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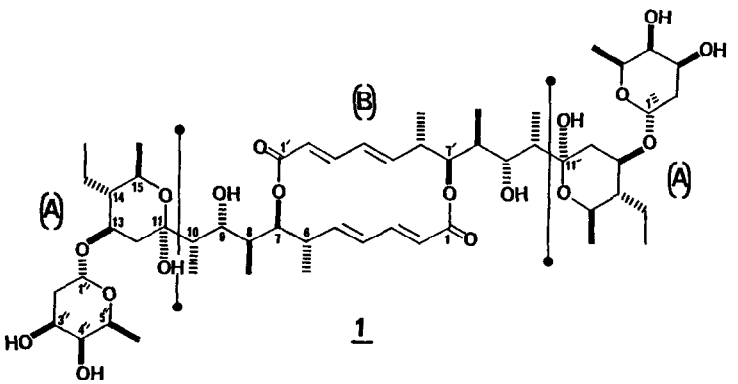
SYNTHETIC STUDIES ON ANTIBIOTIC MACRODIOLIDE: SYNTHESIS OF THE A-SEGMENT OF ELAIOPHYLIN

Takeshi Wakamatsu,* Hideo Nakamura, and Eiichi Naka
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Yoshio Ban
School of Pharmaceutical Science, Toho University, Miyama 2-2-1, Funabashi, Chiba 274, Japan

Summary: A-segment(C_{11}-C_{15}) containing L-oliose moiety in both side of elaiophylin(1) was synthesized enantio- and stereoselectively in the form of (4) which involves 7 asymmetric carbons of seco acid, by a coupling of the fragment (2) with (3). These chiral fragments were prepared from methyl-α-D-glucopyranoside(5) or levoglucosan(1,6-anhydro-β-D-glucopyranose)(10), respectively.

Elaiophylin(1), 16-membered macrodiolide with C_2-symmetry, was isolated from cultures of Streptomyces melanosporus[1a] and exhibits activity against gram-positive bacteria. Subsequently, elaiophylin(1) was also isolated from other strains of Streptomyces.[1b-e] The structure was elucidated by X-ray crystallographic analysis[2] as (1) that is the bis-lactone with L-oliose(2-deoxyfucopyranose). Most recently, Seebach and his collaborators have published the first total synthesis of (+)-11,11'-di-O-methylelaiophylidene[3] which is an aglycon of elaiophylin. In connection with our own program directed toward the synthesis of (1), we describe herein stereocontrolled synthesis of the A-segment in optically active form of (4).



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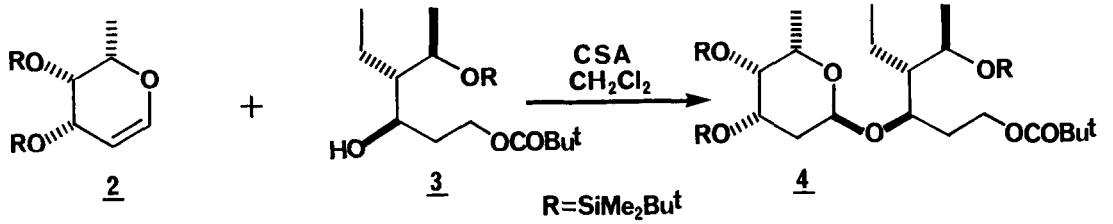
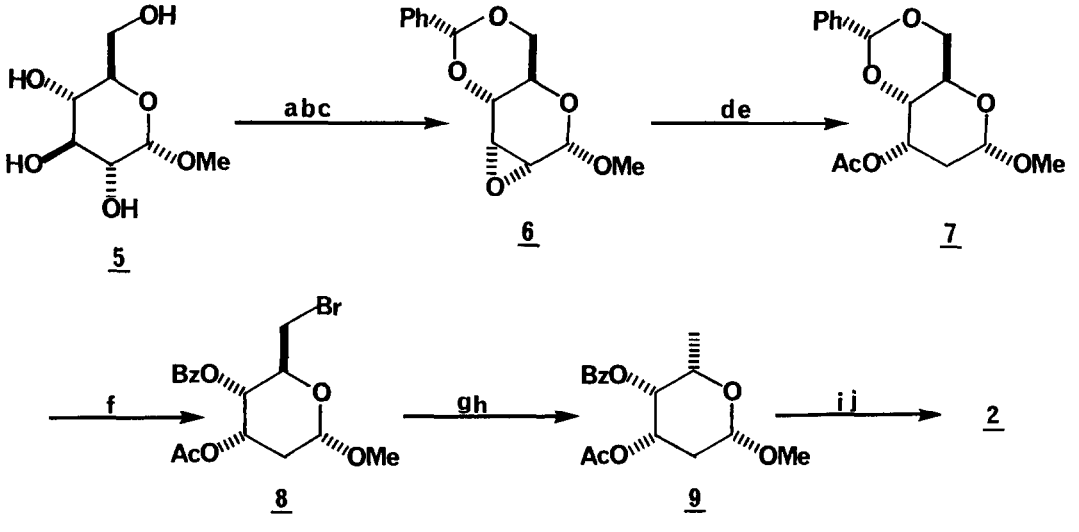
Our synthetic plan toward (4) involves a coupling of the silyl protected fucal derivative(2) with the secondary alcohol(3) as is shown in Scheme 1.

