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Synthetic studies of viridenomycin. Construction of the cyclopentene carboxylic acid part

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Abstract

A highly functionalized cyclopentene carboxylic acid derivative, as an advanced synthetic intermediate of viridenomycin, was synthesized. The synthesis commenced with the previously reported highly functionalized tetrahydrofuran derivative prepared from D-glucose. The stereochemical confirmation of the present final compound was conducted by comparison with a compound synthesized very recently by the Meyers group.

Keywords: antitumor compounds; polyenes; cyclopentenes; cyclization; regiocontrol.

Viridenomycin (**1**) (Fig. 1) was first isolated from the culture broth of *Streptomyces viridochromogenes* in 1975 as a weakly acidic and lipophilic substance, which showed strong inhibitory activity against *Trichomonas vaginalis* and gram-positive bacteria.[1] In 1991 compound **1** was isolated from the culture broth of *Streptomyces gannmycicus* as an agent for prolongation of the survival periods of mice infected with B16 melanoma. Its gross structure and relative stereochemistry (except the benzylic carbon) were fully elucidated by spectral means.[2,3] The antibiotic **1** is classified into a 24-membered polyene macrolide containing a lactam and an enol ester linkage. Another structural characteristic is a tetrasubstituted β-ketocyclopentane carboxylic acid substructure existing as the enol form. One of the consecutive stereogenic carbons in the five-membered ring is an asymmetric quaternary one. Quite recently, Arrington and Meyers reported the asymmetric synthesis of the cyclopentane part of **1**.[4] We wish to disclose herein our synthesis of the cyclopentene carboxylic acid equivalent of **1**.

The retrosynthesis of **A**, a synthetic equivalent of the cyclopentene carboxylic acid part of viridenomycin with differentiable protecting groups, is summarized in Scheme 1. Our approach features a Dieckmann cyclization of a tetrahydrofuran derivative such as **C** bearing two ester functionalities both as side chains (**C** to **B**). The substrate **C** includes a methoxy group with the correct stereochemistry and

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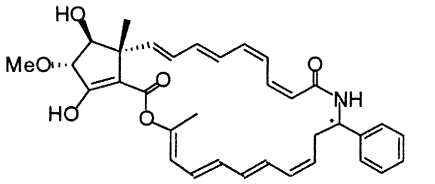
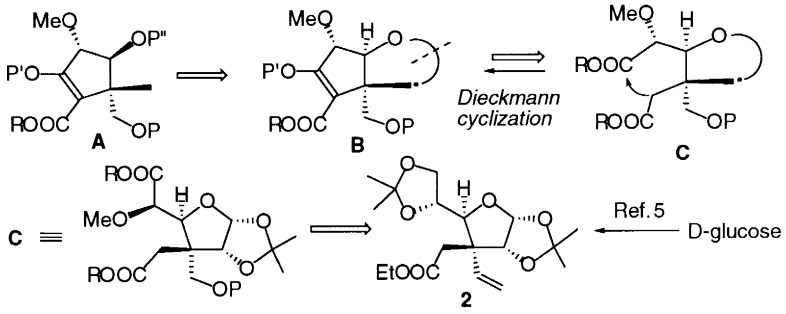


Fig. 1.

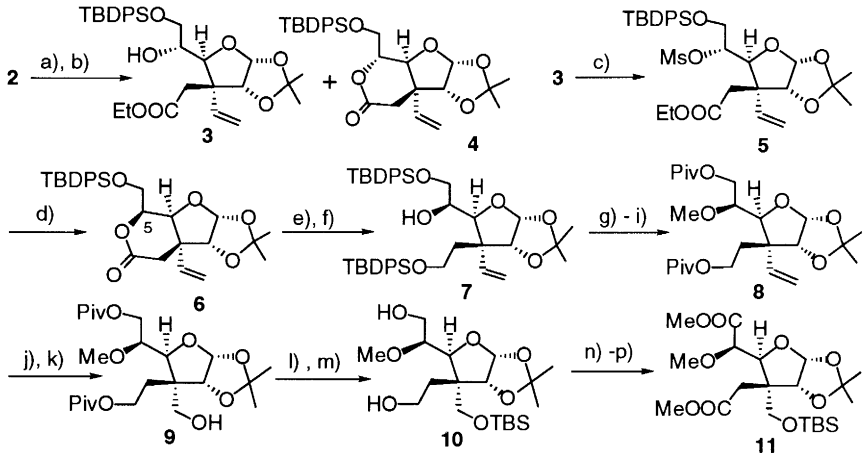
other functionalities for transformation into the cyclopentene carboxylic acid **A**. Cleavage of the tetrahydrofuran ring in the cyclized product **B** and transformation of further functional groups would eventually provide **A**. The synthesis of **C** could be achieved by conventional functional group-transformation of the D-glucose-derived building block **2**. The efficient preparation of **2**[5] and its synthetic utility[6] have been reported by our group.



Scheme 1.

