Enantioselective Synthesis of the (1S,5R)-Enantiomer of Litseaverticillols A and B

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An enantioselective synthesis of the (1S,5R)-enantiomer of litseaverticillols A and B was accomplished in line with our previously reported synthetic pathway for their (1R,5S)-enantiomer. The use of “EtSCeCl₃” prepared from EtSLi and CeCl₃, instead of previously employed EtSLi itself, for the formation of thiol ester intermediates prevented any undesirable epimerization occurring in the process.

Key words: litseaverticillol; enantioselective synthesis; sesquiterpenoid; anti-HIV

Litseaverticillols A and B (1 and 2, respectively; see Scheme 1), monocyclic sesquiterpenoids possessing a novel carbon framework designated as litseane, were isolated together with their congeners (litseaverticillols) from leaves and twigs of the perennial shrub, Litsea verticillata Hance, collected in Vietnam. The terpenoids (1 and 2) exhibited considerably high anti-HIV activity (IC₅₀, 5.0 and 2–3 μg/ml, respectively) by inhibiting the replication of HIV-1, but they also showed cytotoxicity against HOG.R5 cells (a reporter cell line) with CC₅₀ values of 13.2 and 5.7 μg/ml, respectively. Quite interestingly, these natural products were obtained as racemic mixtures (i.e., their specific rotation values were both zero). This unusual observation as natural products, coupled with their unprecedented carbon skeleton and medicinally important bioactivity, have attracted the interest of organic chemists. A series of synthetic studies on litseaverticillols has recently been reported by Vassilikogiannakis et al. which led to the first synthesis of (±)-1 and (±)-2 and also provided a clear explanation for their formation as racemic mixtures. We became interested in these racemic sesquiterpenes of natural origin from another viewpoint that there could be a possibility that one enantiomer might have only anti-HIV activity and the other cytotoxicity. In that case, the anti-HIV enantiomer with no cytotoxicity could be a promising lead compound for practical anti-HIV agents. This presumption prompted our synthetic efforts on the optically active forms of 1 and 2 which have recently culminated in the first enantioselective total synthesis of (1R,5S)-(−)-1 and (1R,5S)-(−)-2. In this note, we describe the synthesis of their enantiomers directed toward an evaluation of the difference in biological activity between the enantiomers of litseaverticillols A and B.

Our synthesis of (1S,5R)-1 and (1S,5R)-2 basically followed our previous synthesis of their corresponding enantiomers, (1R,5S)-1 and (1R,5S)-2, except that (R)-4-benzylxazolidin-2-one was employed as the source of chirality, instead of its (S)-form used in the previous synthesis. Homogaric acid (E/Z = ca. 3:1) was converted via its mixed anhydride form into N-acetyl-α,β-unsaturated α,β-unsaturated γ-lactone derivative 3. The syn-selective Evans asymmetric aldol reaction of 3 with aldehyde afforded a mixture of (E)- and (Z)-5 which could be readily separated by silica gel column chromatography to furnish (E)- and (Z)-5 in isolated yields of 41% and 10%, respectively. The chiral auxiliary of (E)-5 was substituted by an ethylthio group to give (E)-6 without any epimerization at the position α to the carbonyl by using “EtSCeCl₃” prepared by mixing EtSLi and CeCl₃ in a ratio of 1:1; this seems to be the first example, to our knowledge, of utilizing the “RSCeCl₃” species for the preparation of thiol esters. In our previous synthesis of the (1R,5S)-isomer of 1 and 2, we employed EtSLi itself, which resulted, although only occasionally, in a small degree of undesirable epimerization at the α-position to give (E)-6 with a reduced 88% diastereomeric excess (de) in the worst case when we failed to keep the reaction temperature below −15 °C. Diastereomically pure thiol ester (E)-6 was then subjected to the Liebeskind–Srogl esterification reaction at 80 °C under microwave irradiation to give an almost quantitative yield (96%) of (E)-7. The slightly improved chemical yield in the present case (96%) as compared to that in our previous synthesis of (1R,5S)-1 (90%) would be ascribable to the reduced microwave-irradiation time (15 min × 2); the reaction mixture was irradiated at 80 °C for 60 min in total (15 min × 4) in the previous synthesis. Finally, (E)-7 was exposed to a

