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TOTAL SYNTHESIS OF THE AGLYCONE OF VENTURICIDINS A AND B --- I
SYNTHESIS OF C_1-C_{14} SEGMENT

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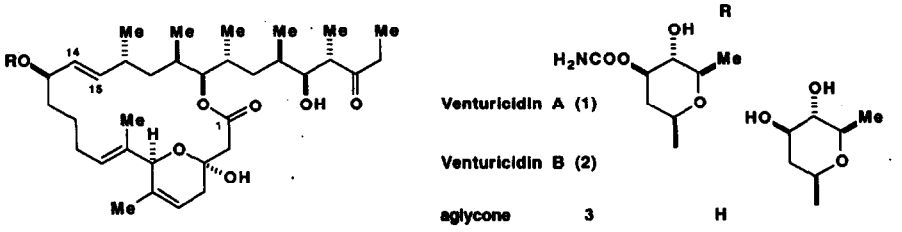
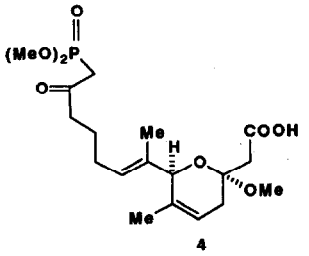
Summary; The C_1-C_{14} segment 4 of venturicidins A and B was synthesized by a strategy based on the biosynthetic consideration.

Venturicidins A (1) and B (2)[1], 20-membered macrolide antibiotics isolated from some streptomyces, exhibit strong bioactivity such as an inhibition of the growth of the phytopathogenic fungi and the mitochondrial H^+-ATPase.[2] We now report the first total synthesis of the aglycone 3 of 1 and 2.



In the present synthesis, construction of a twenty-membered lactone was intended to achieve by the intramolecular Wittig-Horner condensation between the C_{14}- and C_{15}-positions rather than macrolactonization and thus acid 4 and alcohol 5 having suitably masked or modified functional groups were chosen as the requisite building blocks for the final coupling reaction. In this paper, we describe the synthesis of 4 corresponding to the bottom half and in the following paper, the synthesis of 5 corresponding to the upper half and the subsequent coupling with 4 leading to the natural aglycone 3 will be reported.



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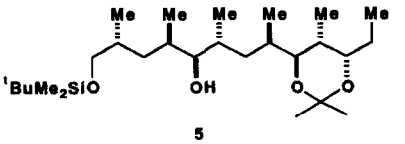

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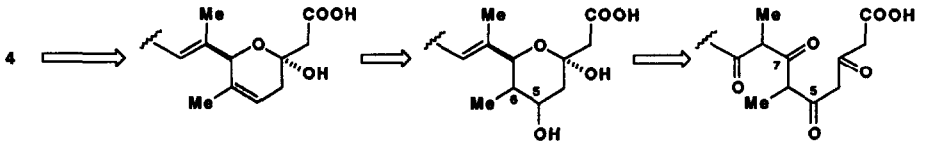
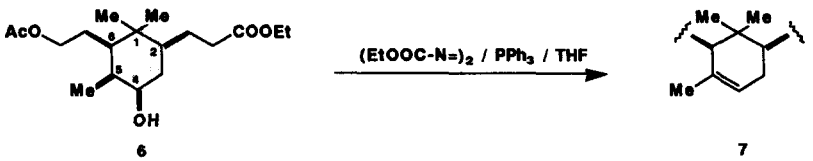
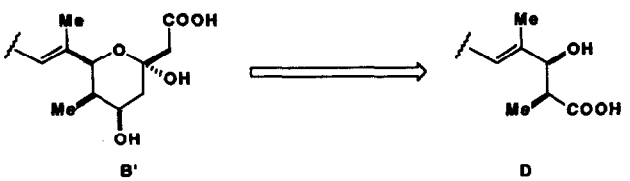
Venturicidins are suggested to be derived from the polyketide precursor.[3] The major framework A in 4 is presumed to be produced from C by reduction of ketones at the 5- and 7-positions followed by intramolecular cyclization leading to B and regioselective dehydration of the hydroxyl group at 5-position. The synthetic strategy for 4 was designed based on this hypothetical biogenetic pathway.



