Tetrahedron Letters,Vol.30,No.34,pp 4551-4554,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TOTAL SYNTHESIS OF (-)-BETAENONE C+

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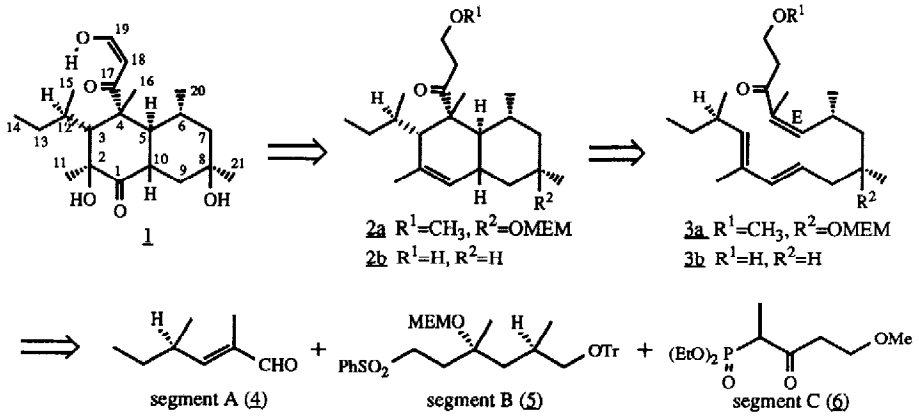
Abstract: Stereoselective synthesis of (-)-betaenone C through intramolecular Diels-Alder reaction has made possible to provide pertinent intermediates for the biosynthetic study of betaenones.

(-)-Betaenone C (1) isolated from the culture filtrate of Phoma betae Fr., causal fungus of leaf spot disease on sugar beet, has among betaenones the highest phytotoxic activity to the host plant and inhibits completely in vivo RNA and protein synthesis of starfish gastrula[1]. Since the fungus also produces aphidicolin and its analogues which markedly inhibit in vivo DNA synthesis of sea urchin and Hela cells[2], the roles of betaenones in the fungal pathogenicity are of interest[3]. Very recently, biosynthetic study on betaenones strongly suggest that betaenone B (16) is derived from probetaenone I (2b), which in fact was obtained by adding ancymidol, a potent p-450 inhibitor, into the culture medium[4]. Probetaenone I (2b) would be derived from presumed trienone 3b through the biological intramolecular Diels-Alder reaction[5].

Recent synthetic approach[6] for betaenones and stemphyloxins[7] prompted us to study the total synthesis of betaenone C (1) according to the retro synthesis involving intramolecular Diels-Alder reaction of the trienone 3a as shown in Scheme 1. The trienone 3a may be devided into the three segments, A (4), B (5) and C (6). The segment C (6) is known compound[8]. Total synthesis of (-)-betaenone C (1) has been completed as shown in Scheme 2.



