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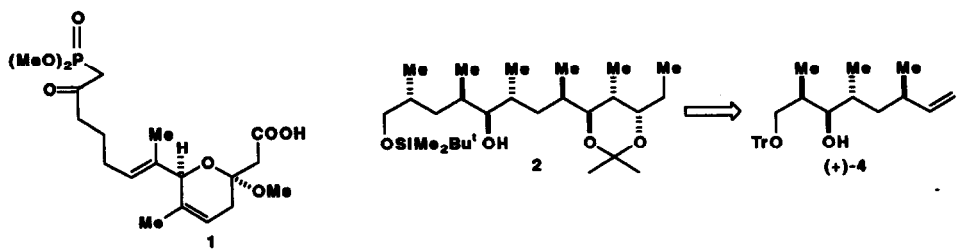
TOTAL SYNTHESIS OF THE AGLYCONE OF VENTURICIDINS A AND B ---II

Hiroyuki Akita,* Harutami Yamada, Hiroko Matsukura, Tadashi Nakata, and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
2-1, Hirosawa, Wako-shi, Saitama 351-01, Japan

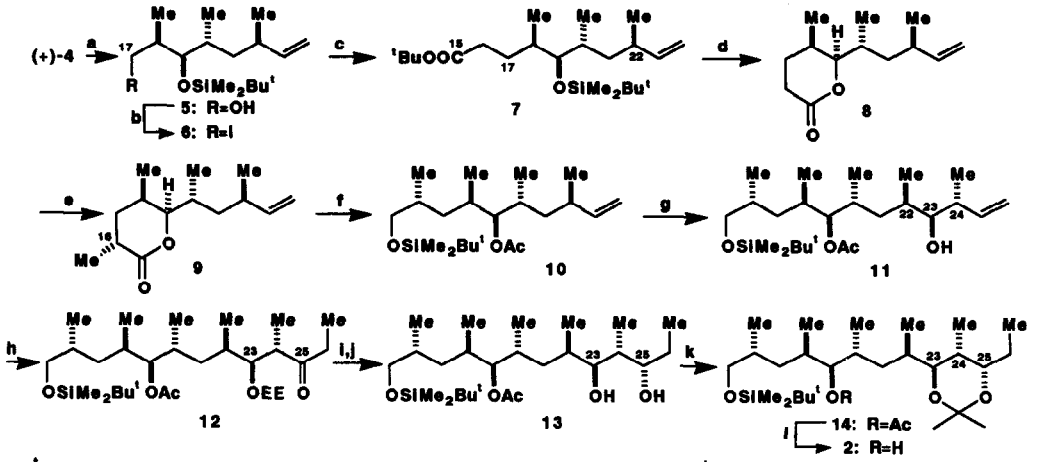
Summary; The C_{15}-C_{27} segment 2 of the aglycone 3 of venturicidins A and B was synthesized and then total synthesis of 3 was accomplished via intramolecular Wittig-Horner reaction of the ester from 2 and the previously synthesized C_1-C_{14} segment 1.

In the preceding paper, the synthesis of the C_1-C_{14} segment 1 corresponding to the bottom half of the aglycone 3 of venturicidins A and B[1] was reported. In this paper, the synthesis of C_{15}-C_{27} segment 2 corresponding to the upper half of 3 and coupling of these two segments leading to 3 are described.



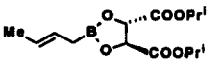
Retrosynthetic analysis of segment 2 suggests that (+)-4 which has already been synthesized in the process of determining the stereostructure of irumamycin should also be used as a key building block.[2]

The trityl derivative (+)-4[2] was converted to alcohol 5 in two steps: 1) protection of secondary alcohol ($^tBuMe_2SiOTf$/2,6-lutidine[3]); 2) detritylation (Et_2AlCl, -23°C[4]); 78% overall yield. Iodide 6 obtained from 5 by mesylation followed by NaI treatment (93% overall yield) was condensed with tert-butyl acetate producing ester 7[5] ($[\alpha]_D^{20}$ +11.3° (c=1.80, $CHCl_3$), 68%), whose CF_3COOH-induced cyclization gave lactone 8 (93%). Methylation (LDA/MeI/HMPA, -78°C)[6] at the C_{16}-position of 8 proceeded with 80:1 selectivity giving 9[7] ($[\alpha]_D^{20}$ +83.6° (c=1.0, $CHCl_3$), 95%), which was transformed into acetate 10 in three steps: 1) reductive opening of lactone ($LiAlH_4$); 2) selective silylation ($^tBuMe_2SiCl$/imidazole); 3) acetylation (Ac_2O/pyridine/DMAP); 93% overall yield. Stereoselective introduction of two chiral centers at the C_{23}- and C_{24}-positions was accomplished using Roush's methodology.[8] Ozonolysis of 10 and the subsequent treatment of the resulting aldehyde with optically active crotylboronate[8] produced 22,23-syn-23,24-anti-11 $[\alpha]_D^{20}$ +23.3° (c=2.05, $CHCl_3$)) in 77% overall yield as a sole product. Conversion of 11 into the ethyl ketone derivative 12 was achieved in four steps: 1)



