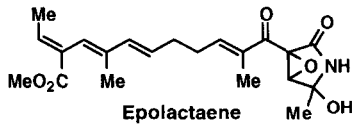
Asymmetric Total Synthesis of Epolactaene

Yujiro Hayashi and Koichi Narasaka
Department of Chemistry, School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

(Received December 26, 1997; CL-970979)

The first asymmetric total synthesis of epolactaene, a neuritogenic compound, was accomplished in 16 steps and its absolute stereochemistry was determined.

Epolactaene **1** is a microbial metabolite isolated by Kakeya and Osada et al. from fungal strain, *Penicillium sp.* BM 1689-P, collected in the sea bottom of Uchiura bay, Japan.[1] It is effective to the neurite outgrowth of a human neuroblastoma cell line (SH-SY5Y cells). Structurally epolactaene has a labile (*E,E,E*)-triene and a novel 3-alkenoyl-3,4-epoxy-2-pyrrolidinone moiety, the absolute stereochemistry of which is not determined. The scarcity of epolactaene from natural sources combined with its interesting biological properties prompted us to synthesize epolactaene enantioselectively.



Epolactaene

First, the construction of the (*E,E,E*)-triene part was started from tetrahydropyran-1-ol **2**. Wittig coupling of **2** with (ethoxycarbonylethylidene)triphenylphosphorane in toluene at 90 °C for 1 h afforded (*E*)-unsaturated ester **3** stereoselectively (*E* : *Z* = >95:<5), the hydroxy group of which was protected by the treatment with *t*-butyldimethylsilyl chloride (TBSCl) and imidazole in CH_2Cl_2 to give TBS ether **4** in 96% yield in two steps. Conversion of **4** to methyl (*E,E*)-2,4-nonadienoate **7** was accomplished stereoselectively by the following sequence: 1) Reduction of the ester **4** to allylic alcohol **5** by diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 from -78 °C to 0 °C; 2) oxidation of the allylic alcohol **5** to aldehyde **6** by Griffith-Ley oxidation[2] with 4-methylmorpholine *N*-oxide and a catalytic tetrapropylammonium perruthenate in the presence of Molecular Sieves 4A in CH_2Cl_2 for 1 h; 3) Horner-Emmons reaction of **6** with methyl dimethylphosphonoacetate and *n*-BuLi afforded **7** in 75% total yield in 3 steps. Aldol condensation of lithium enolate generated from **7** and lithium diisopropylamide (LDA) in THF-HMPA at -78 °C with acetaldehyde at -78 °C for 3 h gave *syn*- and *anti*-aldols **8** in 78% yield in 1:1.6 ratio, which could be separated by column chromatography but were used as a mixture in the next step. The diene moiety of these aldol isomers has *E,E* geometry. This high *E,E* selectivity is attributed to the selective kinetic deprotonation of Ha proton from the most stable conformation which minimizes the repulsion of methyl and R groups as shown in Figure 1.

