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ENANTIOSPECIFIC SYNTHESIS OF THE SPIROACETAL UNIT OF AVERMECTIN B_{1a}

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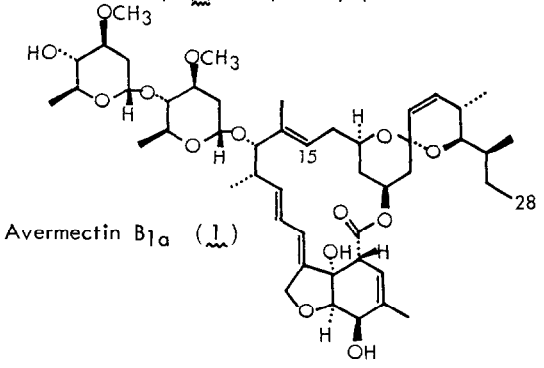
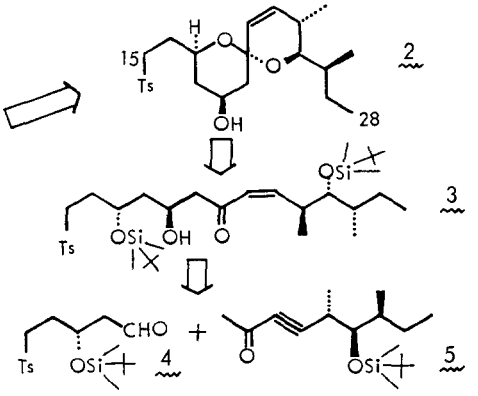
Summary: The spiroacetal unit (C_{15}-C_{28}) of avermectin B_{1a} has been enantiospecifically synthesized by taking advantage of stereocontrolled baker's yeast reduction.

Avermectins are novel macrocyclic lactones[1] produced by Streptomyces avermitilis[2] and exhibit exceptionally potent activity against a variety of parasites (nematodes and arthropods).[3] Because of their unique structural features and bioactivity, we have lounched a synthetic study[4] toward avermectin B_{1a} (1), the most active member of the family. We present herein a stereocontrolled synthesis of its spiroacetal moiety (2) in optically pure form.

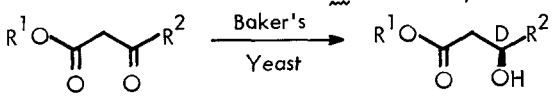


Avermectin B_{1a} (1)

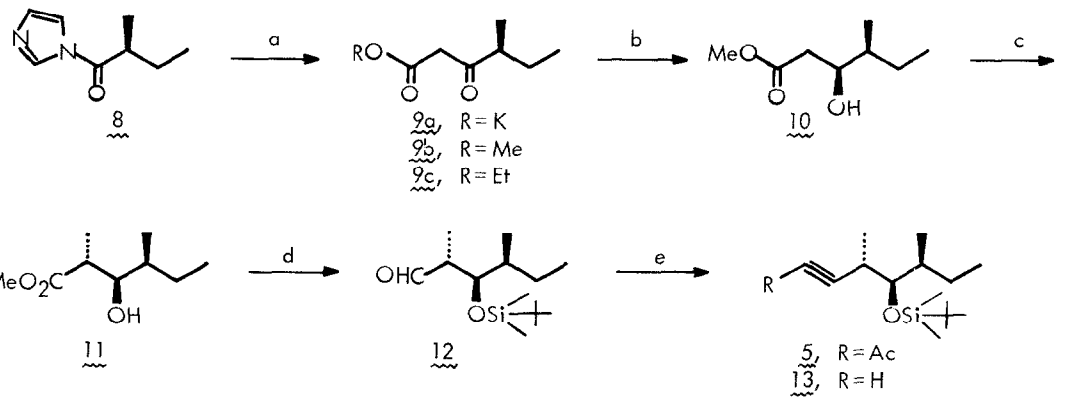


Our synthetic strategy of 2 rests on a stereoselective spiroacetalization of suitably functionalized acyclic precursor, such as 3, constructed expeditiously by the coupling of the two segments 4 and 5. The chiralities at the carbinyl carbons in the latter two are enantiospecifically introduced by baker's yeast reduction.

