CHEMISTRY LETTERS, pp. 1101-1104, 1992. 

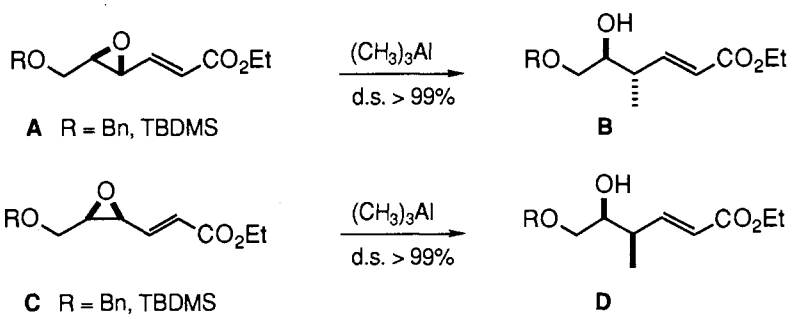
# Synthesis of the Prelog-Djerassi Lactone and Protomycinolide IV Based on the Stereospecific Methylation of γ,δ-Epoxy Acrylates by Trimethylaluminum

Masaaki MIYASHITA,* Masahide HOSHINO,† the late Akira YOSHIKOSHI,†
Katsumi KAWAMINE, Kousei YOSHIHARA, and Hiroshi IRIE
Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852
†The Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Aoba-ku, Sendai 980

The Prelog-Djerassi lactone, a key intermediate for the synthesis of several medicinally important macrolide antibiotics, and protomycinolide IV, a 16-membered macrolide, have been synthesized by employing the recently developed stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum as key steps.

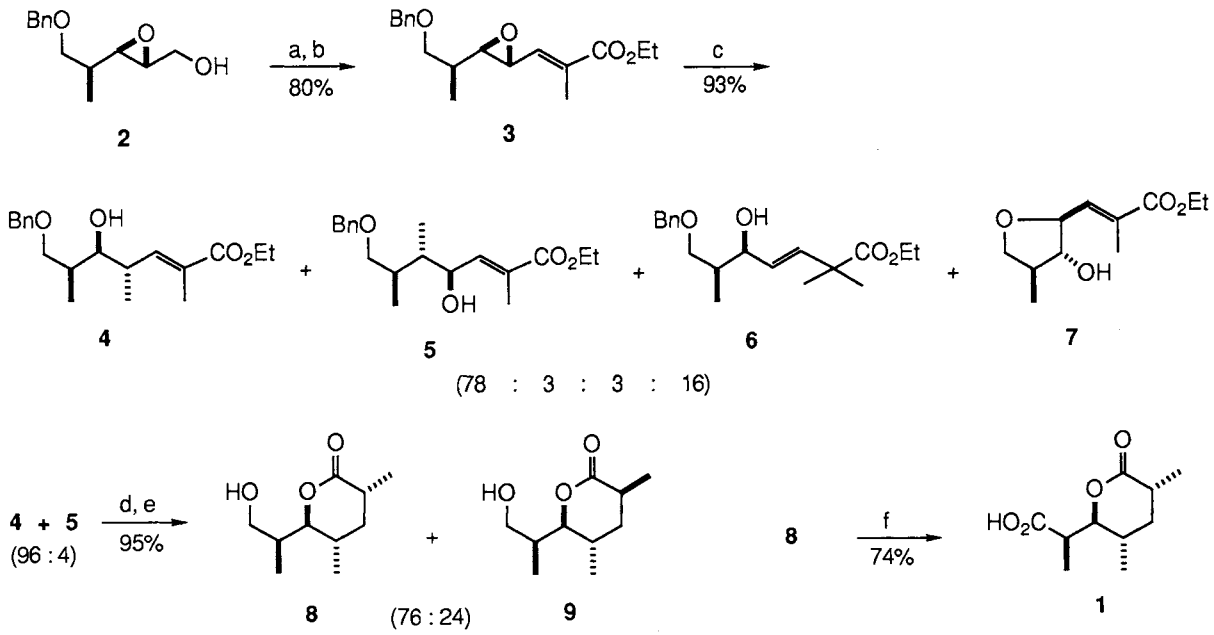
The macrolide antibiotics have been the focus of extensive synthetic investigation for over two decades.[1] The synthetic quest toward these medicinally important natural products has stimulated important methodological developments in acyclic and macrocyclic stereocontrol.[1,2] We recently developed a new methodology for the construction of polypropionate chains which involves the stereospecific methylation of γ,δ–epoxy acrylates by trimethylaluminum ($(CH_3)_3Al$). As shown in Scheme 1, the reaction of γ,δ-(*E*)-epoxy acrylates (**A**) with $(CH_3)_3Al$ gives the anti compounds (**B**), while the reaction of the analogous (*Z*)-epoxy acrylates (**C**) produces the syn compounds (**D**), each with diastereoselectivity greater than 99%.[3] As a program on the synthesis of the polypropionate-derived antibiotics based on the above methodology we report here a stereocontrolled synthesis of the Prelog-Djerassi lactone, a degradation product of methymycin[4] and a crucial intermediates for the synthesis of several macrolide antibiotics,[1] and a formal synthesis of protomycinolide IV, a 16-membered macrolide isolated from the culture of *Micromonospora griseorubida* sp. nov.[5]

