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Stereocontrolled First Total Synthesis of Mycinolide IV#

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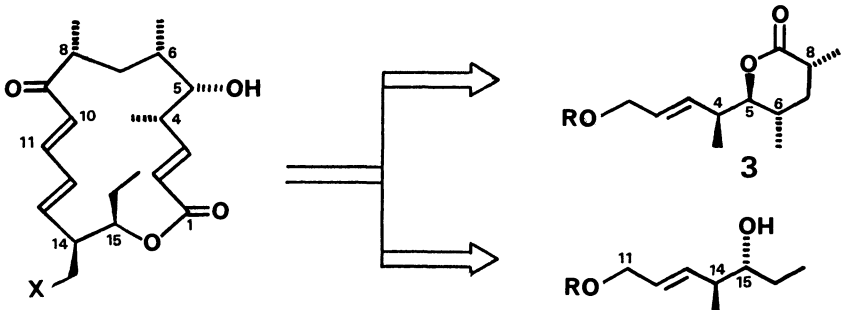
First total synthesis of mycinolide IV (2) was accomplished. Novel rearrangement of epoxyalcohol derivatives was applied to the synthesis of the C(11)-C(17) portion, assembly of which with the C(1)-C(10) portion (prepared via pinacol-type rearrangement) enabled a simple and stereoselective synthesis of 2.

As the fascinating synthetic targets, macrolides have significantly stimulated the recent development of new synthetic methods associated with their total synthesis, i.e. macrolactonization, acyclic stereocontrol and so on.[1)]

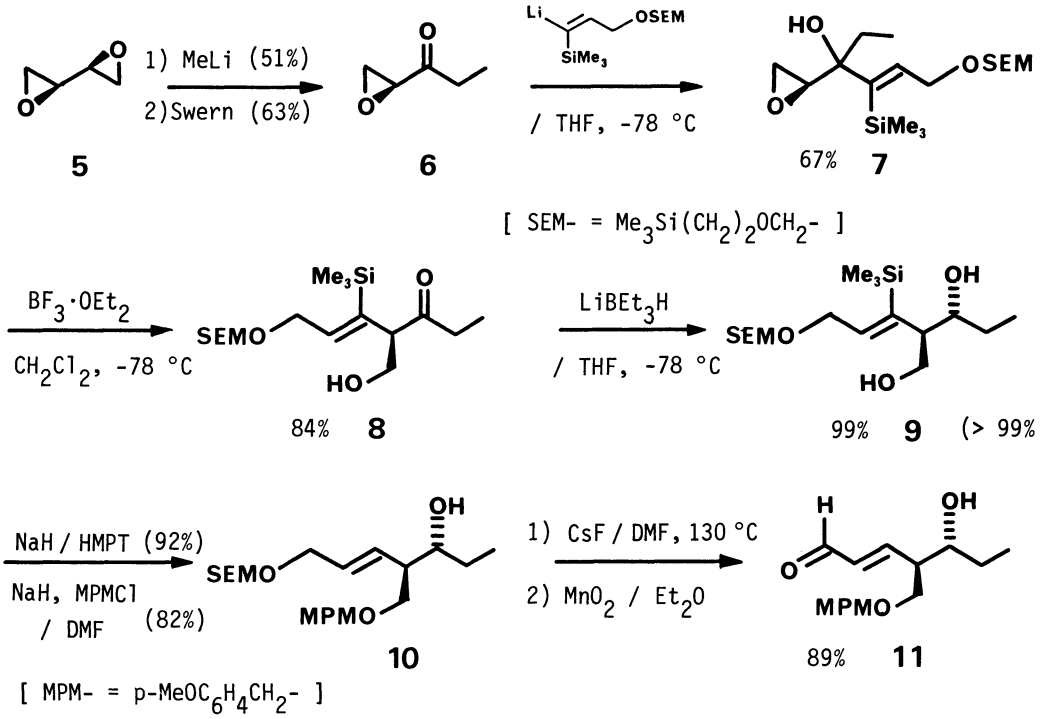
We recently uncovered a new promising opportunity for the acyclic stereocontrol based on the stereospecific 1,2-rearranegement, which can provide a new and efficient methodology for the macrolide synthesis.[2)] To evaluate the efficacy of the process, we embarked on the synthetic study of the mycinamicin macrolides[3)] isolated from *Micromonospora griseorubida* sp. nov., having heretofore culminated in the stereocontrolled total synthesis of protomycinolide IV (1).[2)]