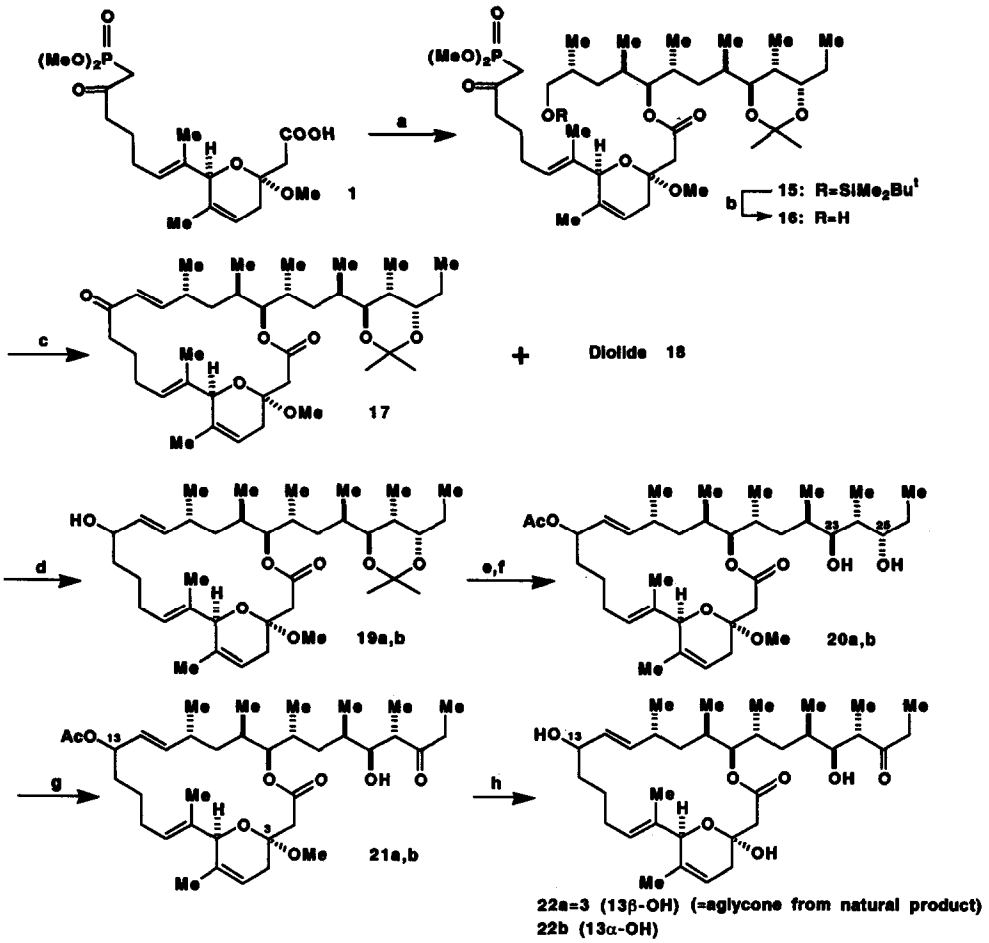
a: 1) ^{t}BuMe$_2$SiOTf/2,6-lutidine 2) Et$_2$AlCl b: 1) MsCl/Et$_3$N 2) NaI c: MeCOOBu^t/LDA d: CF$_3$COOH e: LDA/MeI/HMPA
f: 1) LiAlH$_4$ 2) ^{t}BuMe$_2$SiCl/imidazole 3) Ac$_2$O/pyridine/HMPA g: 1) O$_3$/Me$_2$S 2) chiral crotylboronate h: 1) EVE/PPTS
2) O$_3$/Me$_2$S 3) EtMgBr 4) PDC/Zeolite 3A i: PPTS/MeOH j: Me$_4$NBH(OAc)$_3$ k: (MeO)$_2$CMe$_2$/CSA l: DIBAH

chiral crotylboronate:



protection with ethoxy ethyl group (EVE/PPTS); 2) ozonolysis (O_3/Me_2S); 3) Grignard reaction (EtMgBr); 4) oxidation (PDC/Zeolite 3A); 49% overall yield.

