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Convergent total synthesis of epolactaene: application of bridgehead oxiranyl anion strategy

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Abstract

Total synthesis of (+)-epolactaene was accomplished by a convergent approach utilizing the fluoride anion-catalyzed aldol-type reaction of (−)-α-trimethylsilylangelica lactone epoxide with tetraene aldehyde as a key reaction. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: oxiranyl anion; β-angelica lactone epoxide; fluoride-catalyzed aldol reaction; epolactaene.

Epolactaene, isolated from fungal strain *Penicillium* sp. BM1689-P by Osada et al.[2] possesses potent neurite outgrowth activity in a human neuroblastoma cell line SH-SY5Y. The characteristic features of epolactaene include the highly functionalized α,β-epoxy-γ-lactam core and the conjugated triene moiety in the side chain. Significant biological activity as well as the structural complexity of epolactaene have stimulated intensive synthetic interest, culminating in the recent total synthesis by two groups.[3] As discussed in the preceding paper,[4] we developed a fluoride anion-catalyzed reaction of a bridgehead oxiranyl anion derived from α,β-epoxylactone with aldehydes via α-trimethylsilyl derivative. This paper describes the application of the methodology to the total synthesis of epolactaene.

Scheme 1 outlines a strategy for epolactaene based on the oxiranyl anion approach. Epolactaene might be synthesized from the key intermediate **1**, which would be obtained by the condensation of epoxylactone **2** and aldehyde **3**. Chiral epoxylactone **2** could be derived from L-xylose according to Ogawa's method,[5] and the side-chain aldehyde **3** could be prepared from dienyl iodide **4** and vinylstannane **5** using Stille coupling as a key reaction.

The preparation of the dienyl iodide **4** and the vinylstannane **5** are shown in Scheme 2. Wittig reaction of **6**,[6] prepared from 1,4-butanediol by two steps, with the known phosphonium salt **7**,[7] gave the enyne derivative **8** as a mixture (*E*:*Z*=ca. 5.7:1). Without separation of isomers, the enyne **8** was deprotected to **9** with K_2CO_3–methanol,[8] and the latter was subjected to stereoselective carbometallation[9] with Cp_2TiCl_2–Me_3Al followed by the treatment with iodine, affording the dienyl iodide **4**.[10] The

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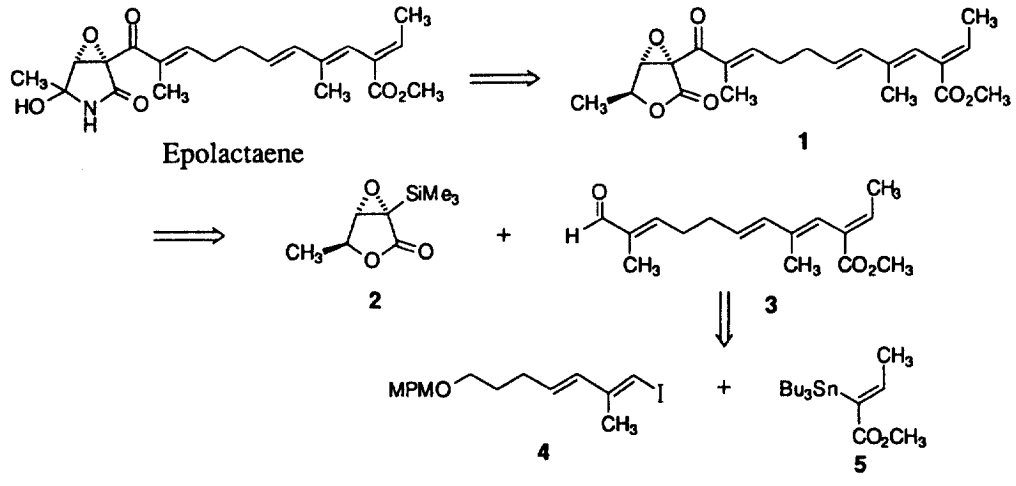
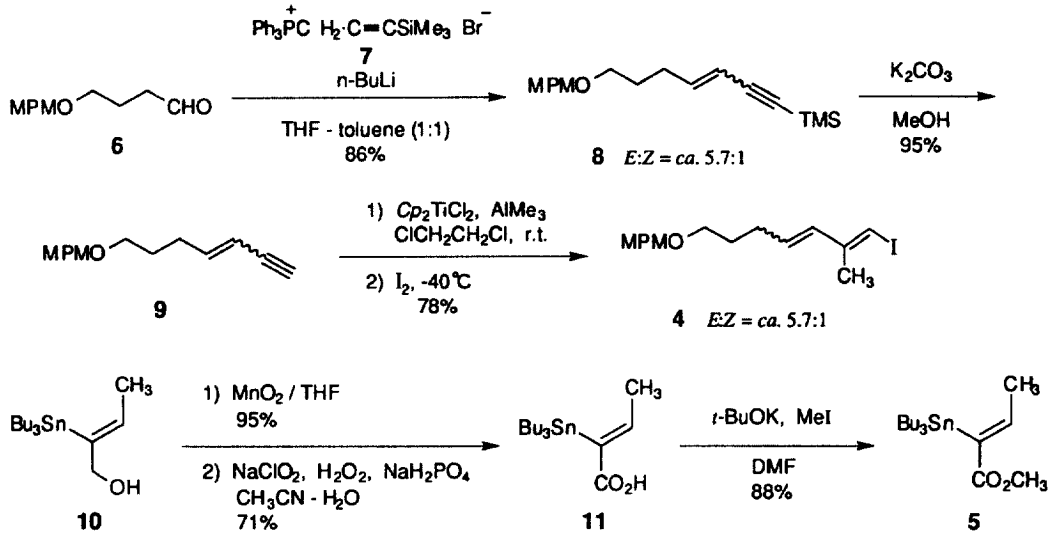