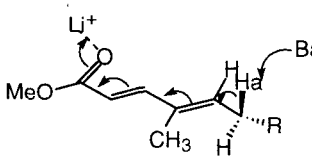


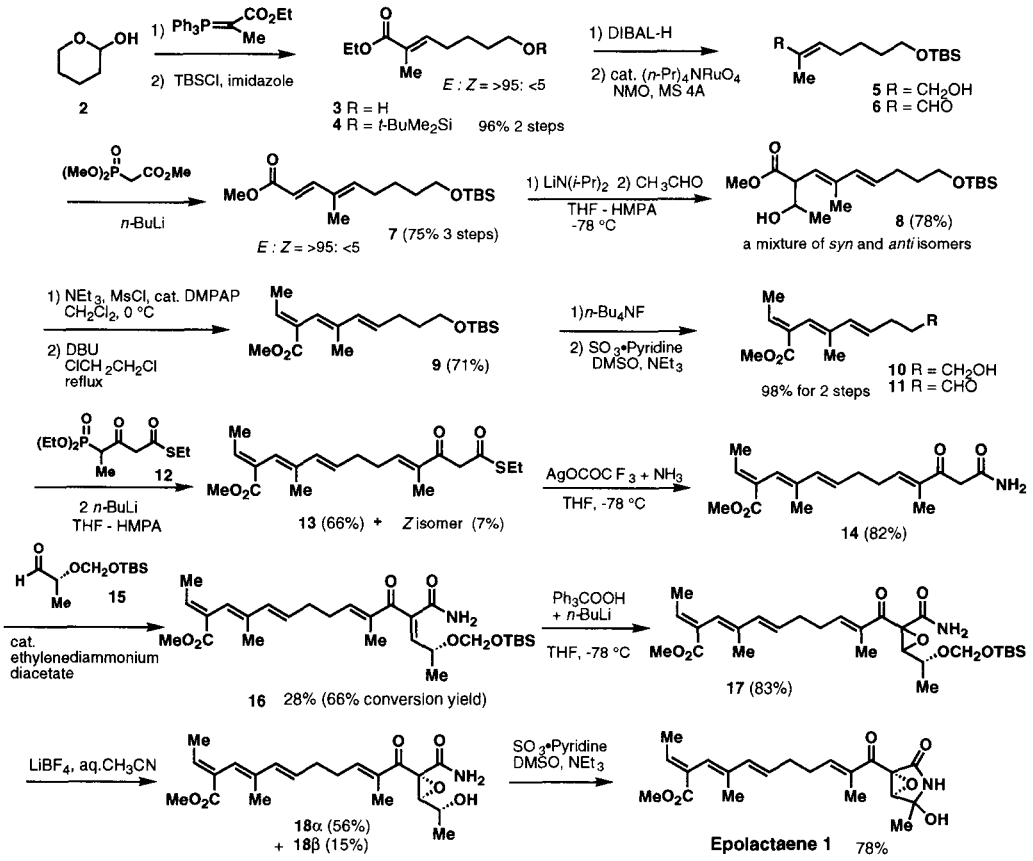
Figure 1.

The mixture of the *syn*- and *anti*-aldols was converted to methyl (3*E*,5*E*)-2-[(*E*)-ethylidene]-4-methyl-3,5-nonadienoate derivative **9** as follows: The aldols **8** were transformed into their mesylates (methanesulfonyl chloride, triethylamine, and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2). The elimination of methanesulfonic acid using diazabicycloundecene (DBU) from the crude mesylates afforded the (*E*)-ethylidene derivative **9** in 71% yield. The followings were noteworthy in this transformation; 1) The (*E*)-ethylidene derivative **9** was stereoselectively formed from the *syn*-aldol at rt by the treatment with DBU, while a mixture of (*Z*)- and (*E*)-isomers were obtained from the *anti*-aldol. 2) Isomerization of the (*Z*)-isomer to the (*E*)-isomer **9** proceeded at 90 °C in the presence of DBU.

Since the triene **9** was prepared stereoselectively, the construction of 3-alkenoyl-3,4-epoxy-2-pyrrolidinone moiety was examined from **9**. Deprotection of the silyl ether by *n*-Bu_4NF in THF at rt for 2 h, followed by the treatment with SO_3•pyridine,[3] triethylamine and DMSO in CH_2Cl_2 from 0 °C to rt for 2 h afforded aldehyde **11** in 98% yield from **9**. The Horner-Emmons reaction of **11** with 1.1 molar amounts of newly designed ethyl 4-diethylphosphono-3-oxopentanethiolate **12**[4] and 2.1 molar amount of *n*-BuLi in THF-HMPA at -78 °C for 20 min then at 0 °C for 10 min provided (4*E*)-γ,δ-unsaturated-β-keto thioester **13** in 66% yield along with the *Z*-isomer (7%). The thioester **13** was converted to amide **14** by the reaction with NH_3 in the presence of silver trifluoroacetate[5] in THF at -78 °C for 20 min. The Knoevenagel condensation of the β-ketoamide **14** and (*R*)-2-(*t*-butyldimethylsiloxymethoxy)propanal **15**[6] in the presence of a catalytic amount of ethylenediammonium diacetate[7] for 10 h at rt gave (*Z*)-olefin **16**[8] and the (*E*)-isomer in 28% (66% conversion yield) and 9% yield, respectively, with the recovery of the β-ketoamide **14** (58%). Epoxidation of **16** was accomplished with Ph_3COOH and *n*-BuLi at -78 °C for 3 h without affecting other olefinic parts, affording an inseparable diastereomer mixture (about 3:1) of epoxides **17** in 83% yield. Deprotection of the TBS ether **17** was achieved by the treatment with $LiBF_4$[9] in CH_3CN containing 2% H_2O at rt for 9 h to provide α-epoxy amide **18α**[10] and its diastereomer **18β**[10] in 56% and 15% yield, respectively. Oxidation of the major isomer **18α** by SO_3•pyridine, Et_3N and DMSO in CH_2Cl_2 at 0 °C for 1 h produced **18** to epolactaene in 78% yield.

