Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 5707–5709
Tetrahedron Letters

Asymmetric synthesis of the polyol subunit of the macrolide antibiotic, ossamycin

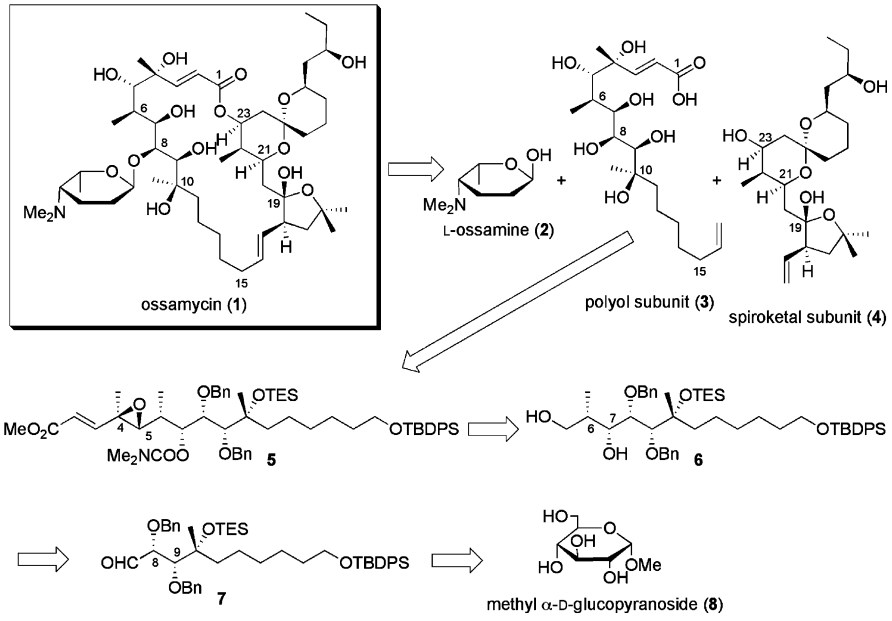
Noriki Kutsumura and Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan

Received 26 May 2005; revised 14 June 2005; accepted 16 June 2005
Available online 1 July 2005

Abstract—An asymmetric synthesis of the C1–C16 polyol subunit of the macrolide antibiotic, ossamycin, has been achieved through stepwise carbon-chain elongation reaction from D-glucose.

Ossamycin **1**, isolated in 1965 from the culture broth of *Streptomyces* sp.,[1] is a member of such macrolide antibiotics, as cytovaricin,[2] oligomycins,[3] A82548A,[4] and rutamycins.[5] This 24-membered macrolide inhibits oxidative phosphorylation by targeting the mitochondrial F_0F_1 ATP synthase, and might be a promising candidate for effective antitumor agents from recent biological examination.[6] We initiated a synthetic study of **1** to understand its chemical feature, and to develop an effective synthetic methodology, which would make it possible to acquire related, more biologically effective substances. We describe herein our synthetic process of the polyol subunit of **1**.



Scheme 1. Retrosynthetic analysis.

Keywords: Ossamycin; Asymmetric synthesis; Macrolide; Antitumor.
* Corresponding author. Tel./fax: +81 4556 61717; e-mail: nisiyama@chem.keio.ac.jp

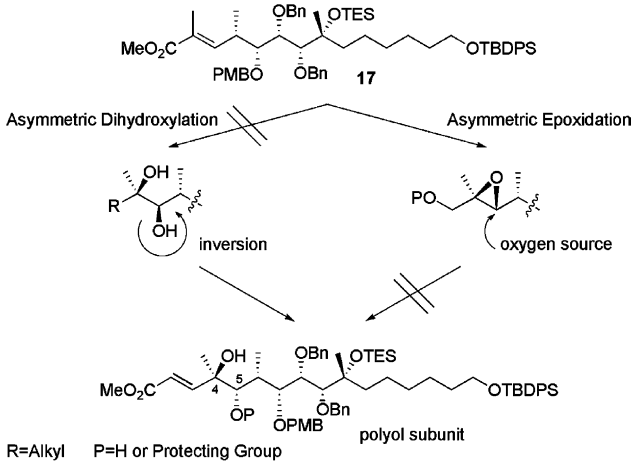
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.079

As shown in Scheme 1, retrosynthetic analysis indicated that the aglycone of ossamycin may be produced by coupling between the polyol **3** and spiroketal subunits **4** via olefination and macrolactonization. The strategy of the asymmetric synthesis of the polyol subunit **3** included stepwise carbon-chain elongation reaction of methyl α-D-glucopyranoside **8**, followed by asymmetric dihydroxylation/epoxydation.

