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Determination of the absolute configuration and the first total synthesis of (−)- and (+)-linderol A

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Abstract—Racemic triol 4-acetyl-3,6-dihydroxy-6-hydroxymethyl-1-methoxy-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran, (±)-**2**, an intermediate of the total synthesis of (±)-linderol A **1**, was acetylated and resolved by HPLC on chiral stationary phases into the respective enantiomers (−)- and (+)-**3**. Enantiopure (−)-**2**, obtained by hydrolysis of (−)-**3**, was treated with (−)-camphanic chloride to give the crystalline camphanate (−)-**4**, the absolute configuration of which was determined by X-ray crystallography. Triols (−)- and (+)-**2** were converted to (−)- and (+)-**1** without disrupting their stereogenic centers according to the previously reported synthesis of (±)-**1**. As natural (−)-linderol A **1** was derived from (−)-**2**, its absolute configuration was elucidated to be 5a*R*,6*R*,9*R*,9a*S*.

1. Introduction

In 1995, Sashida et al. reported the isolation of (−)-linderol A **1** from the fresh bark of *Lindera umbellata* (Lauraceae) (Fig. 1). The structure and the relative configuration of (−)-**1** were unambiguously determined on the basis of their spectral data as (5a*R**,6*R**,9*R**,9a*S**)-4-cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran (Fig. 1).[1] They also reported the potent inhibitory activity of **1** on melanin biosynthesis of cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs.[1] We have taken much interest in (−)-**1** in view of these structural and biological aspects. We have already succeeded and reported the first total synthesis of (±)-**1**.[2] As the absolute configuration of (−)-**1** was not determined, we planned its elucidation in terms of the medicinal chemistry. Herein, we report the determination of the absolute configuration as well as the first total synthesis of natural (−)-linderol A **1**.

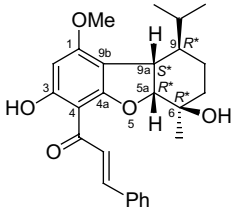

Figure 1. (−)-Linderol A **1**.

2. Results and discussion

We planned the resolution of an intermediate, which appeared in the total synthesis of (±)-**1**. First, esterifications of the triol (±)-**2**[2] with optically active acids followed by separation of the resulting diastereomeric mixtures were tried. However, all attempts (including HPLC separation and lipase-catalyzed kinetic resolution) failed. Next, monoacetate (±)-**3** was subjected to HPLC separation on chiral stationary phases. After several experiments, HPLC with CHIRALPAK® AD-H [2 cm (ϕ) × 25 cm (L), Daicel Chemical Industries, Ltd] with *n*-hexane/ethanol (7/3) as an eluent showed good separation of the enantiomers. Isolated (−)- and (+)-**3** were hydrolyzed by K_2CO_3 in methanol to give each triol (−)- and (+)-**2** (Scheme 1).

In order to prepare single crystals for X-ray crystallography, (+)- or (−)-**2** was converted to several enantiomerically pure esters with optically active acylating or sulfonylating agents. Carboxylic acid ester (−)-**4** derived

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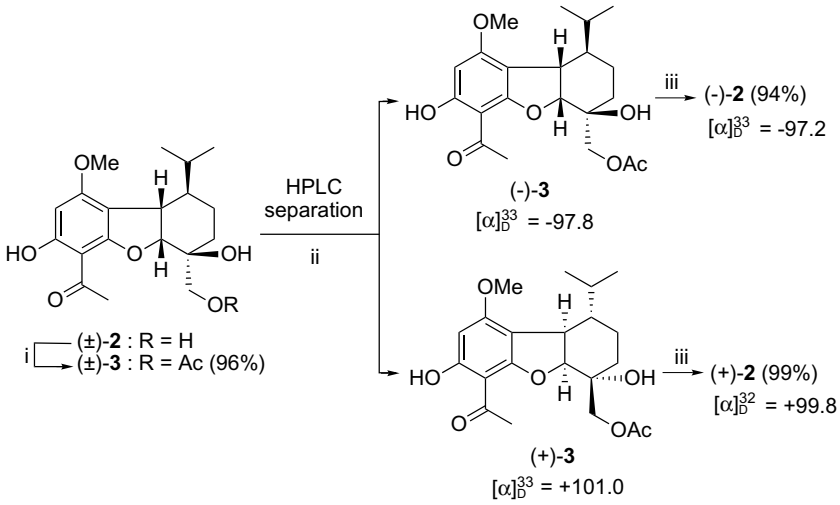
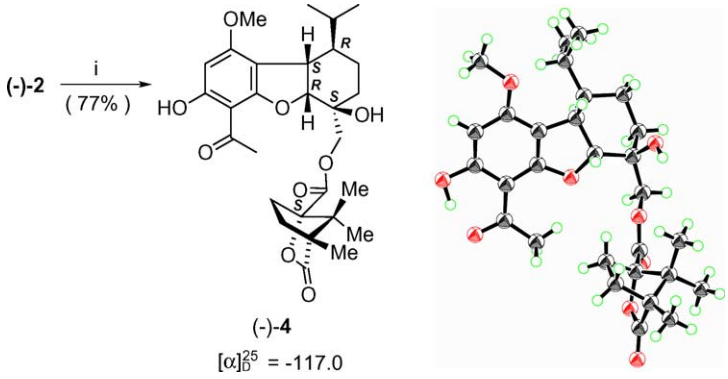