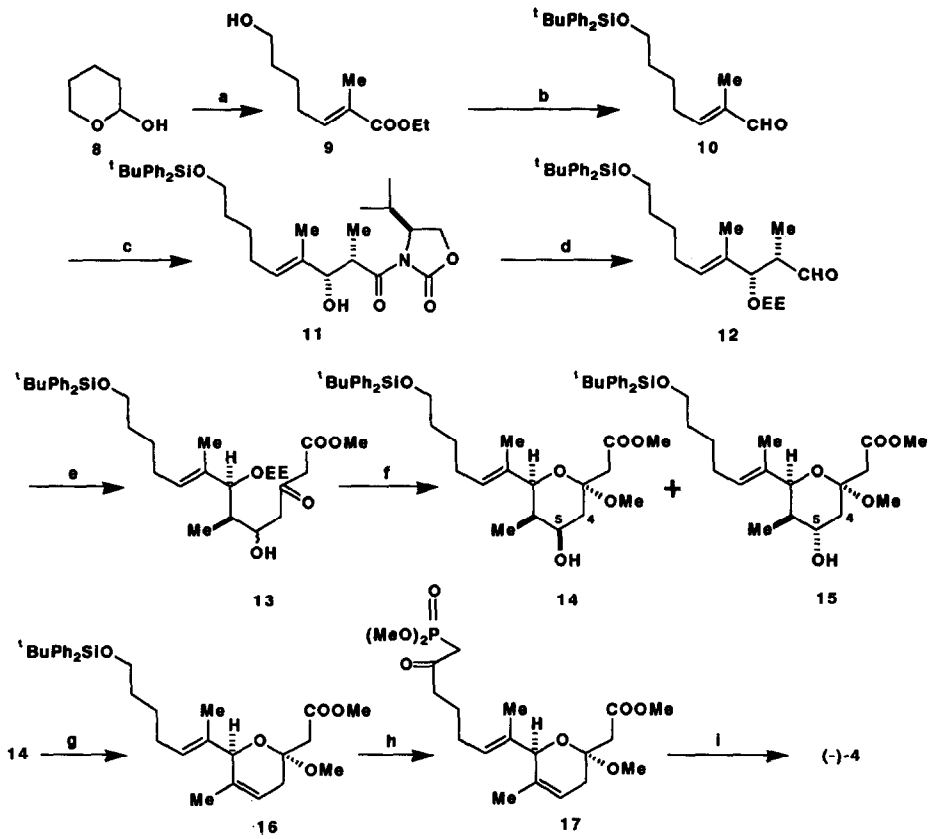
In this strategy, the crucial step is obviously the directed dehydration from B to A. We have observed the same type of regioselective dehydration in the related system[4]: namely, in the process of synthetic studies of taxane framework, the 5β-Me, 4β-OH-cyclohexane derivative 6 having large equatrial substituents at C_2- and C_6-positions was found to produce 7 under Mitsunobu's reaction conditions.[5]



In order to examine whether the same stereochemical effect of substituents is operative in the present system, we carried out the model experiments extensively.[6] The results suggest that the intermediate B should give the desired $\Delta^{5,6}$-dihydropyran derivative A when the C_5-OH and C_6-Me groups were (equatrial) and (axial), respectively. Thus, we first examined the stereoselective synthesis of the optically active B' and its precursor D whose OH and Me groups are in syn-relationship.



Lactol 8 was condensed with phosphorane giving an enoate 9[7] in 98% yield, which was converted to enal 10 in 3 steps : 1. protection of the primary hydroxyl group ($^tBuPh_2SiCl$/imidazole), 2. reduction of ester group (DIBAH), 3. oxidation of resulting allylic alcohol (PDC/Zeolite 3A), 87% overall yield. Asymmetric aldol condensation of aldehyde 10 with the Evans reagent[8),9] gave imide 11[10] in 69% yield which after protection of hydroxyl group with ethoxyethyl group was reduced with $LiAlH_4$ and the resulting primary alcohol was oxidized to aldehyde 12 (68% overall yield). Aldol condensation of 12 with dianion derived from methyl acetoacetate afforded a mixture of



a; Ph_3P=CH(Me)COOEt b; 1) $^tBuPh_2SiCl$/Imidazole 2) DIBAH 3) PDC/Zeolite 3A

c;  /Bu_2BOTf/$^iPr_2NEt$ d; 1) EVE/PPTS 2) $LiAlH_4$ 3) PDC/Zeolite 3A

e; $MeCOCH_2COOMe$/NaH, n-BuLi f; $CH(OMe)_3$/PPTS/MeOH g; DEAD/Ph_3P/toluene/80°C

