

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

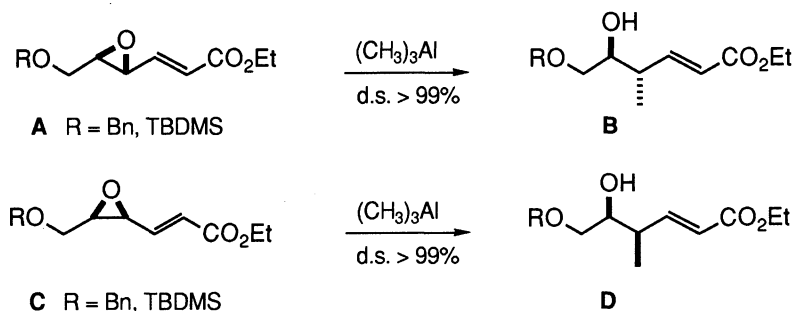
Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852

[†]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.

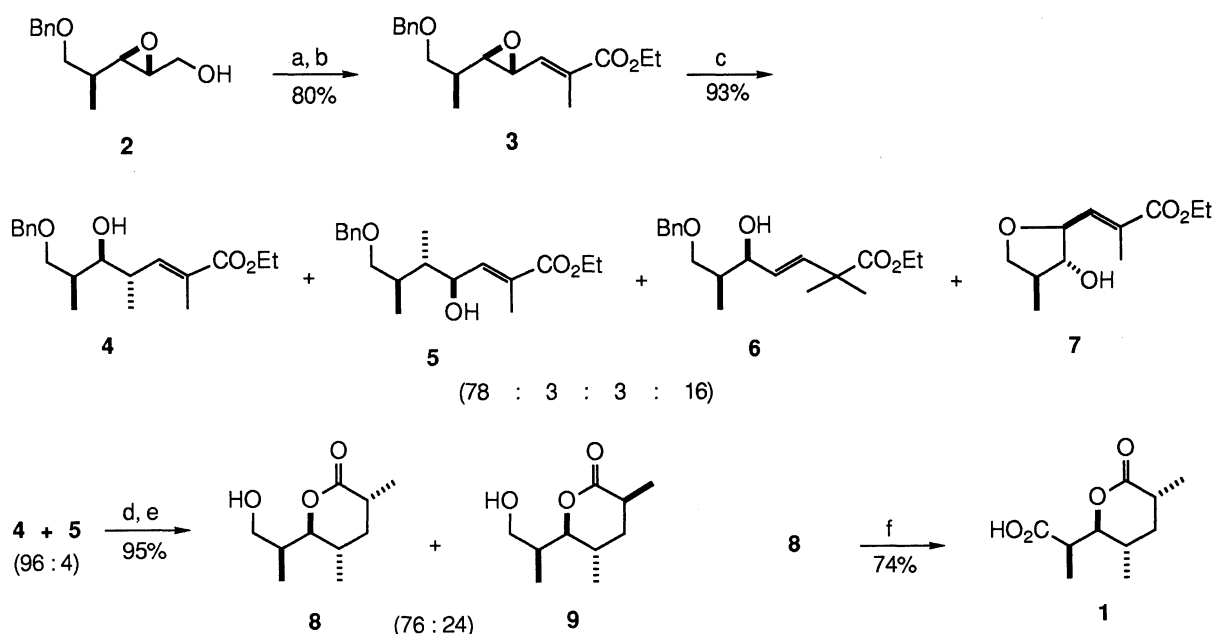
The macrolide antibiotics have been the focus of extensive synthetic investigation for over two decades.¹⁾ The synthetic quest toward these medicinally important natural products has stimulated important methodological developments in acyclic and macrocyclic stereocontrol.^{1,2)} We recently developed a new methodology for the construction of polypropionate chains which involves the stereospecific methylation of γ,δ -epoxy acrylates by trimethylaluminum ($(\text{CH}_3)_3\text{Al}$). As shown in Scheme 1, the reaction of γ,δ -(*E*)-epoxy acrylates (**A**) with $(\text{CH}_3)_3\text{Al}$ 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 methymycin⁴⁾ 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 $(\text{CH}_3)_3\text{Al}$. Contrary to our expectation, however, addition of $(\text{CH}_3)_3\text{Al}$ (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 $\text{S}_{\text{N}}2'$ 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 $(\text{CH}_3)_3\text{Al}$ (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 ($[\text{Rh}(\text{NBD})(\text{DIPHOS-4})]\text{BF}_4$) as catalyst according to the Evans' protocol⁹⁾ 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