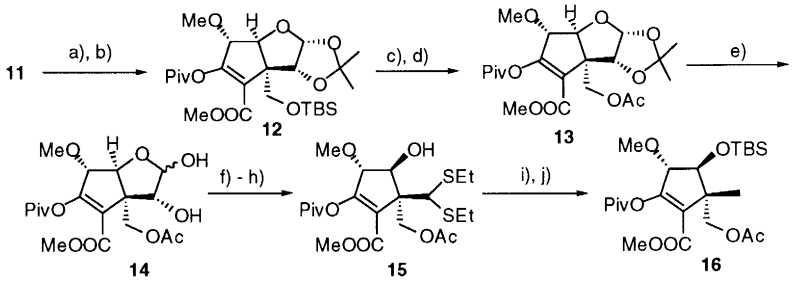
The synthesis of the substrate **11** for the Dieckmann cyclization is shown in Scheme 2. Mild acid hydrolysis of **2** gave an inseparable mixture of a diol and its δ-lactone, which was silylated with *t*-butyldiphenylsilyl chloride (TBDPSCl) to give **3**[7] and **4**. Mesylation of the major product **3** gave **5**. Treatment of **5** with 4 M KOH aqueous solution and acidification of the solution afforded the δ-lactone **6** quantitatively. Spectral comparison of **6** with **4** verified the stereochemical inversion of C-5. This reaction is likely to proceed through the saponification of the ester followed by the attack of the resulting carboxylate to C-5 in an S_N2 fashion. Furthermore, the δ-lactone **4** was converted to **6**.[8] Reduction of the lactone ring in **6** with $NaBH_4$ in *t*-BuOH in the presence of MeOH[9] afforded the diol, in which the primary hydroxyl group was selectively protected as the TBDPS ether providing **7**. Compound **7** was converted to **8** in three steps [*O*-methylation, de-*O*-silylation, then di-*O*-pivaloylation]. Ozonolysis of the vinyl group in **8** followed by $NaBH_4$ reduction gave **9**. The hydroxyl group in **9** was protected as a *t*-butyldimethylsilyl (TBS) ether. The pivaloyl groups in the resulting silyl ether were deprotected to give diol **10**. The hydroxyl groups in **10** were simultaneously oxidized to carboxylic acids in a two-step oxidation.[10,11] The resulting two carboxylic acids were esterified with CH_2N_2 to give the substrate **11**.

The Dieckmann cyclization of **11** was investigated under a variety of basic conditions. We found that excess (2.2 molar equivalents) of potassium hexamethyldisilazide (KHMDS) was the base of choice, which provided the desired cyclopentene carboxylic acid exclusively (Scheme 3).[12] The enol in the cyclization product was protected as the pivaloyl ester providing **12**. An exchange of the silyl ether in **12** to the acetate **13** was required for the advanced step, which was achieved by desilylation and successive acetylation. Acid hydrolysis of the acetal in **13** and glycol cleavage of the resulting hemiacetal **14**, followed by dithioacetalization provided **15** after methanolysis of the intermediary formyl ester. Desulfurization of **15** with Raney nickel and protection of the hydroxyl group provided the TBS ether



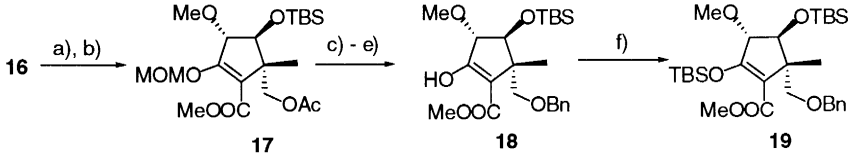
Scheme 2. (a) 60% AcOHaq.; (b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (**3**: 63%, **4**: 27%); (c) MsCl, pyr.; (d) 4 M KOHaq., MeOH then 4 M HClaq.; (e) $NaBH_4$, *t*-BuOH:MeOH (5:1), reflux; (f) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (76% from **3**); (g) NaH, MeI, THF; (h) *n*-Bu_4NF, THF; (i) PivCl, pyr. (80% from **7**); (j) O_3, MeOH, −78°C then Ph_3P; (k) $NaBH_4$, MeOH (87% from **8**); (l) TBSOTf, 2,6-lutidine, CH_2Cl_2; (m) DIBAL-H, CH_2Cl_2, −78°C (98% from **9**); (n) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C then Et_3N; (o) $NaClO_2$, NH_2SO_3Haq., Na_2HPO_4aq., *t*-BuOH; (p) CH_2N_2, Et_2O, CH_2Cl_2, 0°C (68% from **10**)

16.[13] This compound **16** is an enantiopure synthetic equivalent of the cyclopentene carboxylic acid part of viridenomycin.