Scheme 1.

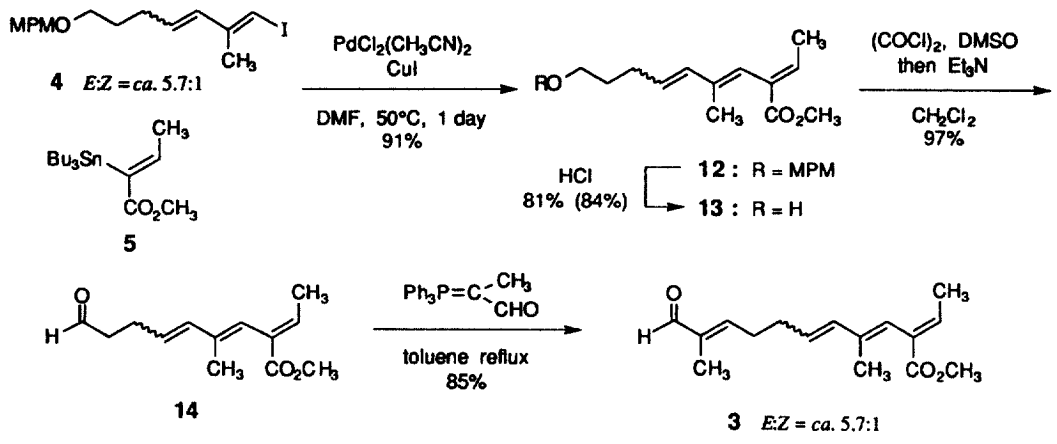
vinylstannane **5** was prepared from the known stannyl alcohol **10**.[11] Two-step oxidation [(i) MnO_2 95%; (ii) $NaClO_2$–H_2O_2,[12] 71%] of the alcohol **10** gave the carboxylic acid **11**, which was transformed to **5**[10] in 88% yield by treatment with CH_3I and *t*-BuOK.



Scheme 2.

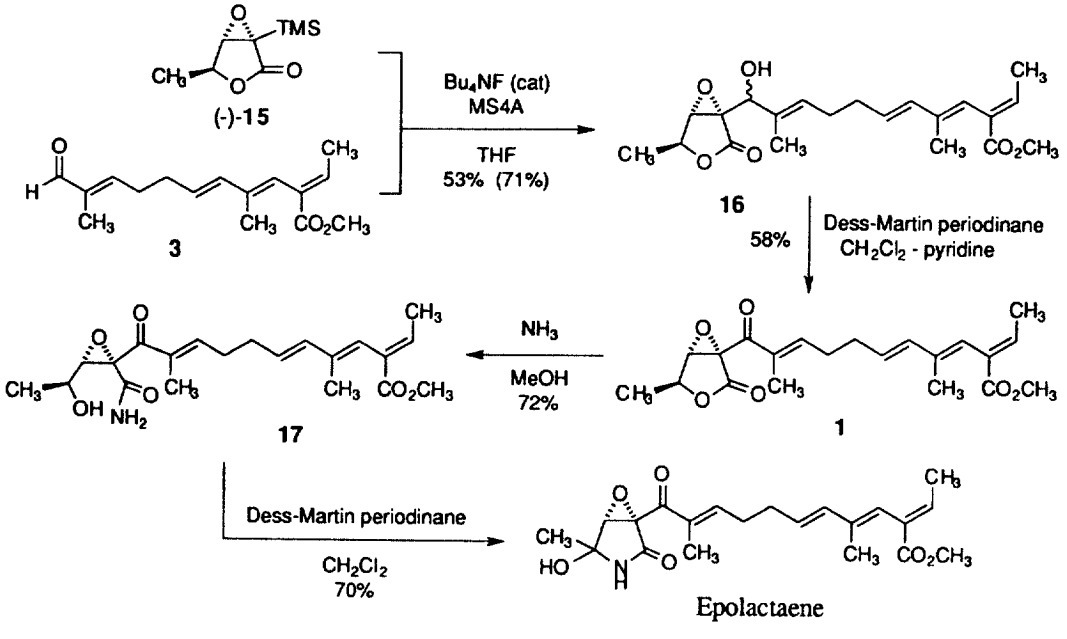
Construction of the conjugated triene moiety was achieved in 91% yield by $PdCl_2(CH_3CN)_2$-catalyzed Stille coupling of dienyl iodide **4** and vinylstannane **5** in the presence of Cu(I).[13] The MPM group in **12** was cleanly cleaved by heating at 60°C in 1N HCl:dioxane (1:1) affording **13** in 81% yield. The conventional method using DDQ or CAN[14] was unsuccessful, resulting in the formation of a complex mixture of products. After Swern oxidation,[15] the resulting aldehyde **14** was subjected to the Wittig reaction[16] to afford the side-chain aldehyde **3** (Scheme 3). The separation of stereoisomers was most easily carried out at this stage and the stereochemically pure **3**[10] was obtained.