Our previous findings[5] indicated, in accord with Prelog's rule,[6] that baker's yeast reduction of prochiral β-keto acid derivatives 6 with hydrophobic R^2 yielded higher selectivity for (D)-alcohol 7 as R^1 became smaller and/or more hydrophilic. A similar trend was anticipated in the reduction of chiral γ-branched β-keto acid derivatives 9 (Scheme 1). Thus, the esters 9b[7] and 9c were prepared from the corresponding acetates and the acid imidazolide 8[7,8] readily available from 2(S)-methylbutanol;



6 7



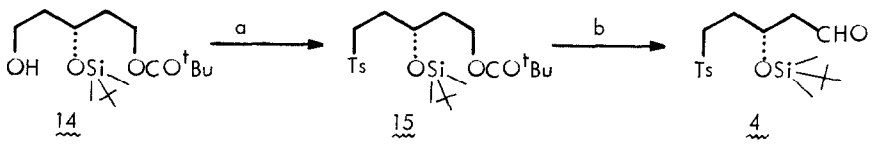
Scheme I. (a)ROAc, LDA, -78°, 62%. (b)baker's yeast, glucose, 2 days. (c)LDA(2.2 mol.eq.), -50°, THF, 2 h→5%HMPA, MeI(10 eq.), -50°, 30 min. (d)(i)t-BuMe$_2$SiCl, imidazole, DMF, 93%; (ii)DIBAL, 0°, ether, 70%; (iii)PCC, 70%. (e)(i)CBr_4, PPh_3, CH_2Cl_2, 92%; (ii)n-BuLi(2.1 mol.eq.), -78°, THF →$BF_3 \cdot OEt_2$(1.1 eq.), -78°, 10 min→Me_2NAc(2 eq.), -78°, 30 min.

potassium salt 9a was prepared by alkaline hydrolysis of 9c. The yeast reduction of 9a and 9b under the standard conditions[5a] showed the expected stereoselectivity, 3S(D):3R(L)=99:1[9] (16% yield) and 98:2[9] (19%; 27% based on the consumed 9b) respectively, while the selectivity for 9c decreased to 94.5:5.5[9] (22% yield). The absolute configuration of the major product 10[7] was confirmed to be 3S,4S by the comparison of its physical data with those of the authentic specimen reported by Murai et al.[10] Thus, short-step synthesis of the chiral 10, which is also an important unit of polypeptin-permetin family of antibiotics,[10] has been accomplished.

The introduction of a methyl group at C2 in 10 in the anti fashion relative to the hydroxyl group was achieved utilizing Fráter and Seebach's method.[11] Lithium dianion of 10, prepared from 9b, was treated with MeI to afford 11[7,12] in 60-65% yield, although it was contaminated by 10% of 2,3-syn isomer.[13] After converting 11 to the aldehyde 12[7] with t-butyldimethylsilyloxy group, 12 was reacted with CBr_4-PPh_3 and then with n-BuLi. The resulting lithium acetylide was acetylated with N,N-dimethylacetamide in the presence of BF_3 etherate[14] to give the segment 5[7] in 47% overall yield (70% based on recovered alkyne 13[7]).

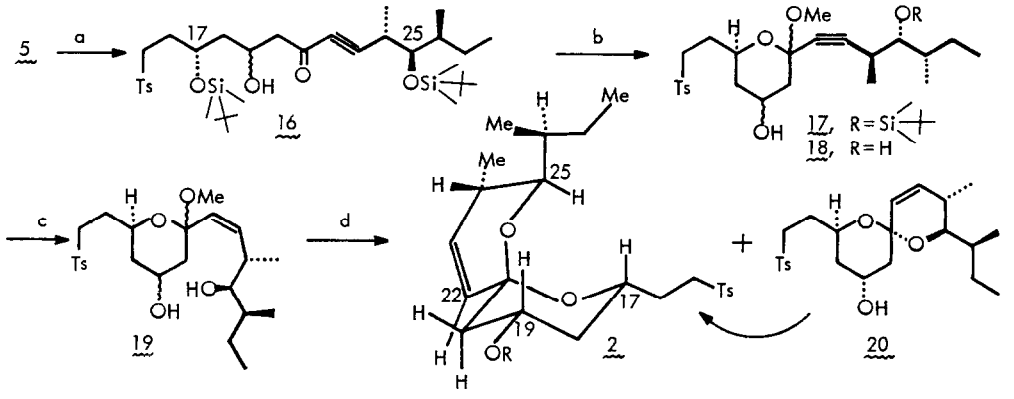
The homochiral segment 4[7] was prepared in four steps (Scheme II, 46% overall) from the pentane-1,3,5-triol derivative 14,[7,15] whose chirality had been also introduced by baker's yeast reduction.

The aldol condensation (LDA, -78°C) of 5 with 4 produced a 1 : 1 mixture of epimeric alcohols



Scheme II. (a)(i)NBS, PPh_3, CH_2Cl_2, 80%; (ii)$NaSO_2C_6H_4CH_3$-p, DMF, 71%. (b)(i)4% NaOH, MeOH, 99%; (ii)PCC, CH_2Cl_2, molecular sieves 3A, 82%.

