Tetrahedron Letters, Vol.31, No.25, pp 3563-3566, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

Enantioselective Synthesis of The Hexahydrobenzofuran Subunit of The Avermectins and The Milbemycins

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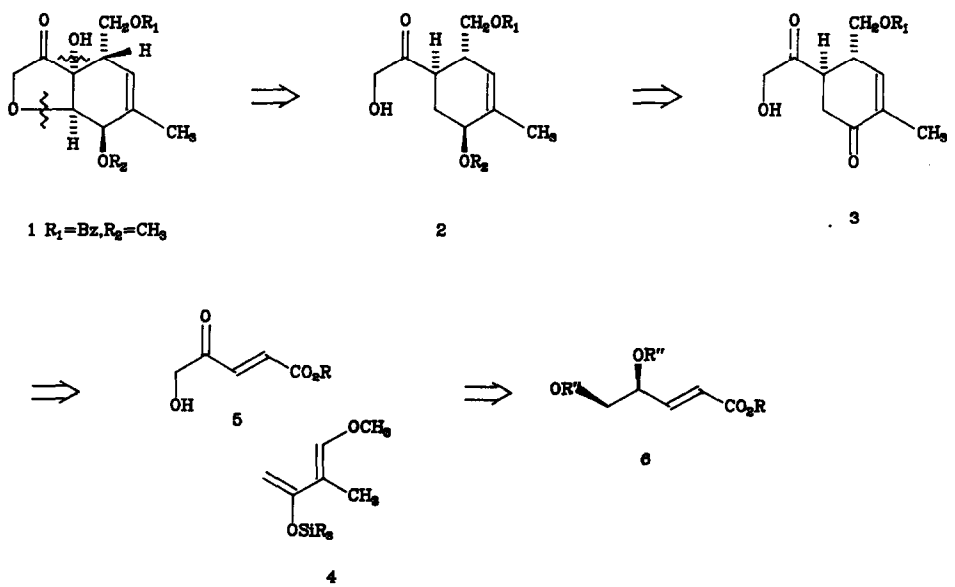
Summary: A highly stereocontrolled route to the hexahydrobenzofuran subunit of the avermectins and the milbemycins via an asymmetric Diels-Alder reaction is described.

The avermectins and the milbemycins are a family of macrolide natural products, isolated from the broths of *Streptomyces avermitilis* and *Streptomyces hygroscopicus* subsp. *aureolacrimosus* cultures respectively.[1] Their unique structures and potent antiparasitic activities has stimulated a great deal of interest in their chemical synthesis.[2] Herein we describe a stereocontrolled synthesis of the crucial extensively functionalized hexahydrobenzofuran subunit 1 in optically active form using an asymmetric Diels-Alder strategy.

Our retrosynthetic analysis for 1 is outlined in Scheme I. After removal of C_7 hydroxyl function and disconnection of O_{10}–C_6 bond, 1 would be retrograded to a cyclohexenol derivative