The coupling of two segments and the completion of the synthesis of epolactaene are summarized in Scheme 4. The enantiomerically pure β-angelica lactone epoxide, prepared from L-xylose according to the procedure reported by Ogawa,[5] was converted into α-trimethylsilyl derivative (–)-**15**.[4] The Bu_4NF-



Scheme 3.

catalyzed condensation of (−)-**15** and **3** was then examined. Although the reaction proceeded very slowly, the desired aldol-type product **16** was obtained in 53% yield. Thus, the mixture of (−)-**15** (71.4 mg, 0.38 mmol) and **3** (50.8 mg, 0.19 mmol), MS4A (315 mg) in THF (3 ml) was added TBAF (28 μl, 1 M THF solution), and the reaction mixture was stirred at room temperature for 24 h. After usual work-up and brief separation by short column chromatography, the mixture of **3** and (−)-**15** was again treated with TBAF and MS4A in THF to obtain **16** in total 53% yield (38.6 mg, and 71% yield based on the recovered **3** (13.4 mg and 26%).



Scheme 4.

Oxidation of **16** with Dess–Martin periodinane[17] produced the corresponding ketone **1**.[10] After ammonolysis of **1**, the resulting hydroxyamide **17**[3b] was oxidized with Dess–Martin periodinane, thus completing the synthesis of (+)-epolactaene which was isolated as 5:1 diastereomixture at C-15. The synthetic epolactaene had $[\alpha]_D^{21}$ +34 (*c* 0.2, MeOH) [lit.: $[\alpha]_D^{26}$ +32 (*c* 0.1, MeOH)] and exhibited spectral data (^{1}H and ^{13}C NMR and HRMS) identical with those reported for the natural product.[2] In

summary, we were able to complete a convergent total synthesis of epolactaene (7% overall yield, 14 steps from 1,4-butanediol). The most significant feature of the present approach is that the trimethylsilylated epoxylactone serves as a potential intermediate for the synthesis of various substituted epolactaene analogs. Several analogs were prepared and are now undergoing biological studies which will be reported in due course.

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10. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and IR spectra, and satisfactory high-resolution MS were obtained for them. Selected ^{1}H NMR spectra follows: **4** (*E*-isomer): δ 1.70 (2H, tt, *J*=6.3, 7.6 Hz), 1.92 (3H, d, *J*=1.0 Hz), 2.15 (2H, dt, *J*=6.9, 7.6 Hz), 3.44 (2H, t, *J*=6.3 Hz), 3.81 (3H, s), 4.42 (2H, s), 5.74 (1H, td, *J*=6.9, 15.5 Hz), 6.13 (1H, d, 15.5 Hz), 6.17 (1H, s), 6.88 (2H, *J*=8.6 Hz), 7.26 (2H, *J*=8.6 Hz). **5**: δ 0.89 (9H, t, *J*=7.3 Hz), 1.01 (6H, t, *J*=8.0 Hz), 1.27–1.35 (6H, m), 1.45–1.49 (6H, m), 1.89 (3H, d, *J*=6.9 Hz), 3.69 (3H, s), 7.45 (1H, q, *J*=6.9 Hz). **3** (*E*-isomer): δ 1.63 (3H, d, 1.0 Hz), 1.73 (3H, dd, *J*=1.0, 7.3 Hz), 1.76 (3H, d, *J*=1.3 Hz), 2.36 (2H, m), 2.50 (2H, m), 3.74 (3H, s), 5.72 (1H, m), 5.97 (1H, br s), 6.27 (1H, d, *J*=15.7 Hz), 6.51 (1H, dt, *J*=1.3, 7.3 Hz), 6.95 (1H, dq, *J*=1.0, 7.3 Hz), 9.42 (1H, s). **1**: δ 1.50 (3H, d, *J*=6.8 Hz), 1.63 (3H, d, *J*=1.0 Hz), 1.72 (3H, dd, *J*=1.3, 7.3 Hz), 1.86 (3H, s), 2.35 (2H, m), 2.48 (2H, m), 3.73 (3H, s), 4.07 (1H, s), 4.71 (1H, q, *J*=6.8 Hz), 5.71 (1H, m), 5.96 (1H, br s), 6.26 (1H, d, *J*=15.5 Hz), 6.89 (1H, dt, *J*=1.3, 7.3 Hz), 6.95 (1H, dq, *J*=1.0, 7.3 Hz).
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