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STEREOSELECTIVE SYNTHESIS OF C(1)-C(9) AND C(11)-C(17) FRAGMENTS OF PROTOMYCINOLIDE IV BASED ON ASYMMETRIC PINACOL-TYPE REARRANGEMENT

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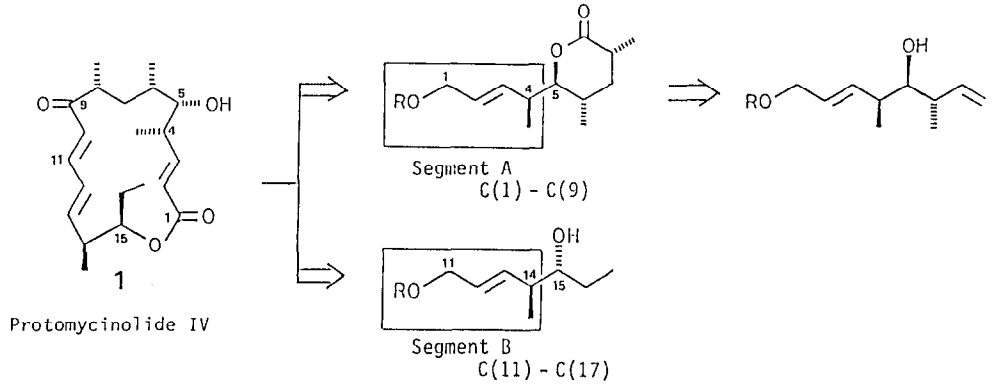
Summary: *Two chiral intermediates, C(1)-C(9) and C(11)-C(17) portions of protomycinolide IV, were synthesized both from (S)-ethyl lactate via asymmetric pinacol-type rearrangement followed by diastereoselective reactions on α-methyl-β,γ-unsaturated carbonyl compounds.*

Protomycinolide IV (1) is a new 16-membered macrolide of the mycinamicin family, isolated from the culture of *Micromonospora griseorubida* sp. nov. by Hayashi *et al.*[1] Retrosynthetic analysis revealed that the two segments (A: C(1)-C(9), B: C(11)-C(17)) are the reasonable precursors to 1. Recently, Yamaguchi *et al.* reported its first total synthesis by way of the related intermediates, each of which was obtained *via* the Sharpless-Katsuki asymmetric epoxidation reaction.[2]

As shown below, these segments possess the same partial structure in common, which could be easily accessible from (S)-ethyl lactate *via* the asymmetric 1,2-rearrangement of the C-3 unit, 3-alkoxy-1-propenyl group.[3] The other chiral centers could be induced by the stereo-regulations on α-methyl-β,γ-unsaturated carbonyl compounds as reported earlier.[4] In this communication, we wish to describe a short and stereoselective approach to both of the segments based on the organoaluminum-promoted asymmetric pinacol-type rearrangement.



1
Protomycinolide IV

Segment A
C(1) - C(9)