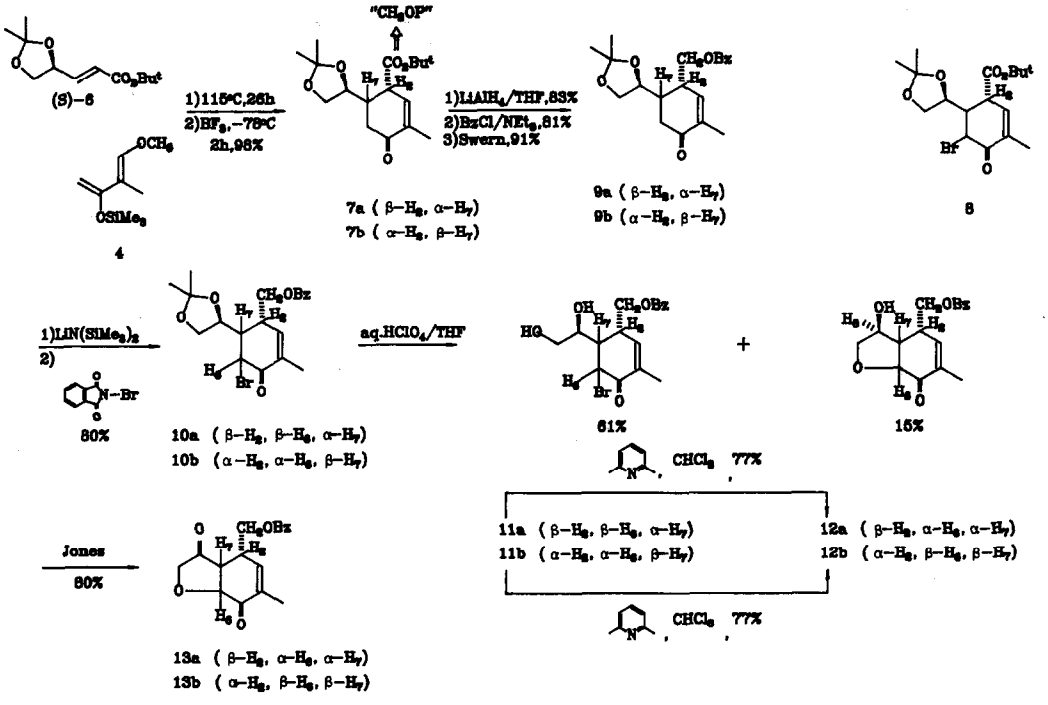
Scheme I



2. In principle cyclohexenol 2 could be obtained by the reduction from the convex face of cyclohexenone 3, which in principle could be prepared by a Diels–Alder reaction using diene 4 and dienophile 5, oriented in a manner as shown in Scheme I. However Diels–Alder cycloadditon of diene 4 and dienophile 5 will also produce the other regioisomer.[3] Hence reduction of C_8 ketone function of 5 to an alcohol 6 would reduce such complexity. Furthermore, the chirality at C_8 of 6 might induce a facial selective addition in the Diels–Alder reaction such that a favorable formation of one diastereomeric cycloadduct will be expected.[4] If the synthesis started with optically active alcohol (S)–6, the target molecule 1 would be synthesized in optically active form with correct antipode.