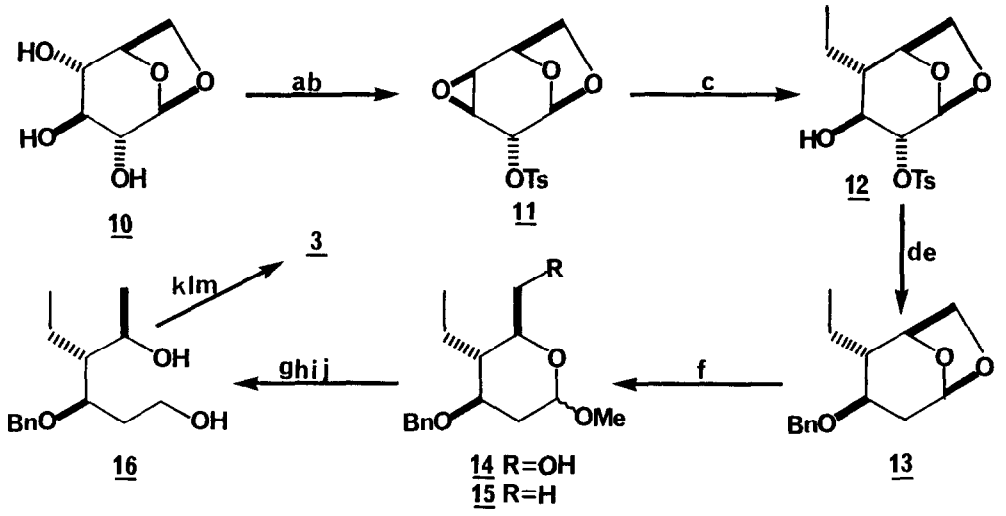


Scheme 1

The benzylidene pyranose(7)[4] was easily prepared from methyl-α-D-glucopyranoside(5) via the following functional group manipulation involving (i) PhCHO, $ZnCl_2$, rt, 71%, (ii) 2 equiv TsCl, pyr, 79%, (iii) $NaOCH_3$, CH_2Cl_2, 88%, (iv) $LiAlH_4$, THF, 82%, (v) Ac_2O, pyr, DMAP, 95%. Photochemical bromination of (7) with N-bromosuccinimide in CCl_4[5] afforded successively the bromo benzoate(8) in 92% yield. This was subjected to dehydrobromination with AgF in pyridine[6] to give rise to the corresponding unstable enol ether which in turn was immediately hydroganated with a catalyst of 10% Pd-C in methanol to yield the 2-deoxyfucoside derivative(9)[7] in 73% yield. Subsequent reduction of (9) with $LiAlH_4$ in THF at room temperature gave the corresponding diol in 74% yield and this was treated with t-butyldimethylsilyl triflate containing 2,6-lutidine in CH_2Cl_2[8] at room temperature to give directly the silyl fucal derivative(2) in 79% yield after purification by chromatography on silica gel.