Synthesis of the Prelog-Djerassi lactone (**1**) was started from the known optically active epoxy alcohol (**2**)[6] (Scheme 2). Swern oxidation of **2** followed by the Wittig reaction of the resulting aldehyde with (carbethoxyethylidene)triphenylphosphorane in THF afforded a 96 : 4 mixture of γ,δ-epoxy-α-methyl-(*E*)-




Scheme 1.

acrylate (**3**) and its *Z* isomer in 83% yield. The epoxy ester (**3**), isolated in pure form by HPLC (GL Sciences Inertsil PREP-SIL column, hexane-AcOEt = 8 : 1), was subjected to the crucial methylation reaction with $(CH_3)_3Al$. Contrary to our expectation, however, addition of $(CH_3)_3Al$ (10 equiv.) into a mixture of **3** and water (6 equiv.) in 1,2-dichloroethane at -30 °C [3] resulted in the formation of a mixture of the desired compound **4**, its regioisomer **5**,[7] an $S_N2'$ substitution product **6**, and an intramolecular cyclization product **7**[7] in a ratio of 54:11:2:33 in 88% combined yield.[8] Eventually, the ratio and yield of the products were improved up to 78:3:3:16 and 93 %, respectively, by employing the inverse addition that a solution of the substrate (**3**) in dichloromethane was added dropwise to a mixture of $(CH_3)_3Al$ (10 equiv.) and water (6 equiv.) in dichloromethane at -45 °C. Although the desired compound (**4**) was thus obtained with high diastereoselectivity toward the regio isomer (**5**) (96 : 4), formation of by-products such as **6** and **7** was inevitable. These results different from the previous ones (Scheme 1) are presumably due to the electron-donating character of an α-methyl substituent of the substrate (**3**). The resulting 96 : 4 mixture of the hydroxy esters (**4**) and (**5**)[8] was subjected to the hydroxyl-directed hydrogenation employing (bicyclo [2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium (I) tetrafluoroborate) ([Rh(NBD)(DIPHOS-4)]$BF_4$) as catalyst according to the Evans' protocol[9] to afford a mixture of two saturated lactones. Subsequent removal of the benzyl group of the lactones by hydrogenolysis over Raney nickel (W-2) in ethanol yielded a mixture of hydroxy lactones **8** and **9** in a ratio of 76 : 24 in 95% overall yield. These lactones were separable into each pure compound by HPLC (GL Sciences Inertsil PREP-SIL column, hexane-AcOEt = 2 : 5).[10] Finally Jones' oxidation of the major hydroxy lactone (**8**) furnished the Prelog-Djerassi lactone (**1**) in 74% yield. All the data of the synthetic

