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Total Synthesis of (±)-Ligantrol, a Linear Polyoxygenated Diterpene

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(±)-Ligantrol (**10**), isolated from *Liatris elegans*, was synthesized from the hypothetical precursor, 18-hydroxygeranylnerol (**2**) which was a isomer of 18-hydroxygeranylgeraniol (**1**) isolated from *Croton sublyratus* as an antigastric ulcer principle.

Keywords——diterpene; synthesis; ligantrol; *Liatris elegans*; epoxidation

In our preceding paper,[2] we have reported structural determination and total synthesis of an acyclic diterpene alcohol (**1**), 18-hydroxygeranylgeraniol, which was isolated from a Thai medicinal plant, *Croton sublyratus* Kurz, as an antipeptic ulcer substance. It called our attention that W. Herz and R. P. Sharma isolated a linear diterpene from *Liatris elegans* (Walt.) Michx., named ligantrol (**10**),[3] presumed to be a compound constructed biogenetically from 18-hydroxygeranylnerol which was the geometric isomer of the antiulcer diterpene (**1**). The hypothetical precursor, 18-hydroxygeranylnerol (**2**) was easily synthesized stereospecifically by the same method as the preparation of **1** applying the β-oxido ylide procedure.[4] In the present paper we report a biogenetic-type synthesis of (±)-ligantrol starting from **2**.

Epoxidation of the terminal double bond in diacetate (**3**) prepared from **2** by usual way was effected by treatment with *m*-chloroperbenzoic acid or N-bromosuccinimide (NBS) oxidation followed by dehydrobromination to give epoxide (**4**), whose proton magnetic resonance (PMR) spectrum showed a triplet at δ 2.50 (J=6.5 Hz) due to the hydrogen attached to the carbon bearing the epoxy oxygen and two singlets at δ 1.21 and 1.19 attributable to C-16 and C-20 methyl groups. On treatment of **4** with 30% perchloric acid in aqueous tetrahydrofuran, the epoxide clove to yield diol (**5**). In its PMR spectrum, the triplet at δ 2.50 appearing in that of **4** shifted downfield to exhibit a quartet at δ 3.30. In addition, the diol structure was proved by the spectrum data of its triacetate (**6**). The diol (**5**) was allowed to react again with *m*-chloroperbenzoic acid in chloroform to give a mixture of ligantrol acetate (**8**) and its isomer (**9**) in the ratio of 1:1. Both isomers were separated by a silica gel column chromatography. PMR spectrum of the more mobile compound (**8**) exhibited three methyl signals at δ 1.14, 1.16 and 1.27 and two signals at δ 3.80 and 3.53 due to hydrogens attached to the carbons having oxygen. Furthermore, the results of the PMR spectrum of acetylation product of (**8**) supported the presence of a secondary hydroxyl group, a tetrahydrofuran ring and none of epoxide. Consequently, **8** was identical with natural ligantrol acetate in all respects of spectral data. The less mobile compound (**9**) was suggested to be the *trans*-isomer of **8** at the two side chains on the tetrahydrofuran ring by considering the mechanism for formation of **8** and **9** from **7**. Epoxide formation at C-10 double bond of **5** could be observed in the reaction mixture as described in experimental section, and the epoxide must be opened by back side attack of the hydroxyl group at C-14 to afford the *cis* and *trans* isomers of the tetrahydrofuran derivatives (**8** and **9**).

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2) A. Ogiso, E. Kitazawa, M. Kurabayashi, A. Sato, S. Takahashi, H. Noguchi, H. Kuwano, S. Kobayashi, and H. Mishima, *Chem. Pharm. Bull.* (Tokyo), **26**, 3117 (1978).
3) W. Herz and R.P. Sharma, *J. Org. Chem.*, **40**, 192 (1975).
4) E.J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6637 (1970); *idem, ibid.*, **92**, 6638 (1970).

