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Determination of the absolute structure of albaconol

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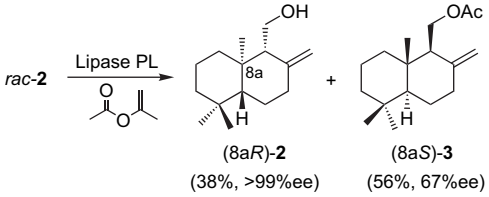
ABSTRACT

The concise synthesis of (8a*R*)-(−)-albaconol (**1**) from (8a*R*)-albicanol (**2**) obtained from the lipase-assisted asymmetric acetylation of *rac*-**2**, was achieved in 45% overall yield (eight steps). By comparison of the sign of specific rotation of between synthetic (8a*R*)-(−)-albaconol (**1**) and natural (+)-albaconol (**1**), the absolute structure of natural (+)-**1** was determined to be 1*R*,2*R*,4a*S*,8a*S* configuration.

1. Introduction

Albaconol (**1**) was isolated from the fresh fruiting bodies of the basidiomycetes *Albatrellus confluens*,[1] and acts as weak antagonists for human vanilloid-receptor (VR1) without agonistic effect.[2] Albaconol (**1**) inhibits significantly the growth of human tumor cell lines in vitro, and stimulates DNA cleavage, stabilizes and increases the topo II-mediated DNA cleavable complex because of inhibition the religation activity of topo II in a dose-dependent manner.[3] Structure of **1** was determined by spectral analysis, including 2D-NMR spectroscopy, but the absolute structure of **1** was not determined yet.[1] Albaconol (**1**) possesses the skeleton of drimane-type sesquiterpenoids, which is directly connected to a resorcinol moiety. On the other hand, lipase-assisted resolution of racemic albicanol (±)-**2** was reported to give (8a*S*)-acetate **3** (56%, 67% ee) and (8a*R*)-**2** (38%, >99% ee) by us.[4] Herein we report the first synthesis of (8a*R*)-**1** from (8a*R*)-**2**, and determination of the absolute structure of natural albaconol (**1**) based on chiral synthesis of (8a*R*)-**1** (Scheme 1).



Scheme 1.

2. Synthesis of (8a*R*)-albaconol (1)

Dess–Martin oxidation of (8a*R*)-albicanol (**2**)[4] gave a (8a*R*)-albicanal (**4**) in 92% yield, which was treated with an anion **5** obtained by reaction of 3,5-di-*O*-methoxymethyltoluene[5] with *n*-BuLi to afford a diastereomeric mixture of (8a*R*)-**6**. Acetylation of (8a*R*)-**6** followed by the Birch reduction provided (8a*R*)-**7** in 82% overall yield from (8a*R*)-**4**. Dihydroxylation of the *exo*-olefin part of (8a*R*)-**7** using $OsO_4/K_3Fe(CN)_6$ gave stereoselectively the desired diol (8a*R*)-**8** (83% yield), which is corresponding to the dihydroxylation product from less-hindered β-side. The relative configuration of C(2)-position in (8a*R*)-**8** could be *S*, because the present (8a*R*)-**8** was finally converted to the enantiomer of natural albaconol (8a*S*)-**1** as mentioned later on. Monotosylation of (8a*R*)-**8** gave selectively primary tosylate (8a*R*)-**9** (94% yield), which was treated with $LiAlH_4$ to afford tertiary alcohol (8a*R*)-**10** in 96% yield. Finally, (8a*R*)-**10** was treated with pyridinium *p*-toluenesulfonate (PPTS) in the presence of ethylene glycol to afford (8a*R*)-albaconol (**1**) in 80% yield (Scheme 2). In this case, PPTS was used as weak acid to avoid formation of ether linkage between phenolic hydroxyl group and C(2)-carbon. The physical data (mp 212–213 °C, ^1H and ^{13}C NMR) of the synthetic (8a*R*)-**1** were identical with those (mp 212–214 °C and ^1H and ^{13}C NMR) of natural albaconol (**1**). The specific rotation {$[\alpha]_D^{23}$ −58.9 (*c* 1.15, MeOH)} of synthetic (8a*R*)-**1** was in accord with that {$[\alpha]_D^{23}$ +63.8 (*c* 0.4, MeOH)} of natural albaconol (**1**)[1] except for the sign of the specific rotation. From these evidences, the absolute structure of natural albaconol (**1**) was determined as shown in Figure 1.

