Pergamon

Tetrahedron Letters, Vol. 37, No. 1, pp. 89-90, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02109-4

Synthesis of (±)-Pentalenene *via* Regioselective Intramolecular Diels-Alder Reaction of Trisubstituted Cyclopentadiene

Minoru Hatanaka,* Fukuko Ueno and Ikuo Ueda

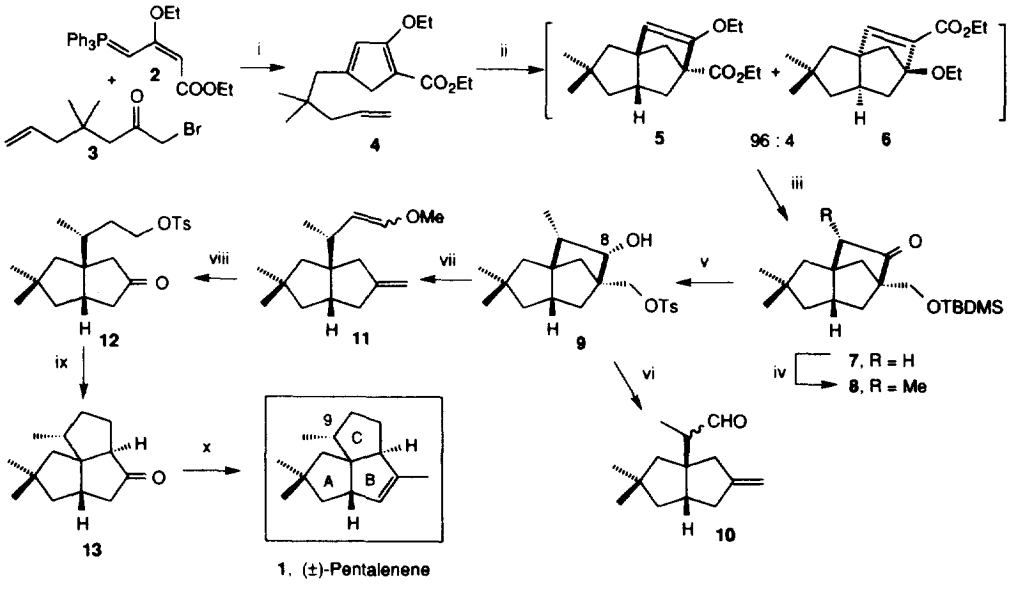
The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan

Abstract: A stereoselective synthesis of (±)-pentalenene has been described *via* an intramolecular Diels-Alder reaction of trisubstituted cyclopentadiene and subsequent elaboration of the C-ring including stereoselective induction of the 9-methyl group.

Construction of complex fused ring systems has been an attractive target of synthetic organic chemists. Pentalenene is a sesquiterpenoid isolated from *Streptomyces griseochromogene* and belongs to a class of non linear fused triquinanes having structural feature of a bridged arrangement of three cyclopentanes.[1] A number of existing syntheses employed a strategy involving the A-B rings construction followed by annulation of the C-ring, although stereocontrol of the methyl group of the C-ring was often achieved with difficulty.[2a,] Here, we report highly stereoselective synthesis of (±)-pentalenene *via* the C ring elaboration including stereoselective induction of the methyl group onto the A-B rings prepared by an intramolecular Diels-Alder reaction of trisubstituted cyclopentadiene.

