



Pergamon

Tetrahedron Letters 41 (2000) 1771–1774

TETRAHEDRON
LETTERS

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

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Received 24 November 1999; revised 15 December 1999; accepted 17 December 1999

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. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: antitumor compounds; polyenes; cyclopentenones; 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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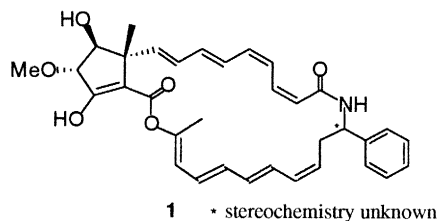
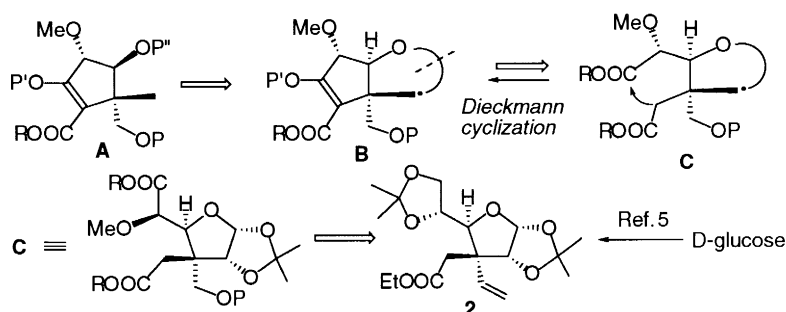


Fig. 1.

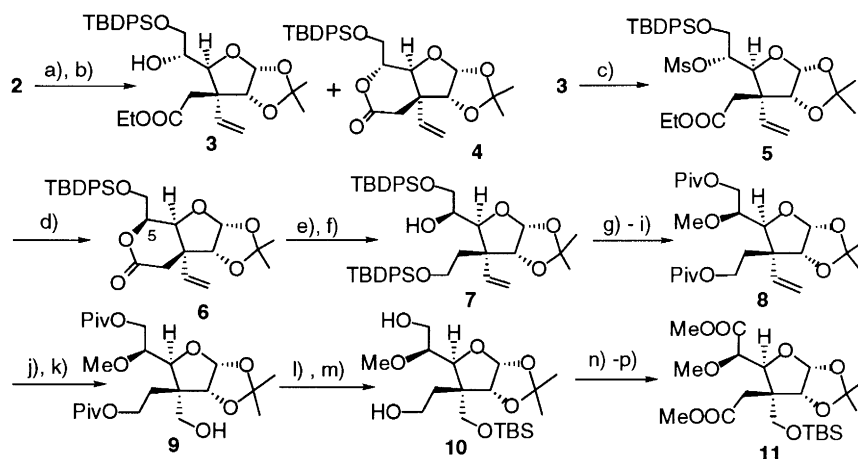
other functionalities for transformation into the cyclopentene carboxylic acid **A**. Cleavage of the tetrahydrofuran ring in the cyclized product **B** and transformation of further functional groups would eventually provide **A**. The synthesis of **C** could be achieved by conventional functional group-transformation of the D-glucose-derived building block **2**. The efficient preparation of **2**⁵ and its synthetic utility⁶ have been reported by our group.



Scheme 1.

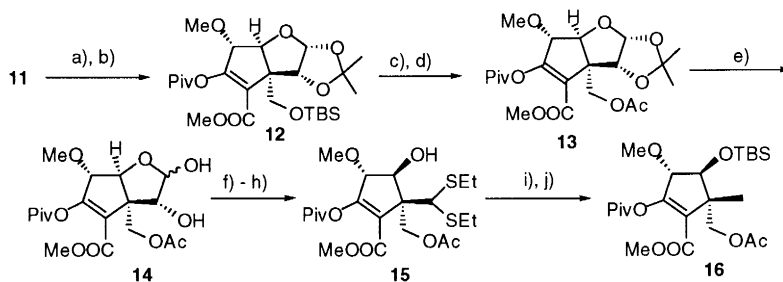
The synthesis of the substrate **11** for the Dieckmann cyclization is shown in Scheme 2. Mild acid hydrolysis of **2** gave an inseparable mixture of a diol and its δ -lactone, which was silylated with *t*-butyldiphenylsilyl chloride (TBDPSCI) to give **3**⁷ and **4**. Mesylation of the major product **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 MeOH⁹ 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