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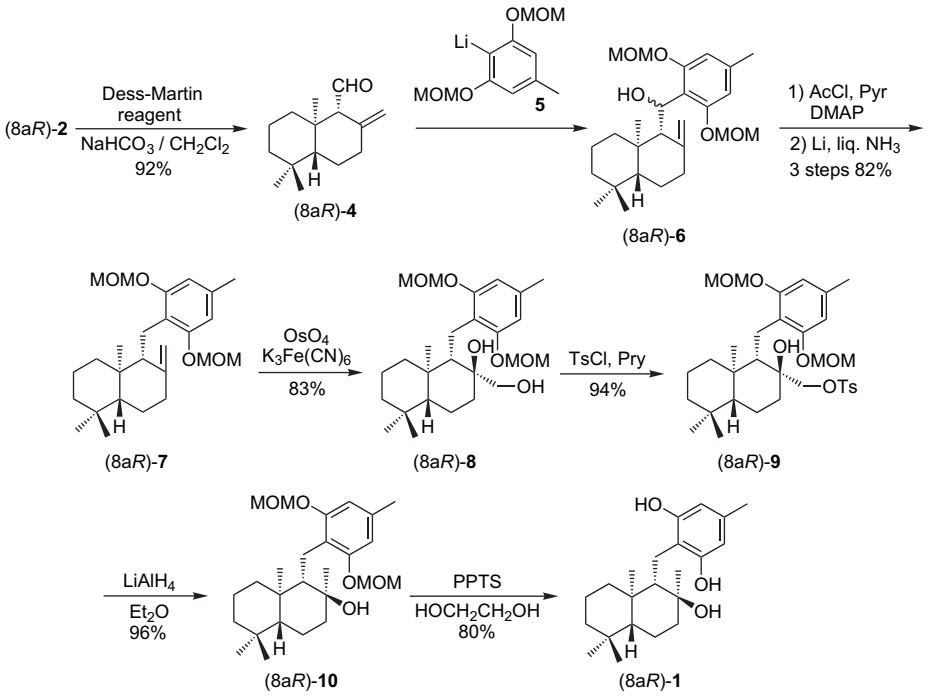

Scheme 2.

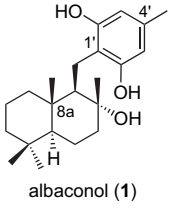

Figure 1.

3. Conclusion

The reaction of (8a*R*)-albicanal (**4**) derived from (8a*R*)-albicanol (**2**) with 4-(3,5-di-*O*-methoxymethyl)tolyl anion **5** gave a diastereomeric mixture of (8a*R*)-**6**, which was subjected to consecutive acetylation and Birch reduction to afford the *exo*-olefin (8a*R*)-**7**. Stereoselective dihydroxylation of (8a*R*)-**7** followed by consecutive monotosylation and $LiAlH_4$ reduction provided the protected albaconol (8a*R*)-**10**, which was deprotected to give (8a*R*)-albaconol (**1**). Overall yield of (8a*R*)-**1** from (8a*R*)-albicanol (**2**) was 45% in eight steps. By comparison of the sign of specific rotation of between synthetic (8a*R*)-(−)-albaconol (**1**) and natural (+)-albaconol (**1**), the absolute configuration of natural (+)-**1** was determined to be 1*R*,2*R*,4a*S*,8a*S*.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-3S melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL AL-400 spectrometer in $CDCl_3$. 2D-NMR measurement (COSY, HMQC, HMBC, NOESY) of (8a*R*)-(−)-albaconol (**1**) was carried out by means of JEOL ECP-500 NMR spectrometer in acetone-d_6. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-AM II 50. IR spectra were recorded with a JASCO FT/IR 4100 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. For column chromatography, silica gel (Kieselgel 60) was employed.

4.2. 1-{[(1*R*,4a*R*,8a*R*)-Decahydro-2-methylene-5,5,8a-trimethylnaphthalen-1-yl]methyl}-2,6-di-*O*-methoxymethyl-4-methylbenzene (7)