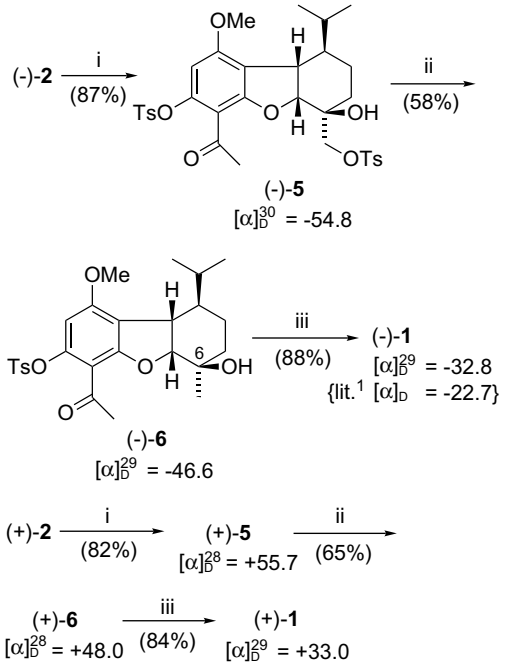
Scheme 1. Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (ii) CHIRALPAK® AD-H, *n*-hexane/ethanol = 7/3; (iii) K_2CO_3, MeOH, rt.



Scheme 2. Reagents and conditions: (i) (−)-camphanic chloride, Et_3N, DMAP, CH_2Cl_2, rt.

from (−)-**2** and (−)-camphanic chloride[3] as a chiral auxiliary, gave good crystals and hence was subjected to X-ray crystallographic analysis (CCDC No. 241976). The obtained result is shown in Scheme 2. On the basis of the stereochemistry of the (−)-camphanoyl group, the stereochemistry of (−)-**4** was determined to be 5a*R*,6*S*,9*R*,9a*S* (Scheme 2).

According to the reported total synthesis of (±)-**1**,[1] (−)- and (+)-**2** were converted to (−)- and (+)-**1**, respectively, by use of reactions, which occurred only on the achiral substituents (Scheme 3). Bistosylate (−)-**5** (87%) was prepared in the usual manner, and its treatment with $NaBH_3CN$ reduced only the C_6–CH_2–OTs portion to the product having a C_6-α-methyl group (−)-**6** in 58% yield.[4] Finally, crossed aldol condensation of (−)-**6** with benzaldehyde in the presence of *t*-BuOK followed by alkaline hydrolysis gave (−)-**1** in 88% yield (Scheme 3). Compound (+)-**2** was treated by the same procedure as mentioned above to give (+)-**1** (Scheme 3). Spectral data (NMR, IR, and MS) of synthetic (−)- and (+)-**1** were identical with those of an authentic sample [natural (−)-**1**[1] and synthetic (±)-**1**[2]]. As the specific rotation of (−)-**1** derived from (−)-**2** was −32.8 (*c* 1.0, $CHCl_3$) (lit.[1] = −22.7, $CHCl_3$),[5] the undefined absolute configuration of natural (−)-**1** could be determined to be 5a*R*,6*R*,9*R*,9a*S*.



Scheme 3. Reagents and conditions: (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (ii) $NaBH_3CN$, HMPA, 120 °C; (iii) PhCHO, *t*-BuOK, *t*-BuOH; then KOH, MeOH, rt.

3. Conclusion

In conclusion, we have separated racemic acetate (±)-**3** by HPLC on chiral stationary phases to each acetate (−)- and (+)-**3**. The absolute configuration of the crystalline (−)-**4** derived from the enantiopure (−)-**2** with (−)-camphanic chloride was determined by X-ray crystallography (CCDC No. 241976). The triols (−)- and (+)-**2** were derived to optically active (−)- and (+)-linderol A **1**, respectively, without affecting their stereogenic centers. As natural (−)-**1** was derived from (−)-**2**, its absolute configuration was elucidated to be 5a*R*,6*R*,9*R*,9a*S*.

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5. Concentration did not appear in lit.[1]