a) PhCHO/ZnCl2 ; b) TsCl/Pyr ; c) NaOMe,CH2Cl2 ; d) LiAlH4,THF ; e) Ac2O/Pyr/DMAP ; f) NBS,hν,CCl4 ; g) AgF/Pyr ; h) H2/Pd-C ; i) LiAlH4,THF ; j) CF3SO3SiMe2Bu^t/2,6-lutidine,CH2Cl2 ;



a) 2 equiv TsCl/Pyr : b) NaOMe,CH_2Cl_2 : c) EtMgCl/CuBr,THF : d) $LiBEt_3H$,THF : e) BnBr/NaH : f) MeOH/BF_3·Et_2O : g) TsCl/Pyr : h) $LiBEt_3H$,THF : i) Dowex50, aq-dioxane : j) $LiAlH_4$,THF : k) ^tBuCOCl/Pyr : l) $^tBuMe_2SiCl$/ Et_3N/DMAP,DMF : m) H_2/Pd-C

Synthesis of alcohol(3) was planned from levoglucosan(10) which was prepared from starch pyrolysis[9] by the partly improved procedure. Levoglucosan(10) was converted to the epoxy tosylate(11)[10] by treatment with 2 equiv of TsCl, followed by reaction with sodium methoxide in CH_2Cl_2. Epoxide ring opening of (11) in which the pyranoside moiety is held in the abnormal $^1C_4$ conformation[11] was regio- and stereoselectively occurred to give tosylate(12) in 62% yield by copper(I) induced reaction[12] with ethylmagnesium chloride in THF. Reductive removal of the tosylate group of (12) was achieved by using $LiBEt_3H$ in THF to give alcohol which was transformed into the benzyl ether(13) in 78% yield. The opening of the 1,6-anhydrobridge of (13) was carried out with BF_3 ether complex in methanol to afford acetal(14) in 98% yield which proved to be an anomeric mixture in 5:1 ratio of α- and β-isomers by PMR analysis. The mixture of (14) was then tosylated with TsCl in pyridine at room temperature to obtain the corresponding tosylate, and then treated with $LiBEt_3H$ in THF to give the anomeric mixture of (15) in nearly quantitative yield. Diol(16) was obtained from (15) by treatment with Dowex50w-X8 in dioxane followed by reduction with $LiAlH_4$ in 71% overall yield. Treatment of (16) with pivaloyl chloride containing pyridine in CH_2Cl_2(90%), followed by silylation with t-$BuMe_2SiCl/Et_3N$/DMAP(quant) gave the protected triol which was easily hydrogenated with 10% Pd-C in EtOAc to yield the desired secondary alcohol(3) in quantitative yield. Finally the coupling reaction of (2) with (3) by using catalytic amounts of dl-10-camphorsulfonic acid in CH_2Cl_2 at room temperature for 1h occurred smoothly to give the A segment(4) in 57% yield in the desired sense. This α-L-glycosidation step proceeded with an excellent stereoselectivity by control known as anomeric effect.[13]

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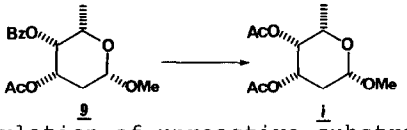
7. When compound (9) was hydrolyzed with NaOMe/MeOH and then acetylated with Ac_2O/Py/DMAP, this was converted into methyl-3,4-di-O-acetyl-2-deoxy-β-L-fucopyranoside(i) which is degradation product obtained from elaiophylin.



9 i

$[\alpha]_D$=+10.8°(c=0.92,$CHCl_3$
lit.[2d] $[\alpha]_D$=+3.5°(c=1.3,$CHCl_3$)

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