(1) To a solution of (8a*R*)-**2** (0.955 g, 4.3 mmol) in CH_2Cl_2 (65.0 mL) were added $NaHCO_3$ (5.89 g, 70.1 mmol) and Dess–Martin reagent (3.15 g, 7.43 mmol) at 0 °C and the reaction mixture was stirred for 2 h at rt. The reaction mixture was directly subjected to chromatography on silica gel [100 g, *n*-hexane/AcOEt=200:1] to give (8a*R*)-**4** (0.871 g, 92% yield) as a colorless oil. Compound (8a*R*)-**4**: ^1H NMR: δ 0.87 (3H, s), 0.89 (3H, s), 1.03 (1H, dd, J=12.6, 2.8 Hz), 1.15 (3H, s), 1.17–1.28 (2H, m), 1.38–1.50 (3H, m), 1.54–1.66 (2H, m), 1.69–1.75 (1H, m), 2.05–2.13 (1H, m), 2.37–2.49 (2H, m), 4.50 (1H, br s), 4.92 (1H, br s), 9.87 (1H, d, J=4.8 Hz). ^{13}C NMR: δ 16.0, 18.7, 21.9, 23.1, 33.4, 33.5, 36.7, 39.0, 39.9, 41.9, 54.0, 67.9, 109.2, 145.0, 205.7. (2) To a solution of 3,5-di-*O*-methoxymethyltoluene (2.53 g, 11.9 mmol) in dried THF (15 mL) was added *n*-butyl lithium (4.35 mL, 11.3 mmol, 2.6 M in *n*-hexane) at 0 °C and the resulting mixture was stirred for 1 h at the same temperature to generate anion **5**. A solution of (8a*R*)-**4** (0.871 g, 3.95 mmol) in THF (2 mL) was added to the solution of anion **5** at 0 °C and the reaction mixture was stirred for 3 h. The mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (50 g), *n*-hexane/ethyl acetate (10:1)] to afford crude product **6** (1.48 g). (3) To a solution of crude **6** in pyridine (30 mL) were added acetic anhydride (4.0 g, 40 mmol) and 4-*N*,*N*-dimethylaminopyridine (96.6 mg, 0.79 mmol), and the reaction mixture was stirred for 13 h at rt. The mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (50 g), *n*-hexane/ethyl

acetate (20:1)] to afford the corresponding acetate (1.93 g). A solution of the acetate in THF (0.5 mL) was added to Li (0.275 g, 40 mmol) in liq. ammonia (ca. 20 mL) at −78 °C and the reaction mixture was stirred for 3 h. The mixture was warmed up to rt and the residue was purified by silica gel column chromatography [silica gel (50 g), *n*-hexane/ethyl acetate (20:1)] to afford (8a*R*)-**7** (1.36 g, 3.27 mmol, 82% yield) from (8a*R*)-**4**. Compound (8a*R*)-**7**: colorless plates [from *n*-hexane/ethyl acetate (20:1)]. Mp: 88–89 °C. $[\alpha]_D^{20}$ +33.5 (*c* 0.60, $CHCl_3$). ^{1}H NMR: δ 0.81 (6H, s), 0.85 (3H, s), 1.08–1.62 (7H, m), 1.65–1.72 (1H, m), 1.83–1.93 (2H, m), 2.25 (3H, s), 2.20–2.32 (1H, m), 2.54 (1H, br d, *J*=10.8 Hz), 2.70 (1H, dd, *J*=3.4, 13.2 Hz), 2.83 (1H, dd, *J*=9.6, 13.2 Hz), 3.48 (6H, s), 4.67 (1H, s), 4.98 (1H, s), 5.14 (2H, d, *J*=6.8 Hz), 5.16 (2H, d, *J*=6.8 Hz), 6.54 (2H, s). ^{13}C NMR: δ 14.2, 19.3, 19.4, 21.7, 21.8, 24.6, 33.6, 33.8, 38.6, 38.8, 40.4, 42.4, 55.2, 56.0, 56.2 (2C), 94.5 (2C), 106.3, 108.7 (2C), 117.6, 136.6, 155.9 (2C). IR (CCl_4): 2925, 1611, 1585, 1153, 1046. HREIMS calcd for $C_{26}H_{40}O_4$: 416.2927, found: 416.2931.

4.3. 1-{[(1*S*,2*S*,4a*R*,8a*R*)-Decahydro-2-hydroxy-2-hydroxylmethyl-5,5,8a-trimethylnaphthalen-1-yl]methyl}-2,6-di-*O*-methoxymethyl-4-methylbenzene (8)