Although 12 involves all of the requisite chiral centers and functionalties, the keto group at the C_{25}-position should be protected before subjecting it to a base-induced macro-ring formation. However, all attempts for direct masking of the keto group failed and thus 12 was, after deprotection of the ethoxy ethyl group (72%), reduced with tetrabutylammonium triacetoxyborohydride[9] and the resulting 23,25-anti-diol 13[10] ($[\alpha]_D^{20}$ +14.4° (c=2.42, $CHCl_3$)) was converted to acetonide 14 (93% yield). The acetonide group thus formed should be hydrolyzed at the final stage of the total synthesis in the presence of the macrolactone ring involving the acid-labile cyclic acetal moiety. Thus, introduction of the anti-diol was designed with the anticipation that the six-membered acetonide derived from it should be more susceptible to acid-induced hydrolysis than the acetonide derived from the syn-diol, since the stereostructure of the former is known to be highly distorted.[11] Reductive deacetylation produced 2 ($[\alpha]_D^{20}$ +32.7° (c=2.14, $CHCl_3$), >99% yield) corresponding to the upper half of 3. Macro-ring formation by combining 2 and the previously synthesized 1 was then undertaken. Initially, ester 15 was formed from alcohol 2 and acid 1 by applying Yamaguchi's method[12] and then the silyl protecting group was removed giving 16 ($[\alpha]_D^{20}$ +6.3° (c=1.43, PhH)) in 68% yield. The primary alcohol 16 was, after PDC oxidation, subjected to the modified intramolecular Wittig-Horner condensation[13] yielding enone 17 ($[\alpha]_D^{20}$ +19.4° (c=0.72, PhH)) along with diolide 18 in 48% and 7% yields, respectively. Reduction of enone 17 with $NaBH_4$-$CeCl_3$[14] gave an epimeric mixture of alcohols, which could be separated to the less polar alcohol 19a and the more polar alcohol 19b in 43% and 55% yields, respectively. After



a: 1) 2,4,6-trichlorobenzoyl chloride/Et_3N 2) 2/DMAP b: n-$Bu_4NF{\cdot}3H_2O$ c: 1) PDC/Zeolite 3A 2) K_2CO_3/18-Crown-6/toluene at r.t. d: $NaBH_4/CeCl_3$ e: Ac_2O/pyridine/DMAP f: PPTS/MeOH g: $RuCl_2(PPh_3)_3/K_2CO_3$ h: 1) K_2CO_3/MeOH 2) AcOH/H_2O (4:1)

acetylation of 19a (82%), hydrolysis of the anti-acetal group was undertaken under mild conditions using PPTS in MeOH. When hydrolysis was stopped before completion, diol 20a was obtained in 38% yield along with the recovered starting material (38% yield). Next step is a regioselective oxidation of two secondary alcohols involved in 20a. In the model reaction using 13, the C_{25}-hydroxyl group was found to be much more susceptible to the reaction with $^tBuMe_2SiCl$/imidazole than the C_{23}-hydroxyl group, which suggested that selective oxidation of the former alcohol could be achieved when the oxidizing reagent was properly selected.

In fact, when 20a was oxidized with $RuCl_2(PPh_3)_3$[15] in the prsence of K_2CO_3, β-hydroxy ketone 21a ($[\alpha]_D^{20}$ +79.6° (c=0.93, PhH)) was produced as a sole product in 44% yield. Finally successive deprotections of C_{13}-acetoxy group (K_2CO_3/MeOH) and the labile C_3-methyl acetal group (AcOH-H_2O (4:1)) provided 22a in overall 20% yield after HPLC

purification. Synthetic compound 22a was found to be identical (400MHz NMR, IR, Mass, mp) with the aglycone 3 derived from natural venturicidin B.[16] In the same way, isomer 19b was converted to compound 22b, whose physical data were not consistent with those of the natural aglycone.

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