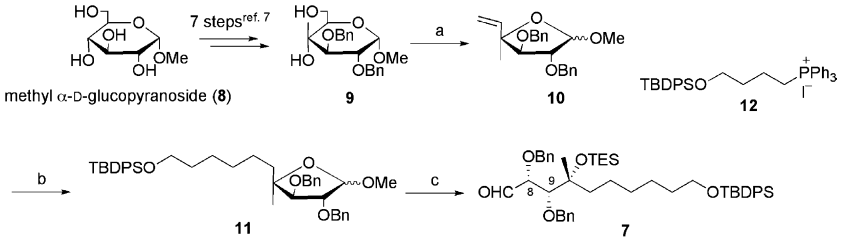
The known branched-chain sugar **9**,[7] readily accessible in seven steps from **8**, was converted into **10** via zinc reduction,[8] and subsequent recyclization (Scheme 2). After carbon-chain elongation of **10** by the Wittig reaction with the phosphonium salt **12**, furanoside **11** was transformed into the acyclic aldehyde **7** in five steps.[9]

Construction of the stereogenic centers at the C6–C7 position was examined in the next stage (Scheme 3). The carbon chain of **7** was elongated by the Wittig reaction, followed by regioselective catalytic OsO_4 dihydroxylation[10] to give **13** in 99% yield (two steps) with good stereoselectivity (a 95:5 ratio was determined by ^1H NMR spectra). After $LiBH_4$ reduction, the triol generated was submitted to cyclic carbonate protection and mesylation to afford **14**. After removal of the cyclic carbonate, the resulting diol was treated under basic conditions to give the epoxy alcohol **15**. Reaction of **15** with $Me_2Cu(CN)Li_2$ effected the predominant introduction of a methyl group at the C2 position, leading to 1,3-diol **6**.[11] To confirm the structure of **6**, this compound was converted in five steps ((i) TrCl, pyr.; (ii) MeI, NaH; (iii) H_2, $Pd(OH)_2$–C; (iv) TsCl, pyr.; (v) Ac_2O, pyr.) to **16**, the NOE experiments of which indicated the configuration of the newly introduced stereochemistry as depicted in Scheme 3. After selective protection of the secondary alcohol of **6**, the remaining primary alcohol was submitted to oxidation, followed by the Wittig reaction to afford **17**.

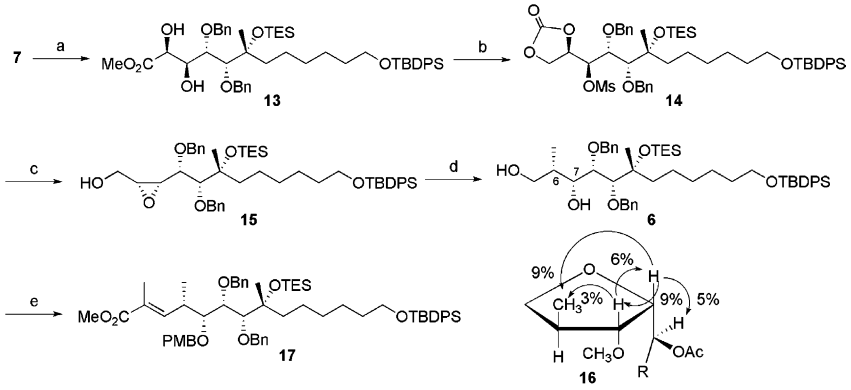
In the next stage, we examined a simultaneous construction of the stereogenic centers at C4 and C5 positions of **17** (Scheme 4). Any efforts to achieve its asymmetric



