extracted with ethyl acetate (3×50 mL), The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to give a pair of diastereoisomers. This crude product was purified by column chromatography to afford (7*S*,9*R*)-(+)-bisacumol, **1** (0.68 g, 33%) and (7*S*,9*S*)-(+)-bisacumol, *epi*-**1** (0.72 g, 35%), respectively.

Data for compound 1: $[\alpha]_D^{20}$ +15.6 (c 8.4, $CHCl_3$, lit.[1] $[\alpha]_D$ +13.9 (c 0.42, EtOH). ^{1}H NMR δ 1.293 (d, 3H, J = 7.1 Hz), 1.581 and 1.736 (s, each 3H), 1.690–1.760 (m, 1H), 1.838–1.922 (m, 1H), 2.385 (s, 3H), 2.916–2.971 (m, 1H), 4.191 (ddd, 1H, J = 8.4, 8.4, 5.0 Hz), 5.205 (dd, 1H, J = 9.6, 1.3 Hz), 7.146 (s, 4H). ^{13}C NMR δ 17.89, 20.61, 22.90, 25.51, 35.71, 45.83, 66.66, 126.79, 128.55, 128.91, 133.89, 135.11, 143.90. MS (EI): m/z 218, 203, 200, 185, 157, 119, 85.

Data for *epi*-1: $[\alpha]_D^{20}$ +9.4 (c 9.7, $CHCl_3$). ^{1}H NMR δ 1.292 (d, 3H, J = 7.0 Hz), 1.579 and 1.782 (s, each 3H), 1.661–1.728 (m, 1H), 1.965–2.037 (m, 1H), 2.373 (s, 3H), 2.750–2.971 (m, 1H), 4.210–4.267 (m, 1H), 5.192 (dd, 1H, J = 9.0, 1.4 Hz), 7.113 (d, 2H, J = 8.4 Hz), 7.142 (d, 2H, J = 8.4 Hz). ^{13}C NMR δ 18.10, 20.62, 22.79, 25.65, 35.93, 45.92, 66.69, 126.72, 128.07, 128.92, 1335.08, 135.16, 144.03. MS (EI): m/z 218, 203, 185, 157, 119, 85.

3.6. (*S*)-(+)-*ar*-Turmerone, 2

To a solution of alcohol **1** and *epi*-**1** (1.1 g, 5 mmol) in carbon tetrachloride (20 mL) was added manganese dioxide (4.4 g), the mixture was stirred at 60°C for 30 min and the oxidant was filtered off, the filtrate was evaporated and the crude product was purified by column chromatography to afford the ketone **2** (1.0 g, 94%), $[\alpha]_D^{20}$ +82.7 (c 6.8, $CHCl_3$, lit.[12] $[\alpha]_D$ +81.56 ($CHCl_3$). ^{1}H NMR δ 1.227 (d, 3H, J = 7.0 Hz), 1.851 and 1.990 (s, each 3H), 2.306 (s, 3H), 2.540–2.776 (m, 2H), 3.244–3.351 (m, 1H), 6.026 (s, 1H), 7.104 (s, 4H). ^{13}C NMR δ 20.59, 20.87, 21.91, 27.49, 35.23, 52.62, 124.06, 126.59, 129.03, 135.42, 143.63, 154.84, 199.68. MS (EI): m/z 216, 201, 132, 119, 83.

3.7. (7*S*,9*R*)-(+)-Bisacumol, 1

Under an atmosphere of Ar, to a solution of ketone **2** (430 mg, 2 mmol) and catalyst **8** (0.2 mmol) in toluene (10 mL) was added dropwise catecholborane (1 M, 4 mL) at −78°C, the mixture was stirred at this temperature for 16 h, then quenched with water. The mixture was allowed to warm to room temperature and stirred for 30 min, after separation of the layer, the aqueous phase was further extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed successively with 2N sodium hydroxide solution, 2N aqueous hydrogen chloride and brine, dried over anhydrous sodium sulfate and evaporated, the crude product was purified by column chromatography to afford the alcohol **1** (390 mg, 89%), $[\alpha]_D^{20}$ +14.4 (c 5.5, $CHCl_3$, d.e.>91%).

Acknowledgements

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