h; 1) n-$Bu_4NF{\cdot}3H_2O$ 2) PDC/Zeolite 3A 3) $MePO(OMe)_2$/n-BuLi 4) PDC/Zeolite 3A i; 0.5N-KOH/MeOH

alcohols 13, which was treated with $CH(OMe)_3$ in the presence of PPTS producing 5β-alcohol 14 ($[\alpha]_D^{20}$ +25.9° (c=2.30, MeOH)) and 5α-isomer 15 ($[\alpha]_D^{20}$ +20.1° (c=3.42, MeOH)) in 20% and 30% yields from 12, respectively. The configurations of the hydroxyl groups were confirmed on the bases of their NMR data (14: $J_{4\alpha,5\alpha}$=5.0 Hz, $J_{4\beta,5\alpha}$=11.6 Hz; 15: $J_{4\alpha,5\beta}$, $J_{4\beta,5\beta}$=1.6, 3.6 Hz). The crucial regioselective dehydration of 14 took place expectedly under Mitsunobu's reaction conditions giving the $\Delta^{5,6}$-dihydropyran derivative 16 ($[\alpha]_D^{20}$ -7.4° (c=1.27, MeOH)) in 62% yield as a sole product. Desilylation of 16 followed by oxidation of the liberated hydroxyl group with PDC furnished aldehyde, which was condensed with $LiCH_2P(O)(OMe)_2$[11] and the resultng mixture was oxidized with PDC-Zeolite 3A giving β-keto phosphonate 17 in 33% overall yield (4 steps). Finally, saponification of the ester group of 17 led to the bottom half 4 ($[\alpha]_D^{20}$ -12.4° (c=1.74, benzene) in 83% yield.

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References and Notes

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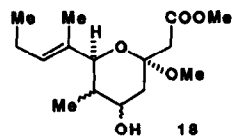
5) O. Mitsunobu, Synthesis, 1 (1981).

6) We examined the dehydration reaction using four possible stereoisomers of 18 under Mitsunobu's reaction conditions. The details will be published elsewhere.



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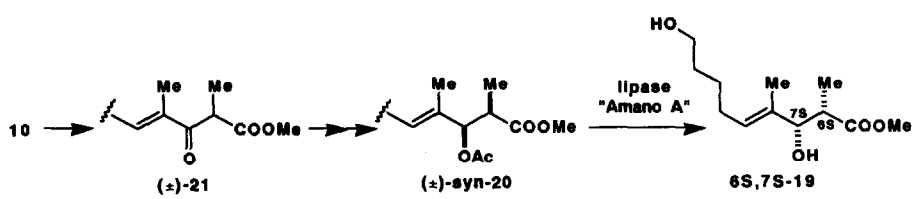
7) Satisfactory analytical data were obtained for all new compounds.

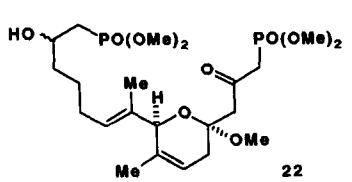
8) D. A. Evans, J. Bartroli and T. L. Shih, J. Am. Chem. Soc., 103, 2127 (1981).

9) We have synthesized 6S,7S-19 by lipase "Amano A" (from Aspergillus niger) induced kinetic hydrolysis of (±)-syn 20 which was synthesized by $Zn(BH_4)_2$ reduction (syn/anti =67:1) of the corresponding (±)-β-keto ester 21. However, the optically purity of 19 (87% ee) was rather unsatisfactory to be used as a starting material.



10) The anti-isomer 11 could not be detected in the present case. Optical purity of syn-11 (94% ee) was determined by measuring the NMR spectrum of (+)-MTPA ester derived from 11 (16% overall yield) in 5 steps: 1. protection of secondary hydroxyl group with ethoxyethyl group (EVE/PPTS); 2. hydrolysis of imide group (LiOH/30% H_2O_2); 3. esterification (CH_2N_2); 4. deprotection of ethoxyethyl group (PPTS/MeOH); 5. esterification ((+)-MTPACl/pyridine).

11) The solution of $LiCH_2P(O)(OMe)_2$ should be added to the solution of aldehyde at -78°C. Addition of the aldehyde to the reagent affords β-keto phosphonate 22 (13%), β-hydroxy phosphonate (24%) and the starting material (29%).



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