A solution of (8a*R*)-**7** (0.200 g, 0.48 mmol) in *tert*-butyl alcohol (10 mL) was added to a mixture of potassium osmate dihydrate (0.03 mmol), $K_3Fe(CN)_6$ (0.984 g, 3.0 mmol), and potassium carbonate (0.414 g, 3.0 mmol) in water (10 mL) and the resulting mixture was stirred for 2 days at rt. Ice-cooled aq sodium sulfite (10%) was added to the mixture and the mixture was extracted with ethyl acetate twice. The organic layers were combined, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (10 g), *n*-hexane/ethyl acetate (2:1)] to afford (8a*R*)-**8** (0.180 g, 0.400 mmol, 83% yield) and recovered starting material (30 mg, 15%). Compound (8a*R*)-**8**: colorless oil. $[\alpha]_D^{20}$ −26.5 (*c* 0.78, $CHCl_3$). ^{1}H NMR: δ 0.71 (1H, dt, *J*=3.6, 13.6 Hz), 0.76 (3H, s), 0.81 (3H, s), 0.87 (3H, s), 1.03 (1H, dt, *J*=3.6, 13.6 Hz), 1.07–1.31 (4H, m), 1.42–1.63 (2H, m), 1.81 (1H, br d, *J*=12.8 Hz), 1.89 (1H, t, *J*=7.4 Hz), 2.24 (3H, s), 2.31 (1H, br d, *J*=12.4 Hz), 2.68 (1H, dd, *J*=3.2, 14.6 Hz), 2.86 (1H, dd, *J*=6.4, 14.6 Hz), 3.46 (6H, s), 3.57 (1H, d, *J*=9.6 Hz), 3.75 (1H, d, *J*=9.6 Hz), 5.15 (4H, s), 6.54 (2H, s). ^{13}C NMR: δ 15.2, 18.1, 18.5, 19.7, 21.5, 21.7, 33.2, 33.4, 37.2, 38.6, 39.4, 41.7, 56.3 (2C), 56.4, 59.5, 63.3, 75.8, 94.5 (2C), 108.5 (2C), 117.7, 137.2, 155.1 (2C). IR (CCl_4): 3503, 2925, 1610, 1584, 1153, 1044. HREIMS calcd for $C_{26}H_{42}O_5$: 450.2981, found: 450.2976.

4.4. 1-{[(1*S*,2*S*,4a*R*,8a*R*)-Decahydro-2-hydroxy-2-tosyloxylmethyl-5,5,8a-trimethylnaphthalen-1-yl]methyl}-2,6-di-*O*-methoxymethyl-4-methylbenzene (9)

To a solution of (8a*R*)-**8** (0.176 g, 0.391 mmol) in pyridine (3 mL) was added *p*-toluenesulfonyl chloride (0.224 g, 1.17 mmol) at rt. The resulting mixture was stirred for 4 h at rt. The mixture was added to ice-cold water and extracted with ethyl acetate twice. The organic layers were combined and dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (10 g), *n*-hexane/ethyl acetate (4:1)] to afford (8a*R*)-**9** (0.225 g, 0.373 mmol, 94% yield). Compound (8a*R*)-**9**: colorless oil. $[\alpha]_D^{20}$ −16.2 (*c* 1.07, $CHCl_3$). ^{1}H NMR: δ 0.69 (3H, s), 0.78 (3H, s), 0.81 (3H, s), 0.74–0.87 (2H, m), 1.04 (1H, dd, *J*=3.2, 13.2 Hz), 1.15 (1H, dd, *J*=3.4, 13.2 Hz), 1.22–1.56 (4H, m), 1.79–1.90 (2H, m), 2.09 (1H, br d, *J*=13.4 Hz), 2.24 (3H, s), 2.41 (3H, s), 2.63 (1H, dd, *J*=6.4, 14.6 Hz), 2.77 (1H, dd, *J*=5.2, 14.6 Hz), 2.92 (1H, br), 3.44 (6H, s), 4.27 (1H, d, *J*=10 Hz), 4.41 (1H, d, *J*=10 Hz), 5.12 (2H, d, *J*=8.8 Hz), 5.14 (2H, d, *J*=8.8 Hz), 6.54 (2H, s), 7.32 (2H, d, *J*=8.0 Hz), 7.81 (2H, d, *J*=8.0 Hz). ^{13}C NMR: δ 15.5, 18.1, 18.5, 19.1, 21.3, 21.5, 21.7, 33.1, 33.3, 37.1, 38.8, 39.3, 41.5, 56.2, 56.2 (2C), 59.5, 71.8, 74.4, 94.4 (2C), 108.5 (2C), 117.2, 128.0 (2C), 129.6 (2C), 133.1, 137.3, 144.5, 155.1 (2C). IR (CCl_4): 3545, 2925, 1610, 1585, 1174, 1153. Anal. for $C_{33}H_{48}O_8S$: C, 65.54; H, 8.00%. Found: C, 65.07; H, 7.91%.