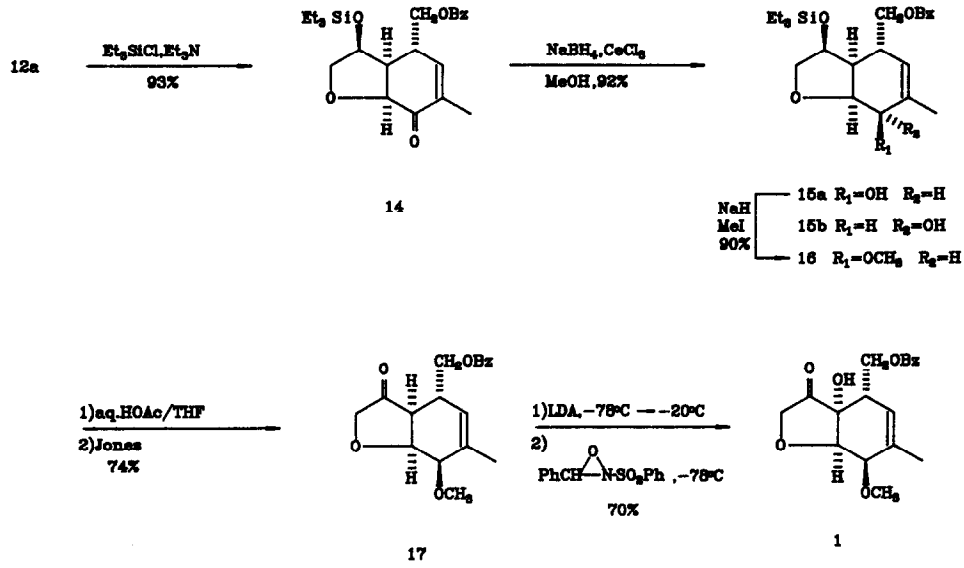
Optically active (S)–6 was prepared according to a literature procedure[5] by the condensation of (R)–2,3–isopropylidene glyceraldehyde and t–butyl acetate. When (S)–6 and diene 4[6] were heated at 115°C for 26 hr, followed by treatment with BF_3 etherate at –78°C for 2 hr, two diastereomric cyclohexenones 7a and 7b (ratio 3:1)[7] were obtained in 98% yield. According to Mulzer's[8] and Takano's[9] observations, the major product was temporally assigned as 7a. Separation of 7a and 7b was achieved by HPLC only at this stage, therefore mixture of isomers was carried over to the next reactions until where easy separation of isomers was found along the synthetic sequence. To construct O_{10}–C_6 bond, we require a leaving group at C_6 position and trans to the substituent on C_7. However unsuccessful monobromination of dianion of 7 produced intractable material, and the desired 6–bromocyclohexenone 8 was not observed. One would expect that change of the ester group of 7 to a protected alcohol might reduce some complexity in the monobromination reaction. Therefore 7 was reduced with LAH/THF at room temperature, followed by treatment with benzoyl chloride (1eq)/Et_3N at 0°C and Swern oxidation[10] to produce 9a and 9b in 61% yield. Treatment of 9a and 9b with lithium hexamethyldisilazide in THF, followed by N–bromophthalimide at –78°C gave 6–bromocyclohexenones 10a and 10b in 80% yield. Hydrolysis of 10a and 10b in aq. $HClO_4$/THF afforded the corresponding diols 11a, 11b, and some ring closure product 12. At this stage these two isomeric diols 11a and 11b could be separated by column chromatography. Formation of hexahydrobenzofuran 12a was effected by treating the major diol 11a with 2,6–lutidine in $CHCl_3$. Similarily 12b was obtained by treating diol 11b under a similar reaction condition. In an NOE experiment, an enhancement of H_8 signal was observed when H_2 of 12b was irradiated. However, no NOE enhancement was observed for 12a in a similar experiment. These suggested that H_2 and H_8 were syn to each other in 12b and anti to each other in 12a. Thus the stereochemical assignments for 7a and 7b were confirmed by this chemical correlation. Jones oxidation of 12a and 12b gave the corresponding ketones 13a and 13b respectively. The ^1H NMR spectra of ketones 13a and 13b were found to be identical after careful examination of these spectra. Since 12a and 12b contained identical configuration on C_8 chiral center and after removal of C_8 chiral center two compounds became to have identical ^1H NMR spectra and TLC behavior, therefore 13a and 13b were enantiomers which also indicated that 7a and 7b were diastereomers with opposite configuration on each of their C_2 and C_7 chiral centers. Thus the Diels–Alder reaction of (S)–6 and diene 4 had a clean regiospecificity.

Scheme II



In principle, chemoselective reduction on enone portion of **13** followed by methylation of the resulting alcohol and oxidation of C_7–H to an alcohol would furnish the hexahydrobenzofuran subunit **1**. However, reduction of **13** with $NaBH_4/CeCl_3$[11] in methanol at 0°C or at –78°C gave a mixture of reduction products which arose from a random reduction on C_5 and C_8 carbonyl groups. Therefore **12a** was silylated with triethylsilyl chloride in the presence of triethylamine to give **14**. Reduction of **14** using $NaBH_4/CeCl_3$ in methanol at –78°C gave **15a** and **15b** (ratio 11:1). The reduction presumably proceeded predominantly from the convex face of the six–five fused oxaindenone.[12] Methylation of **15a** with NaH/CH_3I gave methyl ether **16**. Treatment of **16** with aq. HOAc/THF followed by Jones oxidation gave **17** in 74% yield. Finally, **17** was deprotonated with LDA at –78°C and the resulting enolate was warmed to –20°C for 30 min then was treated with Davis reagent[13] at –78°C for one hour furnished the hexahydrobenzofuran subunit **1** in 70% yield with no sign of the other regioisomer. (Scheme III)

Scheme III



Acknowledgement. This work was supported by the National Science Council, Republic of China.

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(Received in Japan 26 February 1990)