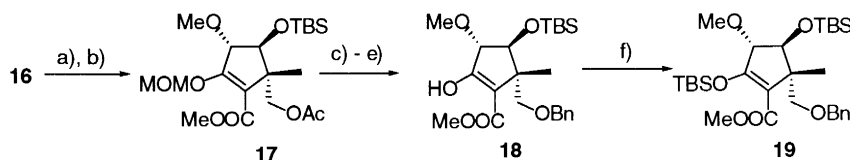
Scheme 2. (a) 60% AcOH_{aq}; (b) TBDPSCl, Et₃N, DMAP, CH₂Cl₂ (**3**: 63%, **4**: 27%); (c) MsCl, pyr.; (d) 4 M KOH_{aq}, MeOH then 4 M HCl_{aq}; (e) NaBH₄, *t*-BuOH:MeOH (5:1), reflux; (f) TBDPSCl, Et₃N, DMAP, CH₂Cl₂ (76% from **3**); (g) NaH, MeI, THF; (h) *n*-Bu₄NF, THF; (i) PivCl, pyr. (80% from **7**); (j) O₃, MeOH, -78°C then Ph₃P; (k) NaBH₄, MeOH (87% from **8**); (l) TBSOTf, 2,6-lutidine, CH₂Cl₂; (m) DIBAL-H, CH₂Cl₂, -78°C (98% from **9**); (n) (COCl)₂, DMSO, CH₂Cl₂, -78°C then Et₃N; (o) NaClO₂, NH₂SO₃H_{aq}, Na₂HPO₄_{aq}, *t*-BuOH; (p) CH₂N₂, Et₂O, CH₂Cl₂, 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:H₂O:THF (8:1:1); (d) Ac₂O, pyr. (90% from **12**, 3% recovery of **12**); (e) 60% TFA_{aq}, 0°C (92%); (f) NaIO₄, MeOH:H₂O (5:3); (g) EtSH, BF₃·Et₂O, CH₂Cl₂, 0°C; (h) Et₃N, MeOH (94% from **14**); (i) Raney Ni T-4, acetone, reflux; (j) TBSOTf, 2,6-lutidine, CH₂Cl₂ (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 {[α]_D²⁰ +25.1 (*c* 0.22, CHCl₃)} was identical with Meyers' synthetic {[α]_D +24.4 (*c* 1.05, CHCl₃)} by comparison with the ¹H and ¹³C NMR spectra.



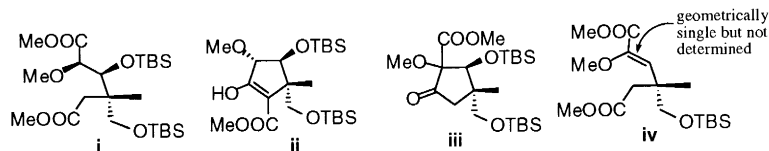
Scheme 4. (a) 14 M NH₃_{aq}, MeOH; (b) MOMCl, *i*Pr₂NEt, CHCl₃ (94% from **16**); (c) NaOMe, MeOH; (d) BnOC(=NH)CCl₃, TfOH, CH₂Cl₂, 0°C (formation of a mixture of **18** and its O-MOM enol form); (e) TfOH, CH₂Cl₂ (72% from **17**); (f) TBSCl, 2,6-lutidine, CH₂Cl₂ (80%)

Acknowledgements

We thank Professor Albert I. Meyers (Colorado State University) for providing us with copies (^1H and ^{13}C NMR) of **19** and experimental details of their work. This work was supported by the CIBA-GEIGY Foundation (Japan) for the Promotion of Science, to whom our thanks are due.

References

- Hasegawa, T.; Kamiya, T.; Henmi, T.; Iwasaki, H.; Yamatodani, S. *J. Antibiot.* **1975**, *28*, 167.
- Nakagawa, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 659.
- Nakagawa, M.; Toda, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1992**, *45*, 1133.
- Arrington, M. P.; Meyers, A. I. *Chem. Commun.* **1999**, 1371.
- Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1201.
- For recent natural product synthesis starting from **2**, see: Ishihara, J.; Nonaka, R.; Terasawa, Y.; Shiraki, R.; Yabu, K.; Kataoka, H.; Ochiai, Y.; Tadano, K. *J. Org. Chem.* **1998**, *63*, 2679.
- All new compounds were fully characterized by spectroscopic means [^1H (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.
- 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 KOH aq. MeOH then 4 M HCl aq.; (9) TBDPSCl, Et_3N , DMAP, CH_2Cl_2 (80% for two steps)
- Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.
- Muncuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
- For NaClO_2 oxidation, see: Kraus, G. A.; Tashner, M. J. *J. Org. Chem.* **1980**, *45*, 1175; Dalcanele, E.; Montanari, F. *ibid.* **1986**, *51*, 567.
- 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).



- Spectral data for **16**: $[\alpha]_D^{21} +52.4$ (c 0.96, CHCl_3); ^1H NMR (270 MHz) δ 0.06, 0.11 (2s, $3\text{H}\times 2$), 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, $1\text{H}\times 2$, $J=11.0$ 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 $\text{C}_{23}\text{H}_{40}\text{O}_8\text{Si}$ (M^+) m/z : 472.2492; found: 472.2501.
- Spectral data for **19**: ^1H NMR (300 MHz) δ 0.00, 0.08, 0.167, 0.174 (4s, each 3H), 0.87, 0.95 (2s, $9\text{H}\times 2$), 1.00 (s, 3H), 3.22, 3.65 (2d, $1\text{H}\times 2$, $J=8.8$ Hz), 3.34 (s, 3H), 3.64 (s, 3H), 4.07 (d, 1H , $J=6.3$ Hz), 4.31 (d, 1H , $J=6.3\text{Hz}$), 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 $\text{C}_{29}\text{H}_{49}\text{O}_6\text{Si}_2$ ($\text{M}^+ - \text{H}$) m/z : 549.3068; found: 549.3045.