Finally, (±)-ligantrol was obtained on hydrolysis of **8** in methanolic potassium carbonate. The synthetic ligantrol was identified with an authentic sample of natural product by their spectra.[4]

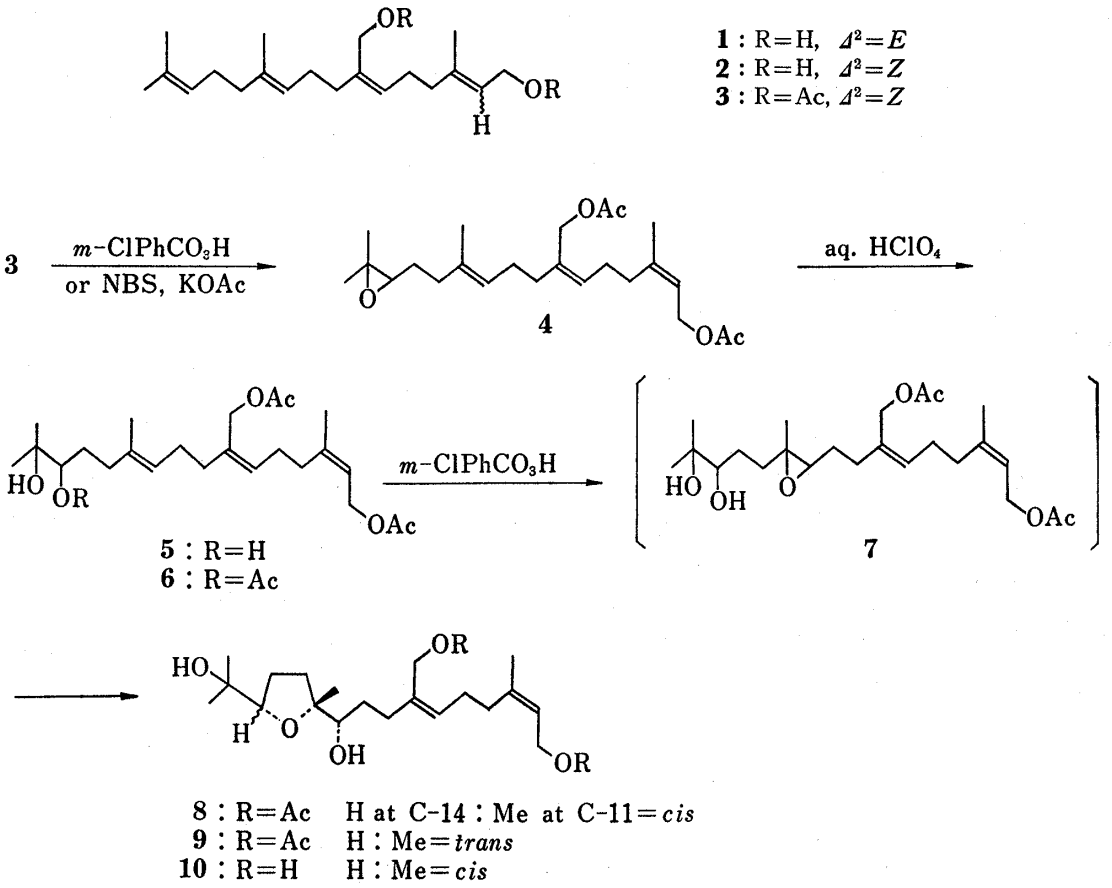

Chart 1

Experimental[5]