4.5. 1-{[(1*S*,2*S*,4a*R*,8a*R*)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalen-1-yl]methyl}-2,6-di-*O*-methoxymethyl-4-methylbenzene (10)

To a solution of (8a*R*)-**9** (0.200 g, 0.331 mmol) in ether (10 mL) was added $LiAlH_4$ (38 mg, 1 mmol) at rt and the resulting mixture was refluxed for 6 h. Ice-cold water (0.2 mL), aq sodium hydroxide (1 M, 0.2 mL), and Celite 545 (1 g) were added to the mixture and the resulting mixture was filtrated through a pad of Celite 545 and the residue was washed with ether. The filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (10 g), *n*-hexane/ethyl acetate (2:1)] to afford (8a*R*)-**10** (0.180 g, 0.234 mol, 94% yield). Compound (8a*R*)-**10**: colorless oil. $[\alpha]_D^{20}$ −13.0 (*c* 0.65, $CHCl_3$). ^{1}H NMR: δ 0.72–0.92 (1H, m), 0.74 (3H, s), 0.83 (3H, s), 0.94 (3H, s), 1.07 (1H, dt, *J*=4.4, 13.2 Hz), 1.17–1.33 (3H, m), 1.27 (3H, s), 1.38 (1H, dt, *J*=3.6, 13.0 Hz), 1.46–1.63 (2H, m), 1.72 (1H, t, *J*=5.4 Hz), 1.80–1.88 (2H, m), 2.26 (3H, s), 2.71 (1H, dd, *J*=5.2, 14.4 Hz), 2.86 (1H, dd, *J*=5.0, 14.4 Hz), 3.03 (1H, br), 3.48 (6H, s), 5.17 (4H, s), 6.56 (2H, s). ^{13}C NMR: δ 15.0, 18.6, 18.7, 20.3 21.6, 21.7, 23.6, 33.3, 33.5, 39.1, 39.6, 41.9, 44.3, 56.3 (2C), 56.4, 60.4, 76.7, 94.5 (2C), 108.7 (2C), 118.7, 136.9, 155.3 (2C). IR (CCl_4): 3564, 2923, 1610, 1584. HREIMS calcd for $C_{26}H_{42}O_5$: 434.3032, found: 434.3035.

4.6. (8a*R*)-Albaconol (1)

To a solution of (8a*R*)-**10** (75.0 mg 0.123 mmol) and ethylene glycol (0.1 mL) in ethanol (3 mL) was added pyridinium *p*-toluenesulfonate (30.0 mg, 0.12 mmol) and the resulting mixture was stirred for 2 days at 50 °C. The mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (10 g), *n*-hexane/ethyl acetate (1:1)] to afford (8a*R*)-**1** (47.9 mg, 0.138 mmol, 80% yield). Compound (8a*R*)-**1**: colorless needles. Mp 212–213 °C (from ethyl acetate) (lit.[1] mp 212–214 °C). $[\alpha]_D^{23}$ −58.9 (*c* 1.15, MeOH) (lit.[1] $[\alpha]_D^{23}$ +63.8 (*c* 0.40, MeOH)). ^{1}H NMR (acetone-d_6): δ 0.57 (1H, td, *J*=13.2, 3.6 Hz), 0.82 (3H, s), 0.85 (3H, s), 0.98 (3H, s), 0.89–0.96 (1H, m), 1.06 (1H, td, *J*=13.2, 4.0 Hz), 1.06–1.15 (2H, m), 1.30 (3H, s), 1.25–1.45 (3H, m), 1.48–1.60 (5H, m), 1.88–1.97 (2H, m), 2.02–2.19 (3H, m), 2.17 (3H, s), 2.45 (1H, d, *J*=15.2 Hz), 3.02 (1H, dd, *J*=5.6, 15.2 Hz), 5.00 (1H, s), 6.10 (2H, s), 8.56 (2H, s). ^{13}C NMR (acetone-d_6): δ 15.4, 18.7, 19.0, 21.1, 21.2, 21.9, 24.4, 33.7, 33.8, 38.5, 40.0, 42.6, 44.6, 57.1, 61.4, 75.5, 108.6 (2C), 114.1, 136.6, 156.6 (2C). IR (CCl_4): 3345, 2924, 1584. HREIMS calcd for $C_{22}H_{34}O_3$: 346.2508, found: 346.2366.

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5. This compound was obtained by the reaction of commercially available 5-methylresorcinol with methoxymethyl chloride (MOM-Cl) in the presence of diisopropylethylamine.