Scheme 3. (a) KHMDS, THF −78°C; (b) PivCl, pyr., DMAP (68% from **11**); (c) AcOH:H_2O:THF (8:1:1); (d) Ac_2O, pyr. (90% from **12**, 3% recovery of **12**); (e) 60% TFAaq., 0°C (92%); (f) $NaIO_4$, MeOH:H_2O (5:3); (g) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C; (h) Et_3N, MeOH (94% from **14**); (i) Raney Ni T-4, acetone, reflux; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2 (82% from **15**)

Finally, compound **16** was converted to Meyers' product **19**[4] as shown in Scheme 4 for confirmation of our stereochemical assignment. Our synthetic **19**[14] {$[\alpha]^{20}_D$ +25.1 (*c* 0.22, $CHCl_3$)}was identical with Meyers' synthetic {$[\alpha]_D$ +24.4 (*c* 1.05, $CHCl_3$)} by comparison with the ^1H and ^{13}C NMR spectra.



Scheme 4. (a) 14 M NH_3aq., MeOH; (b) MOMCl, *i*Pr_2NEt, $CHCl_3$ (94% from **16**); (c) NaOMe, MeOH; (d) BnOC(=NH)CCl_3, TfOH, CH_2Cl_2, 0°C (formation of a mixture of **18** and its O-MOM enol form); (e) TfOH, CH_2Cl_2 (72% from **17**); (f) TBSCl, 2,6-lutidine, CH_2Cl_2 (80%)

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7. All new compounds were fully characterized by spectroscopic means [^{1}H (270 or 300 MHz) and ^{13}C (67.5 or 75 MHz) NMR, IR] and gave satisfactory HRMS except for some unstable intermediates. Yields refer to homogeneous samples purified by chromatography on silica gel.
8. The conversion of **4** to **6** was carried out as follows: (1) DIBAL-H, CH_2Cl_2, −78°C; (2) $NaBH_4$, MeOH (89% for two steps); (3) PivCl, pyr., DMAP (96%); (4) MsCl, pyr. (88%); (5) DIBAL-H, CH_2Cl_2, −78 °C; (6) Jones' reagent, acetone, 0°C; (7) CH_2N_2, Et_2O, 0°C (95% for three steps); (8) 4 M KOHaq. MeOH then 4 M HClaq.; (9) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (80% for two steps)
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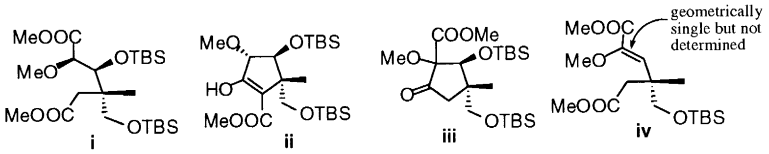
12. We also synthesized an acyclic diester **i** (see below). The Dieckmann cyclization of **i** provided three products, i.e., the desired **ii**, undesired cyclization product **iii**, and a β-eliminated product **iv**. The results were as follows: (1) KHMDS, THF, −78°C (**iii**, 30%; **iv**, 33%); (2) KHMDS, DMF, −78°C (**ii**, 23%; **iv**, 39%); (3) LiHMDS, THF/HMPA, −78°C (**ii**, 41%; **iv**, 26%); (4) *t*-BuOK, DMF, rt (decomposition).



13. Spectral data for **16**: $[\alpha]^{21}_D$ +52.4 (*c* 0.96, $CHCl_3$); ^{1}H NMR (270 MHz) δ 0.06, 0.11 (2s, 3H×2), 0.91 (s, 9H), 1.14 (s, 3H), 1.33 (s, 9H), 2.02 (s, 3H), 3.47 (s, 3H), 3.69 (s, 3H), 3.88, 4.38 (ABq, 1H×2, *J*=11.0 Hz), 4.10 (d, 1H, *J*=6.7 Hz), 4.32 (d, 1H, *J*=6.7 Hz). ^{13}C NMR (75 MHz) δ −5.2, −4.6, 16.9, 18.0, 20.8, 25.7, 26.9, 39.1, 46.6, 51.2, 59.1, 65.3, 76.8, 86.2, 121.9, 155.7, 162.9, 170.8, 174.9; HRMS calcd for $C_{23}H_{40}O_8Si$ (M^+) *m/z*: 472.2492; found: 472.2501.
14. Spectral data for **19**: ^{1}H NMR (300 MHz) δ 0.00, 0.08, 0.167, 0.174 (4s, each 3H), 0.87, 0.95 (2s, 9H×2), 1.00 (s, 3H), 3.22, 3.65 (2d, 1H×2, *J*=8.8 Hz), 3.34 (s, 3H), 3.64 (s, 3H), 4.07 (d, 1H, *J*=6.3 Hz), 4.31 (d, 1H, *J*=6.3Hz), 4.44 (s, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (75 MHz) δ −4.8, −4.5, −4.4, −4.3, 17.2, 18.1, 18.4, 25.5, 25.8, 47.2, 50.5, 55.2, 72.1, 72.9, 73.5, 87.1, 114.6, 127.2, 127.5, 128.1, 138.9, 159.4, 165.0; HRMS calcd for $C_{29}H_{49}O_6Si_2$ (M^+−H) *m/z*: 549.3068; found: 549.3045.