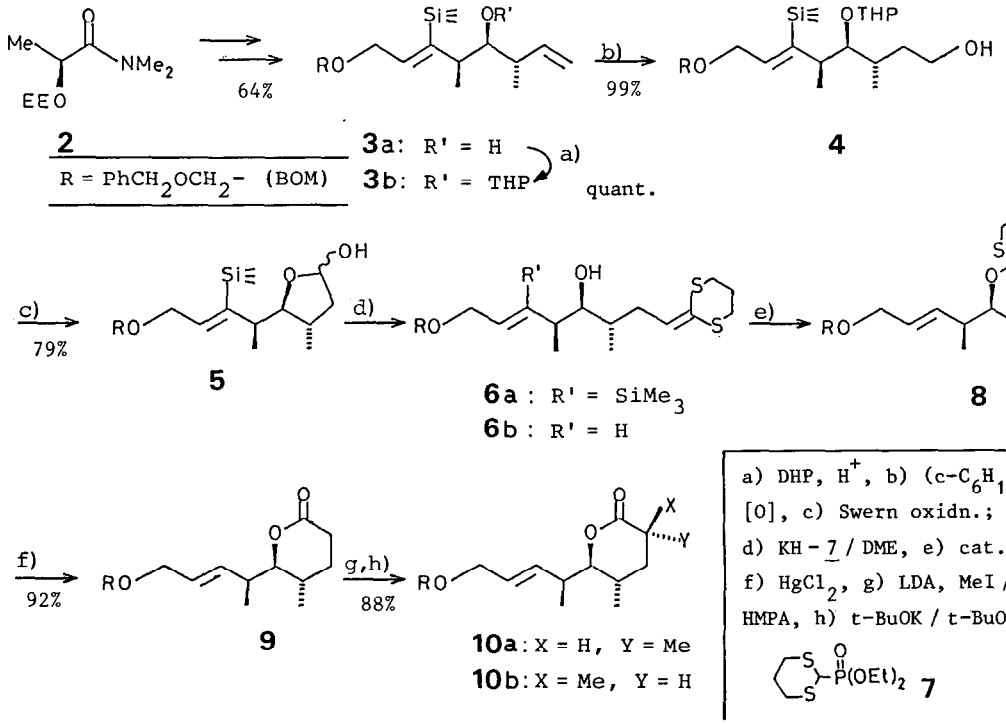
Segment B
C(11) - C(17)

Synthesis of both of the segments started from the lactamide derivative 2.[3]

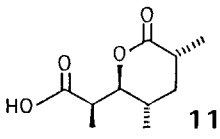
Segment A (C(1)-C(9)): Stereo-defined bis-homoallylic alcohol 3a, easily available from 2 *via* the reductive pinacol-type rearrangement[3b] and the Cr-mediated stereoselective crotylation,[4b,5] was first protected as THP-ether 3b. Regioselective hydroboration of 3b with (cyclo-C_6H_{11})$_2$BH followed by oxidative workup afforded the alcohol 4. The Swern oxidation[6] of 4 followed by the acid treatment gave the lactol 5 in 78% overall yield from 3a.

One-carbon homologation of 5 was next investigated. Among the reagents screened, the PO-activated 1,3-dithiane derivative 7 was the reagent of choice to give the ketene dithioacetal 6a.[7] In this transformation, a marked effect by the counter cation was noted: The yield was only modest using the Li^+ salt of 7, while the corresponding Na^+ reagent gave 6a in 91% yield. Most notably, use of the K^+ salt of 7 (KH - 7 / DME, 0°C → rt) led to the desilylated product 6b by the spontaneous Brook-type rearrangement of the intermediary potassium alkoxide of 6a.

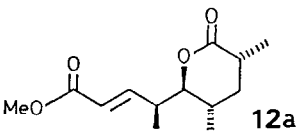
Cyclization to the spiroketal 8 was effected by simply dissolving 6b in chloroform.[8] Treatment of 8 with $HgCl_2$ in buffered acetonitrile gave the lactone 9 in 92% yield, and subsequent methylation afforded 10 as an almost 1 / 1 mixture of epimers. Base-catalyzed equilibration (t-BuOK / t-BuOH, 25°C) improved the ratio up to 10a / 10b = 6 / 1.[9] These isomers were separated with a medium-pressure chromatography on silica gel (C_6H_6-Et_2O = 19 / 1).[10,11]



For the structure elucidation, the lactones 10a and 10b were ozonized (O_3, -78°C; H_2O_2), where the Prelog-Djerassi lactone (11) was derived from 10a.[12] The lactone 10a was also easily converted to the α,β-unsaturated ester 12a, one of the key intermediates in the Yamaguchi's synthesis of 1.[2] The conversion of 10a to 12a involved (i) deprotection ($BF_3 \cdot OEt_2$ - PhSH / CH_2Cl_2, 0°C) and (ii) allylic oxidation (MnO_2 / hexane; MnO_2 - NaCN / MeOH),[13] where further structure confirmation was attained.[14] Thus, the lactone 10a is the vinylog (two-carbon homolog) of the Prelog-Djerassi lactone, and hence, is a versatile intermediate in the synthesis of various macrolides including 1.