18-Hydroxygeranylnerol Diacetate (3)——To a suspension of 9.0 g of (E)-5,9-dimethyl-4,8-decadien-1-yltriphenylphosphonium iodide in 60 ml of anhydrous tetrahydrofuran was added dropwise the equimolar amount of a *n*-butyllithium-hexane solution at 0° in a stream of argon. After stirring for 30 min at room temperature, the reaction mixture was cooled to −78°, and to this mixture was added a solution of (Z)-4-methyl-6-(2′-tetrahydropyranyloxy)-4-hexenal in 20 ml of anhydrous tetrahydrofuran. After stirring for 30 min, the mixture was maintained at −50° and to this was added the equimolar amount of a *sec*-butyllithium-pentane solution. The temperature was slowly raised to −10°, 1.5 g of dry *para*-formaldehyde was added at once thereto. The reaction mixture was then stirred at room temperature for 2 hr, and, after addition of ice-water, extracted with *n*-hexane. From the *n*-hexane extract was obtained 6.8 g of an oil, which was dissolved in 50 ml of methanol containing 100 mg of *p*-toluenesulfonic acid and allowed to stand overnight. After addition of an aqueous sodium hydrogencarbonate solution, the mixture was extracted with ether. The crude product obtained from the ether layer was purified by a silica gel column (60 g), yielding 1.5 g of 18-hydroxygeranylnerol (**2**). A solution of the resulting 18-hydroxygeranylnerol in 10 ml of pyridine and 2 ml of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with *n*-hexane. From the hexane layer 1.5 g of the desired compound (3) was yielded: IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1675, 1230. PMR (CCl_4) δ: 1.49 (6H, s), 1.58 (3H, s), 1.68 (3H, s), 1.85 (3H, s), 1.90 (3H, s), 1.9—2.3 (12H, m), 4.38 (2H, d), 4.40 (2H, s), 5.0—5.3 (4H, m).

5) We are indebted to Dr. W. Herz of Florida State University for the authentic sample of natural ligantrol.
6) The PMR spectra were measured with Varian HA-100 and Hitachi R-24 spectrometer using tetramethylsilane as an internal reference. The infrared (IR) spectra were determined on JASCO IRA-2 spectrophotometer. Mass spectra (MS) were measured on JEOL JMS-01SG and Hitachi RMU-6M spectrometer. For column chromatography, silica gel 60—110 mesh (Kanto Chemical Co., Inc., Tokyo) was used.

(*Z*,*Z*,*E*)-7-Acetoxymethyl-14,15-epoxy-3,11,15-trimethyl-2,6,10-hexadecatrien-1-ol Acetate (4)——a) To a stirred solution of 9.5 g of 18-hydroxygeranylnerol diacetate (3) in 200 ml of chloroform was added a solution of 5.3 g of *m*-chloroperbenzoic acid in 50 ml of chloroform. After 5 hr, the reaction mixture was washed with an aqueous sodium hydrogen carbonate solution and water. The resulting product obtained from the organic layer was chromatographed on a silica gel (200 g) column, developing with benzene-ethyl acetate gradiently to give 3.5 g of the desired epoxide (4): IR $\nu_{max}^{liq.}$ cm^{-1}: 1740. PMR (CCl_4) δ: 1.19 (3H, s), 1.21 (3H, s), 1.60 (3H, s), 1.74 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 2.50 (1H, t), 4.45 (2H, d), 4.50 (2H, s), 5.40 (3H, m).

b) To a stirred solution of 1.1 g of 18-hydroxygeranylnerol diacetate in 20 ml of tetrahydrofuran and 5 ml of water was added 530 mg of NBS at 15°. After keeping for 2 hr and addition of water, the reaction mixture was extracted with ether. The ether layer was successively washed with an aqueous sodium hydrogencarbonate solution and water, and evaporated to give crude bromohydrin. A ethanol solution (20 ml) of the bromohydrin was treated with 500 mg of potassium acetate under reflux for 1 hr. The solution was poured into water and extracted with ether. The crude product was purified by chromatography as the same manner as described above to yield the epoxide (4).