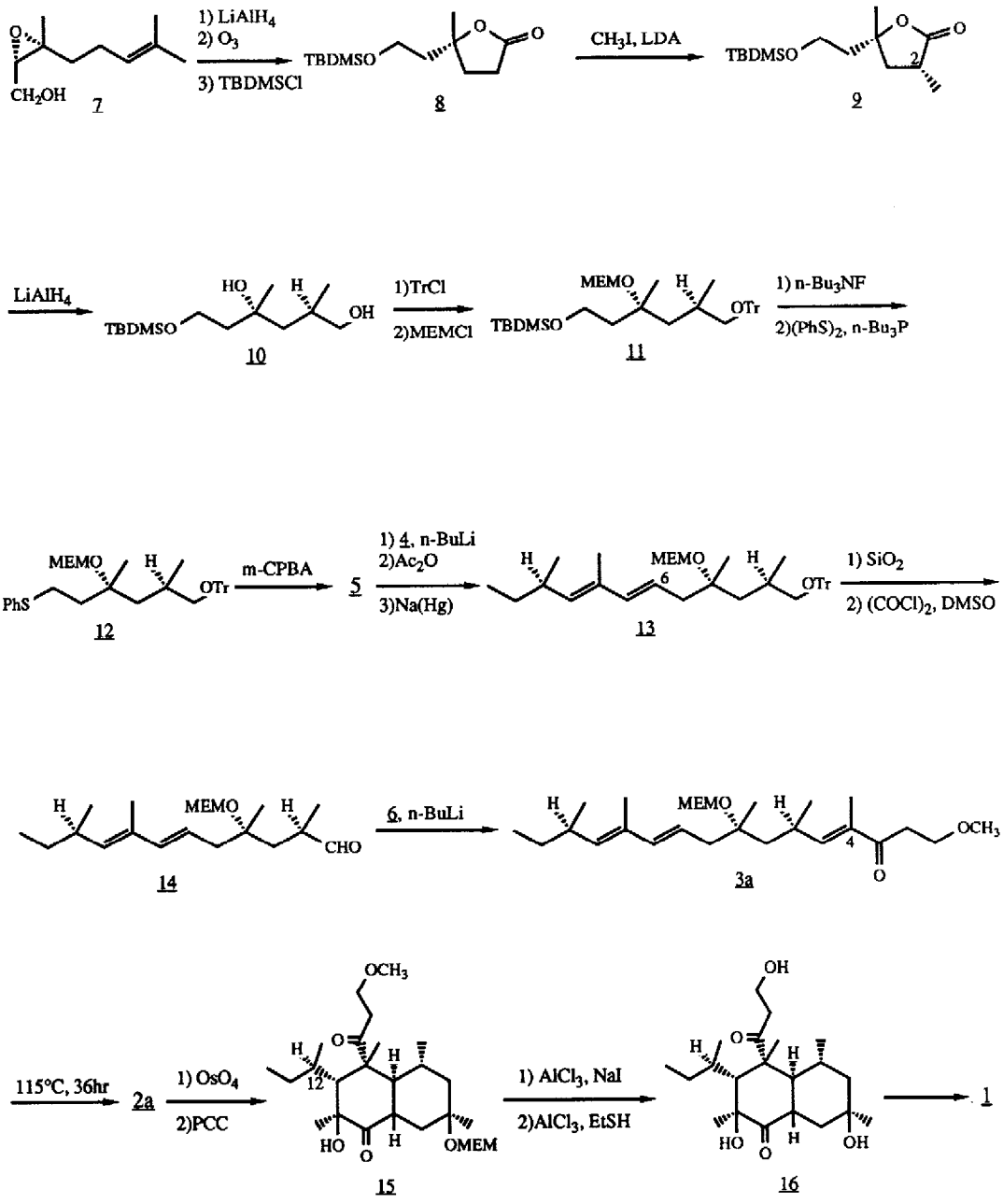
Scheme 1

The starting material, (-)-2-methylbutyric acid, was prepared by the Evans' procedure using prolinol as a chiral auxiliary[9]. The acid was immediately treated with $LiAlH_4$, and resultant alcohol was oxidized to (-)-2-methylbutanal. The Wittig reaction of (-)-2 methylbutanal with (α-carbomethoxy-ethylidene)-triphenyl phosphorane and subsequent reduction (4.3 equiv of $LiAlH_4$ in ether, -55 °C, overnight) yielded (2E, 4R)-2,4-dimethyl-2-hexen-1-ol (49.4 %, 80.7 % ee), which was converted to (2E, 4R)-2,4-dimethylhexanal (4) by oxidation (2.0 equiv of PCC in CH_2Cl_2, 0 °C- rt, 30 min). The aldehyde 4 was immediately used for subsequent reaction because of very volatile nature.

Segment B (5) was prepared starting from an epoxide 7 which was obtained by Sharpless oxidation of nerol[10]. Reduction of 7 (4.25 equiv of $LiAlH_4$ in THF, -40 °C, 6hr, rt, overnight) yielded a diol (80 %), which was ozonized and then decomposed with peracetic acid to give a lactone (90 %). The lactone was protected with silyl group (1.5 equiv of TBDMSCl, 3.15 equiv of imidazole in DMF, rt, overnight) to give a silylated compound 8[11] (60 %). Alkylation of 8 (2.3 equiv of CH_3I and 2.3 equiv of LDA in THF, -40 °C) afforded a diastereomeric mixture (73 %) of 9 and its C-2 epimer in a ratio of 2:3, which were separated easily by medium pressure liquid chromatography (CIG column). The stereochemistry of 9 was confirmed by the NOE experiments in ^1H NMR spectrum. The epimer was easily converted to 9 by treatment with LDA in more than 60 % yield. Reduction (1.3 equiv of $LiAlH_4$ in THF, -50 °C, 1.5 hr) of the lactone 9 gave a diol 10 (91 %), which was protected with trityl chloride (2 equiv in pyridine, rt, 36 hr) and then MEMCl[12] (1.70 equiv in i-Pr_2NEt, rt, 24 hr) to yield a trityl ether 11 (85 %). By removal of the silyl group (2 equiv of n-Bu_4NF in THF, 0 °C, 3.5 hr)[13], and subsequent treatment with diphenyl disulfide (1.56 equiv in pyridine, rt, 24 hr) and n-Bu_3P (1.55 equiv), the trityl ether 11 was converted to a phenyl sulfide (12, 83 %), which was oxidized with m-chloroperbenzoic acid (2 equiv in CH_2Cl_2, -20 -10°C, 14 hr) to give segment B (5, 99.7 %).