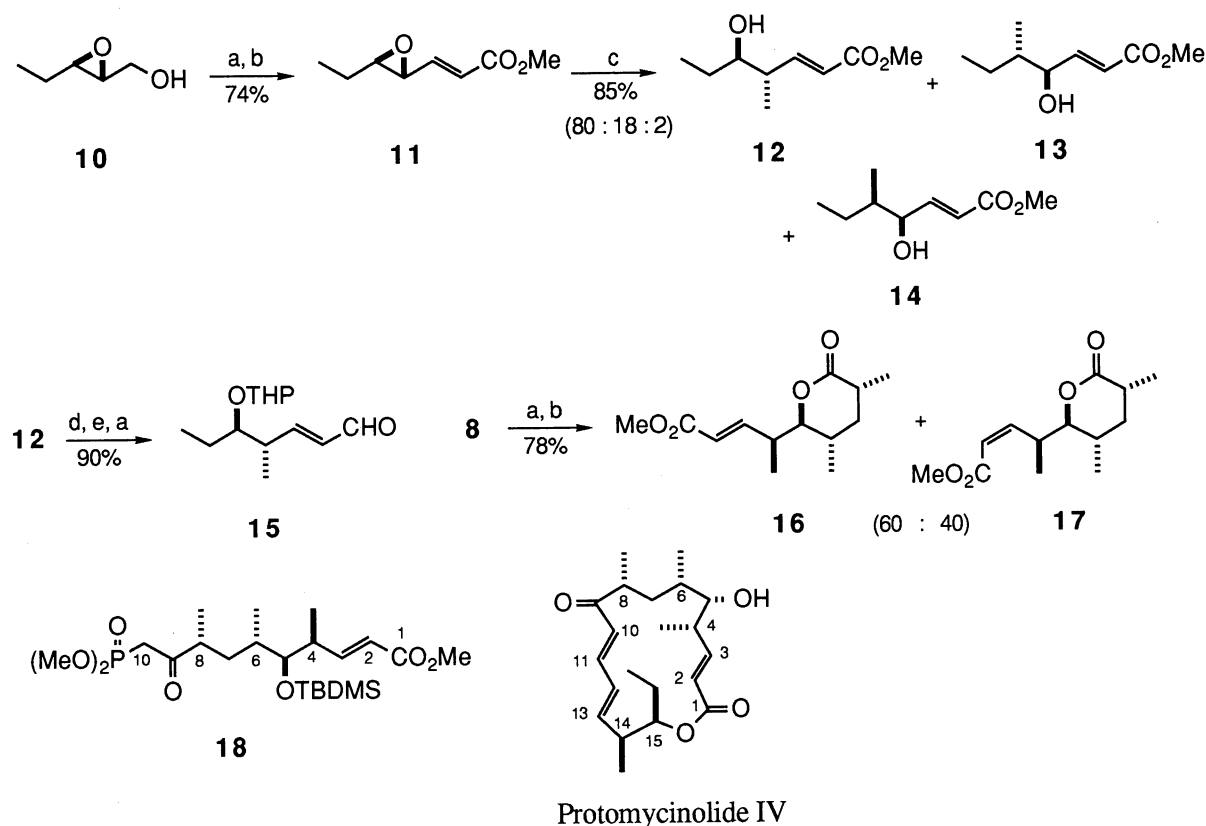


Reagents: a. $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -60°C , then Et_3N . b. $\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{CO}_2\text{Et}$, THF. c. Me_3Al (10 equiv.), H_2O (6 equiv.), CH_2Cl_2 , -45°C . d. H_2 , $[\text{Rh}(\text{NBD})(\text{DIPHOS-4})]\text{BF}_4$, CH_2Cl_2 , 100 atm. e. H_2 , Raney-Ni (W-2), EtOH, 1 atm. f. CrO_3 , aq. H_2SO_4 , CH_3COCH_3 , 0°C .

Scheme 2.

compound (mp 122-124 °C; $[\alpha]_D +42.6^\circ$ (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, $\text{C}_1 - \text{C}_{10}$ and $\text{C}_{11} - \text{C}_{15}$. The $\text{C}_{11} - \text{C}_{15}$ segment was easily synthesized by the previously described $(\text{CH}_3)_3\text{Al}$ 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 $(\text{CH}_3)_3\text{Al}$ (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**) ($[\alpha]_D -7.8^\circ$ (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 ($[\alpha]_D -8.1^\circ$ (c 0.94, MeOH)) prepared by Takano and his co-workers in the synthesis of



Reagents: a. $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -60 °C, then Et_3N . b. $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, NaH, THF, -78 °C. c. Me_3Al (10 equiv.), H_2O (6 equiv.), $\text{ClCH}_2\text{CH}_2\text{Cl}$, -15 to -10 °C. d. DHP, PPTS, CH_2Cl_2 . e. DIBAL-H, $\text{C}_6\text{H}_5\text{CH}_3$, -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 C₁-C₁₀ 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, $[\alpha]_D^{25} +73.5^\circ$ (*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 C₁-C₁₀ 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 sense. Further extensions of the present methodology to the synthesis of complex polypropionates are underway in our laboratory.

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