In a recent paper relating to thermal reaction of alkenylcyclopentadienes we have described that cyclopentadiene **4** which prepared by [3 + 2] annulation of allylidenetriphenylphosphorane **2** and bromoketone **3** underwent highly regioselective [4 + 2] cycloaddition to give **5** and **6** in a ratio of 96:4.[2] The major product **5** possesses the A-B ring system of pentalenene. The remaining problem is reconstruction of the C-ring including stereocontrolled introduction of the methyl group. This is resolved as demonstrated in Scheme 1. The mixture of **5** and **6** was reduced with $LiAlH_4$ and the crude product was treated with aqueous 2M HCl followed by TBDMSCl. Column chromatography gave the ketone **7** in 81% overall yield based on **4**. Methylation of **7** with LiHMDS in THF followed by MeI-DMPU took place from the less hindered α-side in a highly stereoselective fashion to afford α-methyl ketone **8** in 90% yield. The stereochemistry of **8** was confirmed by a combination of ^1H 2D NOESY and COSY NMR spectrometry. Compound **8** was converted into the monotosylate **9**[3] in 79% overall yield by reduction with L-Selectride followed by deprotection and tosylation. Attempted fragmentation of **9** with NaHMDS in THF resulted in the formation of completely epimerized aldehyde in 48% yield. However, when **9** was treated with an equiv. of NaHDMS in the presence of an excess of methoxymethylene-triphenylphosphorane in THF at -78 to 0 °C, the fragmentation proceeded nicely and the resulting aldehyde was trapped efficiently by following Wittig olefination without epimerization to give **11** in 81% yield. Thus, C_7-C_8 bond cleavage and one-carbon homologation were achieved in a single operation. Compound **11** was converted into the ketone **12** in 62% overall yield *via* the following sequeneces, (1) hydrolysis of the methyl vinyl ether, (2) reduction with $NaBH_4$, (3) tosylation and then (4) ozonolysis. Intramolecular alkylation of **12** underwent

nicely by treatment with 1.2 equiv. of NaHMDS in THF at 0 °C to give the tricyclic ketone **13** in 92% yield. Finally, treatment with MeLi-$CeCl_3$ and subsequent dehydration with toluenesulfonic acid furnished (±)-pentalenene (**1**)[4] in an almost quantitative yield. The spectra (^1H NMR, ^{13}C NMR and Mass) of **1** were identical with those of authentic sample.[4]



Scheme 1. Reagents: (i), (ii) see ref. 2. (iii) 1. $LiAlH_4$, THF; 2. aq. 2M HCl/$CHCl_3$; 3. TBDMSCl, imidazole, DMF; 81% from **4**. (iv) LiHMDS, THF, MeI, DMPU, -78 °C; 90%. (v) 1. L-Selectride, THF; 2. TBAF, THF; 3. TsCl, pyridine; 79% from **8**. (vi) NaHMDS, THF, -78 to 0 °C. (vii) NaHMDS (1 equiv.), Ph_3P=CHOMe (5 equiv.), THF, -78 to 0 °C, overnight; 81%. (viii) 1. TsOH, PPTS, aq. acetone, rt, overnight; 2. $NaBH_4$, EtOH, 0 °C; 3. TsCl, pyridine; 4. O_3, MeOH-CH_2Cl_2, Me_2S; 62% from **11**. (ix) NaHMDS (1.2 equiv.), THF, 0 °C, 3 h; 92%. (x) 1. MeLi, $CeCl_3$, THF, -78 °C, 1 h; 2. TsOH, benzene, reflux 2 h; 98% from **13**.

References and Notes

1. Isolation: (a) Seto, H.; Yonehara, H. *J. Antibiot.*, **1980**, *33*, 92. Synthesis: (b) Paquette, L. A.; Han, Y. K. *J. Am. Chem. Soc.* **1983**, *105*, 7358. (c) Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1984**, *25*, 3021. (d) Crimmins, M. T.; Deloach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800. (e) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. (f) Hudlicky, T.; Sinai-Zingde, G; Natchus, M. G.; Ranu, B. C.; Papadopolous. *Tetrahedron* , **1987**, *43*, 5685. (g) Ihara, M.; Katogi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2963. (h) Piers, E.; Karunaratne, V. *Can J. Chem.* **1989**, *67*, 160. (i) Shizuri, Y.; Maki, S.; Ohkubo, M.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 7167. (j) Imanishi, T.; Yamashita, M.; Hirokawa, Y.; Tanaka, T.; Iwata, C. *Chem. Pharm. Bull.* **1990**, *38*, 1124. (k) Frank-Neumann, M. F.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1992**, *33*, 3879. (l) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853. (m) Wu, Y-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104.
2. Himeda, Y.; Hiratani, K.; Hatanaka, M.; Ueda, I. *J. Chem. Soc., Chem. Commun.* **1992**, 1684.
3. Stereochemical assignment bases on the observed coupling constant ($J_{8,9}$= 7.3 Hz) in the ^1H NMR spectra.
4. We are grateful to Professor H. Seto of Tokyo University for providing the spectra of natural pentalenene.

(*Received in Japan* 4 *October* 1995; *revised* 30 *October* 1995; *accepted* 2 *November* 1995)