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solution of TBAF–HF/THF containing a small amount of water (adjusted to pH 7 to prevent possible loss of stereochemical integrity via the retroaldol–aldol process and/or keto–enol equilibration)40 to furnish (1S,5R)-1 ([α]D = 23 +150° (c 0.17, CHCl3); lit.4) [α]D = 23 −151° (c 0.10, CHCl3) for (1R,5S)-1. An evaluation of the biological activity of (1S,5R)-1 and (1S,5R)-2, as well as their previously obtained enantiomers, is now being conducted by Prof. Fong (University of Illinois at Chicago).

**Experimental**

IR, 1H- and 13C-NMR, and mass spectra were recorded by using the same spectrometers and conditions as those reported in Ref. 4. Silica gel column chromatography and the microwave experiments were conducted in a similar manner to those described in Ref. 4. The IR, and 1H- and 13C-NMR spectra of compounds 3, (E)- and (Z)-5, (E)- and (Z)-6, (E)- and (Z)-7, (1S,5R)-1, and (1S,5R)-2 were identical with those reported for the corresponding enantiomers in Ref. 4.

(R)-4-Benzyl-3-(4,8-dimethyl-3,7-nonadienoyl)oxazolidin-2-one (3). Compound 3 (E/Z-mixture, 2.21 g, 55% yield) was obtained as a colorless oil from 2.15 g (11.8 mmol) of homogeneric acid (E/Z = ca. 3:1)39 and 2.21 g (12.5 mmol) of (R)-4-benzyloxazolidin-2-one according to the procedure reported in Ref. 4.

HR-FABMS m/z ([M + H]+): calcd. for C31H33NO5Si, 432.2069; found, 432.2073.

(R)-4-Benzyl-3-{[(2R,3E)-4,8-dimethyl-2-[(1R,2Z)-3-(tributylstannyl)-1-(triethylsilyloxy)-2-butenyl]-3,7-nonadienyl]oxazolidin-2-one ([E]-5), and its (Z)-isomer ([Z]-5). Compounds (E)-5 (329 mg, 41% yield) and (Z)-5 (82.9 mg, 10% yield) were obtained as colorless oils from 0.339 g (0.992 mmol) of 3 and 0.517 g (1.44 mmol) of 4 according to the procedure reported in Ref. 4. (E)-5: [α]D = −37.6° (c 1.33, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C33H35NO5SiSn, 814.4409; found, 814.4404. (Z)-5: [α]D = +26.3° (c 0.455, CHCl3); HRMS (FAB) m/z ([M + H]+): calcd. for C33H35NO5SiSn, 814.4409; found, 814.4407. The magnitude of the specific rotation of (E)-6 (−37.6°) did not correspond to the data previously reported for its enantiomer (+24.8)4. This discrepancy seems to be ascribable to a small amount of impurities contained in the previously synthesized enantiomer.

5-Ethyl (2R,3E)-4,8-Dimethyl-2-[(1R,2Z)-3-(tributylstannyl)-1-(triethylsilyloxy)-2-butenyl]-3,7-nonadienethioate ([E]-6). To a stirred suspension of anhydrous CeCl3 (256 mg, 1.04 mmol) prepared from CeCl3·7H2O according to the literature protocol11 in THF (6 ml) were successively added EtSH (76 µl, 1.03 mmol) and a solution of nBuLi in hexane (1.6 M, 0.620 ml, 0.992 mmol) at −78 °C, and the mixture was stirred at 0 °C for 30 min. A solution of CeCl3·7H2O in THF (1 ml) was then added at −20 °C, and the resulting mixture was stirred overnight at −15 °C. The mixture was quenched with sat. NH4Cl aq., and the mixture was extracted with Et2O. The extract was washed with brine, dried (Na2SO4) and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc =

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**Scheme 1.** Synthesis of the (1S,5R)-Enantiomer of Litseaverticillols A and B [(1S,5R)-1 and (1S,5R)-2, respectively].