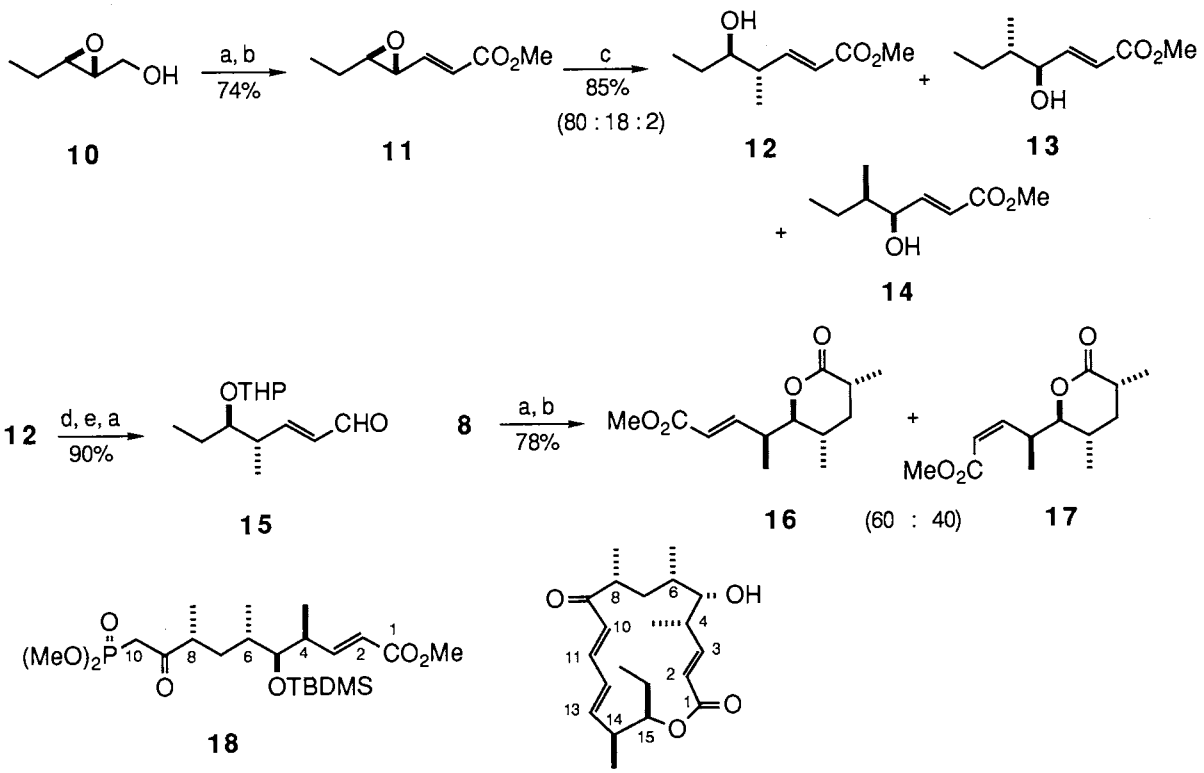



Reagents: a. $(COCl)_2$, DMSO, $CH_2Cl_2$, -60 °C, then $Et_3N$. b. $Ph_3P{=}C(CH_3)CO_2Et$, THF. c. $Me_3Al$ (10 equiv.), $H_2O$ (6 equiv.), $CH_2Cl_2$, -45 °C. d. $H_2$, [Rh(NBD)(DIPHOS-4)]$BF_4$, $CH_2Cl_2$, 100 atm. e. $H_2$, Raney-Ni (W-2), EtOH, 1 atm. f. $CrO_3$, aq. $H_2SO_4$, $CH_3COCH_3$, 0 °C.

Scheme 2.

compound (mp 122-124 °C; $[\alpha]_D$ +42.6° (*c* 0.4, $CHCl_3$)) were identical with those of the reported values.[11] The overall yield of the Prelog-Djerassi lactone (**1**) from **2** was 31% yield for the six steps.

Protomycinolide IV, a 16-membered macrolide, has attracted much attention from organic chemists as the plausible biogenetic precursor of the macrolide antibiotics of the mycinamicin family which have the pronounced activity against the Gram-positive bacteria,[5] and considerable efforts have been made for the synthesis of this compound.[12] We have accomplished a formal total synthesis of this macrolide by employing the hydroxy lactone (**8**) as a key intermediate (Scheme 3). According to the synthetic strategy of Yamaguchi et al.,[12a] the target molecule was divided into two half segments, $C_1$ - $C_{10}$ and $C_{11}$ - $C_{15}$. The $C_{11}$- $C_{15}$ segment was easily synthesized by the previously described $(CH_3)_3Al$ method.[3] Thus the chiral (*E*)-epoxy acrylate (**11**), routinely prepared from epoxy alcohol (**10**)[12a] by Swern oxidation followed by Horner-Emmons reaction, was treated with $(CH_3)_3Al$ (10 equiv.) in 1,2-dichloroethane in the presence of water (6 equiv.) at -15 to -10 °C for 6 h to give an 80 : 18 : 2 mixture of **12**, **13**,[7] and **14**[7] in 85% combined yield (Scheme 3).[3] The major product (**12**) ($[\alpha]_D$ -7.8 ° (*c* 0.99, MeOH)) was cleanly separated from the mixture of **13** and **14** by HPLC (GL Sciences Inertsil PREP-SIL column, hexane-AcOEt = 2 : 1), whose data were identical with those of the authentic sample ($[\alpha]_D$ -8.1 ° (*c* 0.94, MeOH)) prepared by Takano and his co-workers in the synthesis of




Reagents: a. $(COCl)_2$, DMSO, $CH_2Cl_2$, -60 °C, then $Et_3N$. b. $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, -78 °C. c. $Me_3Al$ (10 equiv.), $H_2O$ (6 equiv.), $ClCH_2CH_2Cl$, -15 to -10 °C. d. DHP, PPTS, $CH_2Cl_2$. e. DIBAL-H, $C_6H_5CH_3$, -78 °C.