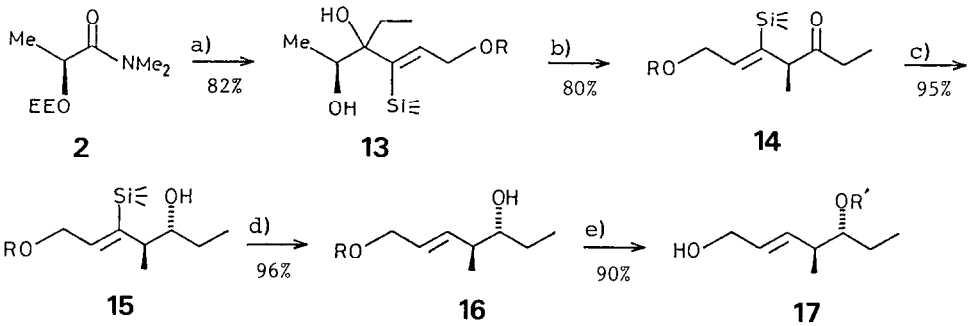


11

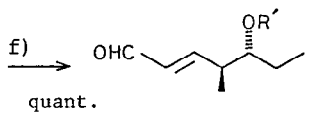


12a

Segment B (C(11)-C(17)): Synthesis of this part was straightforward *via* the pinacol-type rearrangement[3a] and threo-selective reduction.[4a] Sequential introduction of Et and the C-3 unit followed by deprotection gave diol 13 in 82 % yield. Regioselective sulfonylation followed by the Et_3Al-promoted 1,2-rearrangement of the C-3 unit gave the chiral ketone 14 in 80% yield. Reduction of 14 with L-Selectride resulted in the exclusive formation of threo-15,[15] which was desilylated to give 16, corresponding to Segment B.[16] The alcohol 16 was further converted to the aldehyde 18: After protection of the secondary



2 13 14 15 16 17



18

R = $PhCH_2OCH_2$-, R' = $PhOCH_2CO$-

a) EtMgBr; (E)-$ROCH_2CH{=}C(SiMe_3)Br$ - BuLi, -100°C; H^+, b) MsCl - Et_3N; Et_3Al / CH_2Cl_2, -78°C, c) L-Selectride / THF, -78°C, d) NaH / HMPA, e) R'Cl / pyr; $BF_3 \cdot OEt_2$ - PhSH, 0°C, f) Swern oxidn.

hydroxyl, the BOM protecting group was removed (*vide supra*) to afford the allylic alcohol 17, which in turn was oxidized to 18 in quantitative yield.

In this manner, short and stereoselective approach was realized to the two chiral intermediates in the synthesis of protomycinolide IV, the segments A (10a) and B (16), whose structural similarity permitted the convergence using the common chiral source, (S)-ethyl lactate, and the common migrating C-3 unit.

Intensive study is now under way on the total synthesis of protomycinolide IV from these segments and the results will be reported shortly.

Acknowledgments: The authors are grateful to Professor Masaru Yamaguchi, Kyushu University, for kindly providing us with the valuable information on the intermediates. Thanks are also due to Associate Professor Kazuhiko Saigo and Dr. Noriyuki Yonezawa, the University of Tokyo, and to Dr. Shuichi Mitamura, Nippon Steel Corp., for the measurement of ^{1}H and ^{13}C NMR spectra.

References and Notes

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b) K. Suzuki, E. Katayama, K. Tomooka, T. Matsumoto, and G. Tsuchihashi, the preceeding paper in this issue.

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8) E. J. Corey and D. J. Beames, J. Am. Chem. Soc., 95, 5829 (1973).

9) Ratio of 10a / 10b was highly dependent on the conditions of the exposure to the base, ranging from 3.5 / 1 to 6 / 1. Further optimization of the ratio and the generality of the process is currently investigated, which will be disclosed in due course.