Reagents and conditions: a) nBuCl, Et₃N, (R)-4-benzyl-3-lithiooxazolidin-2-one, THF, −78 to −20 °C for 4 h (55%); b) nBu₂SnOTf, Ip₂NET, CH₂Cl₂, −78 °C overnight then 0 °C 30 min; c) TESCl, imidazole, DMF, −20 °C overnight (41% for (E)-5, 10% for (Z)-5); d) EtSH, nBuLi, CeCl₃, −15 °C overnight (80% for (E)-6, 65% for the (Z)-6); e) PdCl₂(PPh₃)₂, Cu(I) thiophene-2-carboxylate, (2-furyl)P, THF, microwave, 80 °C for 15 min × 2 (96% for (E)-7, 91% for (Z)-7); c) TBAF–HF, aq. THF, 0 °C for 10 min (quant. for 1, 83% for 2).
to give 48.2 mg (80%) of (E)-6 as a colorless oil. [α]D22 +46° (c 0.95, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C35H60O2SSiSn, 699.3804; found, 699.3810.

(3Z)-isomer of (E)-6 [(Z)-6]. Compound (Z)-6 (14.6 mg, 65% yield) was obtained as a pale yellow oil from 26.3 mg (32.3 μmol) of (Z)-5 and 50 μl (0.675 mmol) of EtSH in the same manner as that described for (E)-6. [α]D22 +55.8° (c 0.965, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C35H60O2SSiSn, 699.3804; found, 699.3807.

(4S,5R)-5-[(E)-2,6-Dimethyl-1,5-heptadienyl]-2-methyl-4-(triethylsilyloxy)-2-cyclopentenone [(E)-7]. Compound (E)-7 (11.3 mg, 96% yield) was obtained as a pale yellow oil from 23.7 mg (33.7 μmol) of (E)-6 according to the procedure reported in Ref. 4, except that the microwave-irradiation time was reduced to 30 min (15 min × 2). [α]D22 +1.6° (c 0.32, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C21H32O2Si, 349.2563; found, 349.2563.

(1'Z)-isomer of (E)-7 [(Z)-7]. Compound (Z)-7 (7.9 mg, 91% yield) was obtained as a pale yellow oil from 17.5 mg (25.0 μmol) of (Z)-6 in the same manner as that described for (E)-7. [α]D22 +122° (c 0.34, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C21H32O2Si, 349.2563; found, 349.2564.

(4S,5R)-5-[(E)-2,6-Dimethyl-1,5-heptadienyl]-4-hydroxy-2-methyl-2-cyclopentenone [(1S,5R)-1]. Compound (1S,5R)-1 [4.8 mg, quantitative yield; (1S,5R)-1/ (1S,5S)-1 = 43:1] was obtained as a colorless oil from 7.0 mg (20 μmol) of (E)-7 according to the procedure reported in Ref. 4, except that the reaction temperature and the reaction time were respectively reduced to 0°C and 10 min. [α]D24 +120° (c 0.20, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C15H23O2, 235.1698; found, 235.1698.

(4S,5R)-5-[(Z)-2,6-Dimethyl-1,5-heptadienyl]-4-hydroxy-2-methyl-2-cyclopentenone [(1S,5R)-2]. Compound (1S,5R)-2 [4.4 mg, 83% yield; (1S,5R)-2/(1S,5S)-2 = 53:1] was obtained as a colorless oil from 7.9 mg (23 μmol) of (Z)-7 in the same manner as that described for (1S,5R)-1. [α]D23 +150° (c 0.17, CHCl3); HR-FABMS m/z ([M + H]+): calcd. for C15H23O2, 235.1698; found, 235.1700.

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