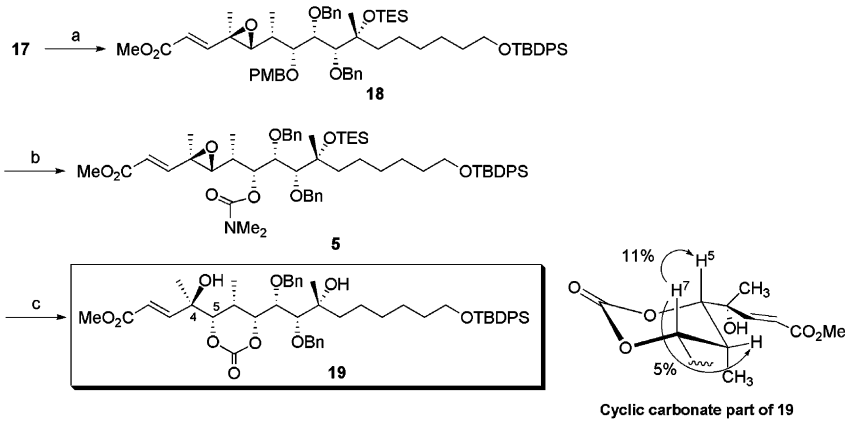
Scheme 4. Asymmetric induction at the C4–C5 position.



Scheme 2. Reagents and conditions: (a) (i) TsCl, pyr.; (ii) NaI/DMF; (iii) Zn powder/EtOH; (iv) Amberlyst 15E/MeOH, 65% in four steps. (b) (i) 9-BBN/THF, then H_2O_2, NaOH/aq; (ii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2; (iii) **12**, *n*BuLi/THF; (iv) H_2, 10% Pd–C/EtOH, 82% in four steps. (c) (i) $BF_3{\cdot}OEt_2$, Ac_2O; (ii) K_2CO_3/MeOH; (iii) $NaBH_4$/MeOH; (iv) TESOTf, 2,6-lutidine/CH_2Cl_2 dichloromethane; (v) $(COCl)_2$, DMSO, then Et_3N/CH_2Cl_2, 90% in five steps.



Scheme 3. Reagents and conditions: (a) (i) $Ph_3P{=}CHCO_2Me$/benzene; (ii) OsO_4, NMO/acetone–H_2O (10:1), 99% in two steps. (b) (i) $LiBH_4$/THF; (ii) $CO(Im)_2$/benzene; (iii) MsCl, DMAP, pyr., 81% in three steps. (c) NaOMe/MeOH, 95%. (d) $Me_2Cu(CN)Li_2/Et_2O$, 87%. (e) (i) *p*-anisaldehyde dimethyl acetal, PPTS/CH_2Cl_2; (ii) DIBAL-H/toluene, 64% in two steps; (iii) Dess–Martin periodinane, $NaHCO_3/CH_2Cl_2$; (iv) $Ph_3P{=}C(Me)CO_2Me$/benzene, 90% in two steps.



Scheme 5. Reagents and conditions: (a) (i) $LiBH_4$/THF; (ii) *m*-CPBA, $NaHCO_3/CH_2Cl_2$, 70% in two steps; (iii) TPAP, NMO/CH_2Cl_2, 76%; (iv) $Ph_3P{=}CHCO_2Me$/benzene, 100%. (b) (i) DDQ/CH_2Cl_2–H_2O (20:1), 86%; (ii) dimetylcarbamyl chloride, NaH/DMF, 65%. (c) $BF_3{\cdot}OEt_2/CH_2Cl_2$, 36%.