The Kocienski-Lythgoe-Julia condensation (1.1 equiv of BuLi, -75 C, 10 min)[14] of segment A (4, 1.3 equiv) with segment B (5, 1 equiv) afforded adducts, which were treated with acetic anhydride (1 equiv) and then sodium amalgam (5 %) to give diene (13, 59.4 %)[15]. By removal of the protective trityl group (SiO_2 in benzene, rt, 36 hr)[16] and Swern oxidation with oxalyl chloride (5.18 equiv, DMSO, -55°C, 20 min)[17], the diene 13 was transformed to aldehyde 14[15] (79 %). The Wittig-Horner reaction of the aldehyde 14 (1 equiv) with segment C (6, 4 equiv) (BuLi, -3-4 °C, 40 hr) afforded trienone 3a (46.8 %) along with the 4-Z isomer (7.8 %).

The intramolecular Diels-Alder reaction of the trienones 3a in toluene was carried out in a sealed tube heating at 115°C for 36 hr to yield cycloadducts 2a (40.5 %). Though the adduct 2a contains about 20 % 12-epimer[18], no other diastereoisomers has been detected[19]. Among four possible transition states involving cycloaddition reaction on the basis of molecular model, the one leading to the product 2a is most favorable because of absence of severe non bonded atoms interaction. By dihydroxylation (1 equiv of OsO_4 in pyridine-ether, -30 °C, rt, 3 hr, 66.1 %) and subsequent oxidation (4.4 equiv of PCC and


1) LiAlH4
2) O3
3) TBDMSCl
CH2OH
7
TBDMSO
8
CH3I, LDA
9
LiAlH4
HO
H
OH
10
1)TrCl
2)MEMCl
MEMO
OTr
11
1) n-Bu3NF
2)(PhS)2, n-Bu3P
m-CPBA
PhS
12
5
1) 4, n-BuLi
2)Ac2O
3)Na(Hg)
6
13
1) SiO2
2) (COCl)2, DMSO
CHO
14
6, n-BuLi
OCH3
3a
115°C, 36hr
2a
1) OsO4
2)PCC
12
OMEM
15
1) AlCl3, NaI
2)AlCl3, EtSH
16
1

Scheme 2

5.8 equiv of AcONa in CH_2Cl_2, rt, 1 hr, 65.3 %), the adduct 2a gave, beside minor amount of 12-epimer (5 %), a ketol 15 (22.3 %) after chromatographic purification. The ketol 15, $[\alpha]_D^{22}$ -35.4° (c 0.08, EtOH), was identical with those of the derivative 15, $[\alpha]_D^{22}$ -42.1° (c 0.08, EtOH), from betaenone B[1] (16) in the spectral data and behavior on TLC. Removal of MEM group (23.5 equiv of $AlCl_3$, 23.5 equiv of NaI in CH_3CN-CH_2Cl_2, -20 °C, 30 min, 91.7 %) and further deprotection of methyl group (3.3 equiv of $AlCl_3$, EtSH, -8 °C, 4 hr) furnished betaenone B (16, 34 %) which is identical with natural sample in all respects.
Since betaenone B (16) has been converted to betaenone C (1), the present synthesis means a formal total synthesis of (-)-1. This synthesis also has made possible to synthesize probetaenone I (2b) and its precursor, trienone 3b, which would be useful for incorporation study in the biosynthesis of betaenones[5].

Acknowledgement: We are indebted to Professor H. Shirahama, Department of Chemistry, Hokkaido University, for molecular mechanics calculation[18].

References and notes

+ Taken from the Ph. D. Thesis of S. Miki, Hokkaido University, 1988.
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(Received in Japan 22 April 1989)