Scheme 3.

protomycinolide IV.[12c] The hydroxy ester (**12**) thus obtained was converted into the C11-C15 segment (**15**) by the following sequence of reactions: 1) Protection of the hydroxyl group with dihydropyran; 2) DIBAL-H reduction of the ester; 3) Swern oxidation. On the other hand, the another $C_1$-$C_{10}$ segment was assembled from the hydroxy lactone (**8**) as follows. Swern oxidation of **8** followed by the Horner-Emmons reaction with trimethylphosphonoacetate / NaH in THF afforded a 3 : 2 mixture of the (*E*)-olefinic lactone (**16**) and its *Z*-isomer (**17**) in 78% yield. These lactones were easily separated by silica gel thin layer chromatography (hexane - AcOEt = 4 : 1), of which the major crystalline compound (**16**) (mp 76-77 °C, $[\alpha]_D$ +73.5 ° (*c* 0.57, MeOH)) was identical with the authentic sample (mp 78-79 °C), synthesized by Yamaguchi et al., [12a] in all respects. Since preparation of the keto phosphonate (**18**), i.e., the $C_1$-$C_{10}$ segment, from the olefinic lactone (**16**) and the coupling reaction of **18** with the aldehyde (**15**) leading to protomycinolide IV have been achieved by Yamaguchi,[12a] our synthesis of the aldehyde (**15**) and the lactone (**16**) demonstrates a total synthesis of protomycinolide IV in formal sence. Further extensions of the present methodology to the synthesis of complex polypropionates are underway in our laboratory.

We thank Professor K. Ogasawara (Tohoku University) for providing us with the $^1$H NMR spectra of the authentic sample. This work was generously supported by Grants-in-Aid for Scientific Research Nos. 01540446 and 02953015.

References

1) R. K. Boeckman and S. W. Goldstein, "The Total Synthesis of Macrocyclic Lactones," in "The Total Synthesis of Natural Products," ed by J. ApSimon, John Weily and Sons, New York (1988), Vol. 8, pp. 1-140.
2) D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, **13**, 1 (1982); T. Mukaiyama, *Org. React.*, **28**, 203 (1982); C. H. Heathcock, "Asymmetric Syntheses," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3; S. Masamune, W. Choy, J. S. Peterson, and L. R. Sila, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985).
3) M. Miyashita, M. Hoshino, and A. Yoshikoshi, *J. Org. Chem.*, **56**, 6483 (1991).
4) C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, **78**, 6390 (1956).
5) M. Hayashi, M. Ohno, and S. Satoi, *J. Chem. Soc., Chem. Commun.*, **1980**, 119. M. Hayashi, H.Ohara, M. Ohno, H. Sakakibara, S. Satoi, K. Harada, and M. Suzuki, *J. Antibiot.*, **34**, 1075 (1981). M. Hayashi, K. Kinoshita, S. Satoi, and K. Nakatsu, *ibid.*, **35**, 1243 (1982).
6) H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).
7) The stereostructure of this compound has been assigned tentatively.
8) Although the $S_N2'$ substitution product (**6**) and the cyclization product (**7**) were separated from the mixture of **4** and **5** in pure form by preparative thin layer chromatography (hexane-AcOEt = 3 : 1) and HPLC (GL Sciences Inertsil PREP-SIL , hexane-AcOEt = 4 : 1), respectively, the mixture of **4** and **5** could not be separated.
9) D. A. Evans, M. M. Morrissey, and R. L. Dow, *Tetrahedron Lett.*, **26**, 6005 (1985).
10) Although the minor product(s) derived from **5** was not investigated carefully, they were probably removed at this stage.
11) R. E. Ireland and J. P. Daub, *J. Org. Chem.*, **46**, 479 (1981); M. Isobe, Y. Ichikawa, and T. Goto, *Tetrahedron Lett.*, **22**, 4287 (1981).
12) a) M. Honda, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 3857 (1984); b) K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 5221 (1986); c) S. Takano, Y. Sekiguchi, Y. Shimazaki, and K. Ogasawara, *Tetrahedron Lett.*, **30**, 4001 (1989).

(Received March 30, 1992)