induction have been unsuccessful. For instance, a route via asymmetric dihydroxylation provided insufficient results (no reaction by AD mix and a 3:1 mixture in 40% yield by OsO_4–Me_3NO). An alternative route via asymmetric epoxidation was ruled out, because of difficulties in the following epoxide ring opening. As we considered these results could be accounted for by steric hindrance of the PMB group at the C7 position, subsequently its removal was undertaken (Scheme 5). Thus, the carbon-chain elongation of **17** was accomplished by $LiBH_4$ reduction and mCPBA epoxidation,[12] followed by TPAP oxidation and the Wittig olefination, exclusively leading to **18**. The PMB group of **18** was removed with DDQ, followed by dimethyl carbamation to afford **5**. At the final stage, exposure of the dimethyl carbamyl epoxide **5** to $BF_3{\cdot}OEt_2$ at room temperature gave the desired polyol subunit cyclic carbonate **19**,[13] which possessed the same carbon framework (C1–C16) as that of **1**. The newly introduced stereochemistry at C4 and 5 of **19** was determined by the NOE experiments (Scheme 5).

In conclusion, the asymmetric synthesis of the polyol subunit **19** of **1** was accomplished in a stepwise carbon chain construction manner. We believe that this C1–C16 polyol subunit would be a useful synthetic intermediate for the total synthesis of ossamycin.

Acknowledgements

This work was supported by Grant-in-Aid for the 21st Century COE program 'Keio Life Conjugate Chemistry', as well as Scientific Research C from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. (a) Schmitz, H.; Jubinski, S. D.; Hooper, I. R.; Crook, K. E., Jr.; Price, K. E.; Lein, J. *J. Antibiot.* **1965**, *18*, 82–88; (b) Kirst, H. A.; Mynderse, J. S.; Martin, J. W.; Baker, P. J.; Paschal, J. W.; Rios Steiner, J. L.; Lobkovsky, E.; Clardy, J. *J. Antibiot.* **1996**, *49*, 162–167.
2. (a) Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1073–1074; (b) Sakurai, T.; Kihara, T.; Isono, K. *Acta Cryst.* **1983**, *C39*, 295–297; (c) Kihara, T.; Isono, K. *J. Antibiot.* **1983**, *36*, 1263; (d) Kihara, T.; Ubukata, M.; Uzawa, J.; Isono, K. *J. Antibiot.* **1989**, *42*, 919–925.
3. (a) Chamberlin, J. W.; Gorman, M.; Agtarap, A. *Biochem. Biophys. Res. Commun.* **1969**, *34*, 448–453; (b) Prouty, W. F.; Thompson, R. M.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1971**, *44*, 619–627; (c) Von Glehn, M.; Norrestam, R.; Kierkegaard, P.; Maron, L.; Ernster, L. *FEBS Lett.* **1972**, *20*, 267–269; (d) Carter, G. T. *J. Org. Chem.* **1986**, *51*, 4264–4271; (e) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M.; Nishimoto, M. *J. Antibiot.* **1987**, *40*, 1053–1057.
4. Kirst, H. A.; Larsen, S. H.; Paschal, J. W.; Occolowitz, J. L.; Creemer, L. C.; Rios Steiner, J. L.; Lobkovsky, E.; Clardy, J. *J. Antibiot.* **1995**, *48*, 990–996.
5. (a) Thompson, R. Q.; Hoehn, M. M.; Higgins, C. E. *Antimicrob. Agents Chemother.* **1962**, 474–480; (b) Wuthier, V. D.; Keller-Schierlein, W. *Helv. Chim. Acta* **1984**, *67*, 1206–1208.
6. (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. P. *Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14766–14771; (b) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71–80.
7. Sato, K.; Kubo, K.; Hong, N.; Kodama, H.; Yoshimura, J. *J. Bull. Chem. Soc. Jpn.* **1982**, *55*, 938–942.
8. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016.
9. For Swern oxidation of primary silyl ethers selectively, Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161–5164.
10. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255; (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882; (c) Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031–8034.
11. (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4343–4346; (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron Lett.* **1982**, *23*, 3755–3768; (c) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131–4132; (d) Chong, J. M.; Cyr, D. R.; Mar, E. K. *Tetrahedron Lett.* **1987**, *28*, 5009–5012.
12. Maruyama, K.; Ueda, M.; Sasaki, S.; Iwata, Y.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 4517–4520.
13. Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123–2126.