10) Attempted kinetic protonation by Grieco's procedure gave almost 1 / 1 recovery of 10's; P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, J. Am. Chem. Soc., 101, 4749 (1979). Similar outcome has been documented; D. J. Morgans, Jr., Tetrahedron Lett., 22, 3721 (1981); W. C. Still and K. R. Shaw, ibid., 22, 3725 (1981).

11) Physical data of the isomeric lactones 10a and 10b are as follows;
10a: $[\alpha]_D^{27}$ +20° (c 0.94, $CHCl_3$). IR (neat): 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.99 (d, 3H, J=6.4 Hz), 1.04 (d, 3H, J=6.8 Hz), 1.27 (d, 3H, J=7.1 Hz), 1.4-2.1 (m, 3H), 2.1-2.7 (m,2H), 3.96 (dd, 1H, J_1=9.8 HZ, J_2=2.4 Hz), 4.09 (d, 2H, J=5.4 Hz), 4.62 (s, 2H), 4.78 (s, 2H), 5.62 (dt, 1H, J_1=15.5 Hz, J_2=5.4 Hz), 5.94 (dd, 1H, J_1=15.5 Hz, J_2= 7.1 Hz), 7.34 (s, 5H). ^{13}C NMR ($CDCl_3$): δ = 12.7, 17.2, 17.4, 30.9, 36.2, 37.4, 38.4, 68.1, 69.3, 89.7, 93.9, 126.4, 127.6, 127.9, 128.4, 136.6, 137.9, 174.4.
10b: $[\alpha]_D^{27}$ +57° (c 0.96, $CHCl_3$). IR (neat): 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.00 (d, 3H, J=6.3 Hz), 1.07 (d, 3H, J=6.4 Hz), 1.20 (d, 3H, J=6.8 Hz), 1.5-2.2 (m, 3H), 2.3-2.8 (m, 2H), 3.91 (dd, 1H, J_1=9.3 Hz, J_2=2.9 Hz), 4.08 (d, 2H, J=5.0 Hz), 4.61 (s, 2H), 4.77 (s, 2H), 5.62 (dt, 1H, J_1=15.6 Hz, J_2=5.0 Hz), 5.89 (dd, 1H, J_1=15.6 Hz, J_2= 6.8 Hz), 7.33 (s, 5H). ^{13}C NMR ($CDCl_3$): δ = 12.9, 16.4, 17.8, 28.4, 32.3, 34.9, 38.1, 68.1, 69.3, 86.1, 93.9, 126.4, 127.6, 127.8, 128.4, 136.3, 137.9, 176.2.

12) A great number of methods have been reported recently on the synthesis of Prelog-Djerassi lactone 11. In the following references, physical data of 11 and its several epimers are available: a) P. A. Bartlett and J. L. Adams, J. Am. Chem. Soc., 102, 337 (1980); b) R. E. Ireland and J. P. Daub, J. Org. Chem., 46, 479 (1981); c) K. Maruyama, Y. Ishihara, and Y. Yamamoto, Tetrahedron Lett., 22, 4235 (1981).

13) E. J. Corey, N. W. Gilman, and B. E. Ganem, J. Am. Chem. Soc., 90, 5616 (1968).

14) ^{1}H NMR was diagnostic in distinguishing 12a and 12b, where the spectrum of 12a was in full accordance with the authentic spectrum, kindly provided by Professor Yamaguchi.

15) The ee of the alcohol 15 was shown to be over 98 % by 400 MHz ^{1}H NMR analysis of its MTPA ester; J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).

16) $[\alpha]_D^{21}$ -10° (c 1.3, $CHCl_3$). ^{1}H NMR (CCl_4): δ = 0.92 (t, 3H, J=6.8 Hz), 1.00 (d, 3H, J=6.8 Hz), 1.1-1.7 (m, 3H), 1.9-2.4 (m, 1H), 3.1-3.3 (m, 1H), 3.98 (d, 2H, J=4.8 Hz), 4.53 (s, 2H), 4.64 (s, 2H), 5.3-5.7 (m, 2H), 7.24 (s, 5H).

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