Synthetic epolactaene **1** exhibited identical properties to those reported for the natural substance[12] (^1H NMR,[13] ^{13}C NMR, and mass spectroscopies). The comparison of the optical rotation (synthetic epolactaene: $[\alpha]_D^{25}$ +31.3 (*c*=0.14, MeOH), natural epolactaene: $[\alpha]_D^{26}$ +32 (*c*=0.1, MeOH)[1]) determined the absolute stereochemistry as shown in **1**.

Thus, epolactaene was synthesized in an enantioselective manner and the absolute configuration could be determined by the present synthesis.



References and Notes

1 H. Kakeya, I. Takahashi, G. Okada, K. Isono, and H. Osada, *J. Antibiot.*, **48**, 733 (1995).

2 W. P. Griffith and S. V. Ley, *Aldrichimica Acta*, **23**, 13 (1990).

3 J. R. Parikh and W. v. E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).

4 **12** was prepared from 2-(diethylphosphono)propanoyl chloride[11] and 1-*t*-butyldimethylsiloxy-1-ethylthioethylene and triethylamine.

5 S. V. Ley and P. R. Woodward, *Tetrahedron Lett.*, **28**, 3019 (1987).

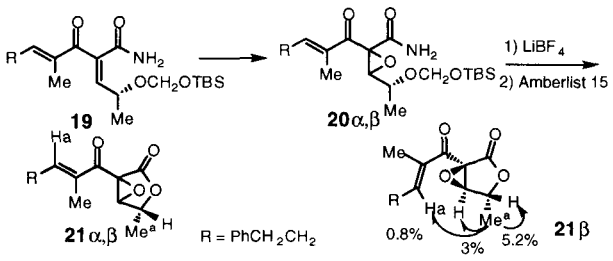
6 **15** was prepared by DIBAL-H reduction of the methyl ester synthesized from methyl (*R*)-(+)-lactate, (*t*-butyldimethylsiloxy)methyl chloride,[14] and diisopropylamine.

7 L. -F. Tietze and G. v. Kiedrowski, *Tetrahedron Lett.*, **1981**, 219.

8 Stereochemistry was determined by 2D-NOESY spectrum.

9 B. W. Metcalf, J. P. Burkhart, and K. Jund, *Tetrahedron Lett.*, **21**, 35 (1980).

10 Relative stereochemistry of the epoxides **18** was determined as follows. The epoxidation of the model olefin **19** synthesized from 3-phenylpropanal instead of the aldehyde **11** gave the two diastereomers **20** in 3:1 ratio. The similar NMR patterns were observed between two major isomers of **17** and **20**, as well as between two minor isomers. The structure of the isomers was assigned by the differential NOE experiments after conversion to the lactones **21**. The lactone **21** derived from the minor isomer of **20** showed the NOEs as depicted below, which determined the stereochemistry as the β-epoxide **21**β, though NOE between Me[a] and Ha was not observed for the lactone **21** derived from the major isomer.



There is no racemization from **14** to **18**, which was checked by the comparison of ^{1}H-NMR (500MHz) spectra of (+)-MTPA esters derived from **18**α and its enantiomer derived from (*S*)-**15**.

11 P. Coutrot and A. Ghribi, *Synthesis*, **1986**, 661.

12 We are grateful to Drs. H. Osada and H. Kakeya for providing the copies of NMR-spectra of natural **1**.

13 Synthetic epolactaene exists as a about 5:1 epimeric mixture at C15 in CD_3OD.

14 L. Gundersen, T. Benneche, and K. Undheim, *Acta Chem. Scand.*, **43**, 706 (1989).