16[7]; the mixture was further transformed without separation (Scheme III), since the undesired 3R epimer was convertible into the 3S isomer afterwards (vide infra). As all attempts to deprotect both silyloxy groups in 16 simultaneously proved to be unsuccessful,[16] the groups were removed stepwise: 16 was converted to the methyl acetal 17 via regioselective deprotection of the C17 silyloxy group on treatment with catalytic amount of p-TsOH in MeOH-$CH(OMe)_3$ at room temperature. Then, the silyl group on C25 hydroxyl was removed with tetrabutylammonium fluoride to yield the diol 18. Subsequent hydrogenation of 18 with Lindlar catalyst followed by treatment with camphorsulfonic acid resulted in smooth formation of a mixture of spiroacetals (2:20=1.7:1). The ratio was improved to 4.1:1 by Collins' oxidation of the mixture and subsequent $LiAlH_4$ (-78°C, ether) reduction, while the reduction with $NaBH_4$ (DME, 0°C) still afforded 1.6:1 ratio.[17] The isomers were easily separable by SiO_2 column chromatography (Rf=0.52 for 2[7]; 0.69 for 20[7] on silica gel TLC, ether) and subsequent recrystallization from ether-hexane to give pure 2, m.p. 106-107.5°C. Its stereochemistry was confirmed by 360 MHz-^1H NMR spectroscopy including NOE experiments.[4b,18]



Scheme III. (a) LDA, -78°, THF, 45%(69% based on recovered 5). (b) CH_3OH, $CH(OCH_3)_3$ (13:1), p-TsOH(cat.), r.t., 5 h, 62%. (c)(i) n-Bu_4NF(6 eq.), THF, r.t., 12 h; (ii) Lindlar cat. ($Pd/CaCO_3/Pb$), H_2, Toluene. (d) DL-CSA(cat.), CH_2Cl_2, 90% overall from 17.

With the spiroacetal unit 2 readily accessible, we have pursued the next stage to attach C11-C14 segment to 2 in a stereocontrolled manner. The task along this line will be reported in due course.

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7) The specific rotations $[\alpha]_D$, (concentration) in $CHCl_3$ at 22-30°C: 8, +26° (1.1); 9b, +23° (1.3); 10, -33° (1.6); 11, -11° (1.4); 12, -25° (1.8); 5, -2.1° (1.1); 13, +2.6° (1.2); 14, -5.6° (1.2); 15, -11° (1.1); 4, -4° (1.2); 16, -4° (0.5); 2, +24° (0.3); 20, +4° (0.2).

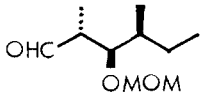
8) The optical purity (92.6% e.e.) was determined by the conversion to the corresponding diastereomeric amide mixture using (S)-naphthylethylamine (Aldrich)[5b] and subsequent HPLC analysis.

9) The ratio was determined by ^1H NMR studies on β-hydroxy methyl ester using chiral shift reagent $Eu(tfc)_3$. These studies are also decisive of the alcohol configuration: ester methyl signal of L-alcohols generally shows a larger down-field shift than that of the corresponding D-alcohols[14]. Such is the case with this, irrespective of the configuration of C4 position, which has been secured by the examination of three stereoisomers of 10, kindly presented by Dr. A. Murai[10].

10) A. Murai, Y. Amino and T. Ando, J. Antibiotics, 1610 (1985), and references cited therein.

11) G. Fráter, Helv. Chim. Acta, 62, 2825 (1979); D. Seebach and D. Wasmuth, ibid., 63, 197 (1980).

12) The stereochemistry of 11 was established by its conversion to the known aldehyde i: the spectral data are identical with those of the compound synthesized by Hanessian et al.[4a]



i

13) The 2,3-syn isomer was not separated from 11 by SiO_2 chromatography, but the stereochemical purification was ultimately achieved at the spiroacetal 2 by recrystallization.

14) M. Yamaguchi, T. Waseda and I. Hirao, Chemistry Lett., 35 (1983).

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16) The silyl ether on C25 was so unreactive that the ketol function could not tolerate basic (F^-) or acidic conditions required.

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18) Chemical shifts of the critical axial or pseudo-axial protons: δ ($CDCl_3$) 1.31 (H_{20a}, t, J ≈ 12 Hz), 2.21 (H_{24}, dqdd, J = 10.0, 7.2, 2.6, 1.8 Hz), 3.22 (H_{25}, dd, J = 10.0, 1.7 Hz), 3.76 (H_{17}, dddd, J = 11.7, 8.7, 3.8, 2.2 Hz), 4.10 (H_{19}, tt, J ≈ 11.5, 4.5 Hz). NOE: [H_{20a}-H_{22} (δ 5.46, dd, J = 10.0, 2.6 Hz)] = 3.2%; [H_{17}-H_{19}] = 5.2%; [H_{17}-H_{25}] = 1.7%.

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