(*Z*,*Z*,*E*)-7-Acetoxymethyl-14,15-dihydroxy-3,11,15-trimethyl-2,5,10-hexadecatrien-1-ol Acetate (5)——To a stirred solution of 3.5 g of the epoxide (4) in 40 ml of tetrahydrofuran and 5 ml of water was added few drops of 30% perchloric acid at 0° and the solution was kept for 30 min. The reaction mixture was poured into water and extracted with ether. The ether layer was washed successively with an aqueous sodium carbonate solution and water. Evaporation of the solvent and purification by a column chromatography on silica gel (50 g) gave 2.0 g of diol (5): IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1740, 1720. PMR ($CDCl_3$) δ: 1.10 (3H, s), 1.13 (3H, s), 1.67 (3H, s), 1.71 (3H, s), 1.99 (6H, s), 3.30 (1H, q), 4.49 (2H, d), 4.53 (2H, s), 5.40 (3H, m).

(*Z*,*Z*,*E*)-7-Acetoxymethyl-14-acetoxy-15-hydroxy-3,11,15-trimethyl-2,5,10-hexadecatrien-1-ol Acetate (6)——The diol (5) (100 mg) was acetylated with 0.5 ml of acetic anhydride in 2 ml of pyridine: IR $\nu_{max}^{liq.}$ cm^{-1}: 3500, 1740, 1720. PMR ($CDCl_3$) δ: 1.15 (6H, s), 1.68 (3H, s), 1.74 (3H, s), 2.00 (6H, s), 2.04 (3H, s), 4.50 (2H, d), 4.54 (2H, s), 4.70 (1H, q), 5.40 (3H, m).

(±)-Ligantrol Diacetate (8) and the Isomer (9)——To a stirred solution of 2.0 g of the diol (5) in 40 ml of chloroform was added dropwise a solution of 1.5 g of *m*-chloroperbenzoic acid in 20 ml of chloroform at 0°. After stirring for 1 hr at room temperature, the reaction mixture showed three spots on a thin-layer chromatography at the *Rf* 0.21, 0.17 and 0.05 (development with benzene–ethyl acetate (1: 1) on Merck silica gel 60 F-254), and after 18 hr, one (*Rf* 0.05) of them disappeared and the other two spots were remained in the ratio of 1: 1 on a thin-layer chromatography. The reaction mixture was worked up as usual and chromatographed on silica gel (100 g) column and eluted with benzene containing 30% to 50% ethyl acetate to give each 600 mg of (±)-ligantrol diacetate (8) and its isomer (9).

(±)-Ligantrol Diacetate (8): IR $\nu_{max}^{liq.}$ cm^{-1}: 3470, 1740. PMR ($CDCl_3$) δ: 1.14 (3H, s), 1.16 (3H, s), 1.27 (3H, s), 1.77 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 3.53 (1H, q), 3.80 (1H, t), 4.55 (2H, d), 4.54 (2H, s), 5.40 (2H, m). MS *m/e*: 441 (M+1), 422, 407, 381, 362, 303, 299, 261, 238, 177, 143 (base), 125.

Isomer (9): IR $\nu_{max}^{liq.}$ cm^{-1}: 3470, 1740. PMR ($CDCl_3$) δ: 1.15 (6H, s), 1.22 (3H, s), 1.77 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 3.49 (1H, q), 3.78 (1H, t), 4.55 (2H, d), 4.60 (2H, s), 5.40 (2H, m). MS *m/e*: 441 (M+1), 422, 407, 381, 362, 303, 299, 261, 238, 177, 143 (base), 125.

(±)-Ligantrol (10)——A solution of 100 mg of (±)-ligantrol diacetate (8) in 2 ml of methanol containing 10 mg of potassium carbonate was stirred for 1 hr at room temperature. The reaction mixture was poured into water and extracted with ether. The ether layer was worked up as usual and chromatographed on silica gel (3 g) column to give 30 mg of the desired (±)-ligantrol: IR ν_{max}^{liq} cm^{-1}: 3350, 1670, 1450, 1385, 1080, 1000, 950, 820, 750. PMR ($CDCl_3$) δ: 1.08 (3H, s), 1.12 (3H, s), 1.23 (3H, s), 1.72 (3H, s), 2.18 (12H, m), 3.70 (2H, m), 4.10 (2H, s), 4.10 (2H, d), 5.40 (2H, m).