1: X=H Protomycinolide IV
2: X=OH Mycinolide IV

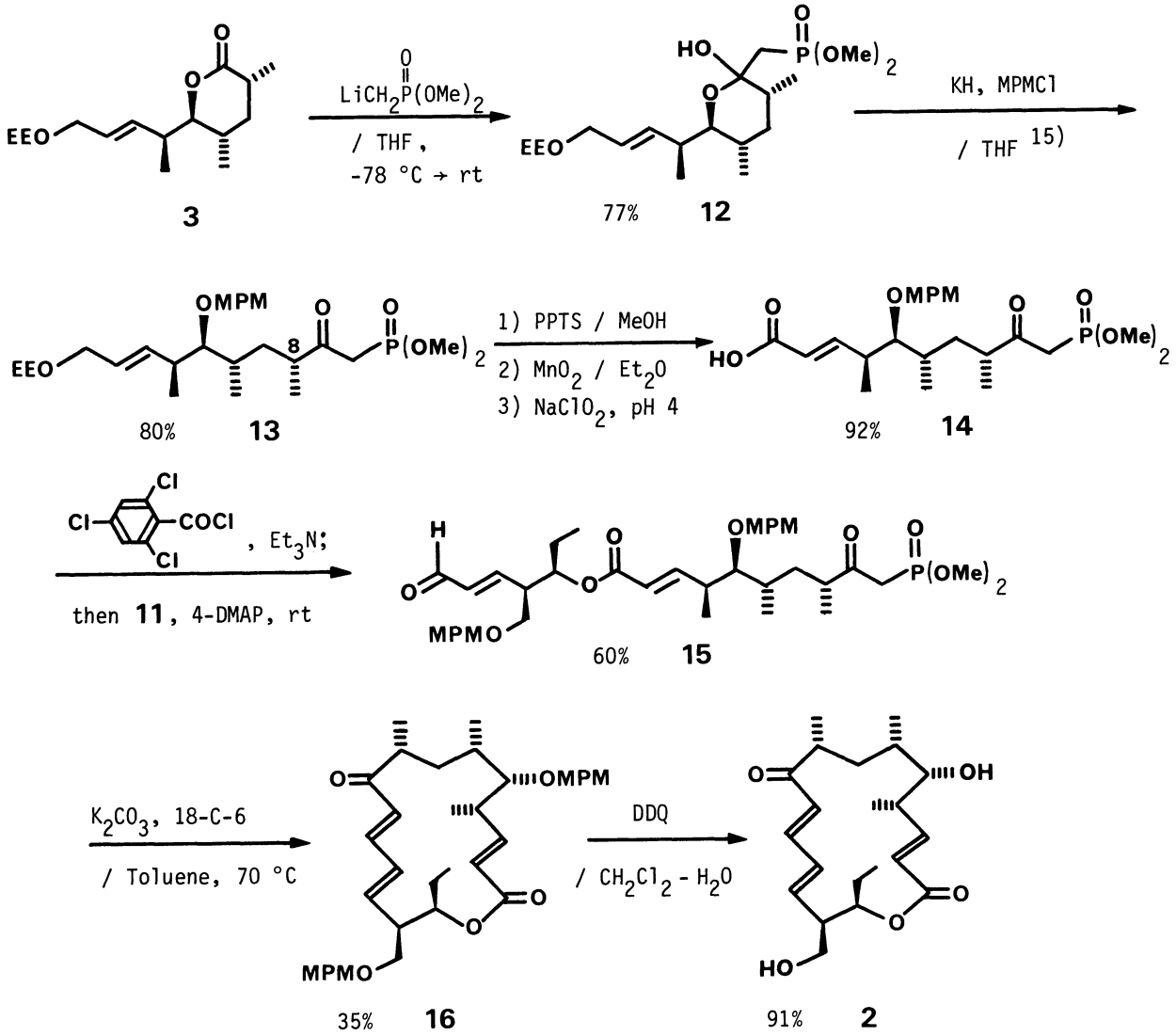
Mycinolide IV (2), the oxygenated congener of 1, is the aglycon of mycinamicin IV, whose structure was unambiguously determined by X-ray analysis.[3)] Since the lactone 3 can be utilized in common, the synthesis of 2 is formally a simple task if the selective construction of the C(11)-C(17) portion (4) can be properly designed. To this end, we exploited a novel rearrangement of the epoxyalcohol derivatives,[4)] which actually worked well for the ready preparation of 4, by the coupled use with the vinylsilane-mediated diastereocontrol.[5)] Herein, we wish to report the stereocontrolled first total synthesis of 2 based on the new tactics.

#*Dedicated to Professor Teruaki Mukaiyama on occasion of his 60th birthday.*



The known L-tartrate-derived bisepoxide 5[6] was converted to epoxyketone 6, to which the migrating three-carbon unit was appended to give 7.[7] Epoxyalcohol 7 was then subjected to the rearrangement. Treatment of 7 with $BF_3.OEt_2$ (2.5 equiv, -78 °C / CH_2Cl_2) cleanly afforded the rearranged product 8 with stereochemical integrity: > 99% ee[8] and no Z/E isomerization of the double bond. The alkenyl aldol 8 was then reduced with $LiBEt_3H$ in THF at -78 °C to furnish 2-alkenyl-1,3-diol 9 as the single isomer.[9] This stereochemical aspect is in line with the efficient stereo-directing effect by the TMS group in the reduction of 2-vinyl aldols.[5,10] After the TMS group of 9 was detached, the primary hydroxyl group was selectively protected with MPM group[11] to give alcohol 10. Finally, deprotection of SEM followed by the selective allylic oxidation gave rise to aldehyde 11 ($[\alpha]_D^{28}$ -28° (c 2.0, $CHCl_3$)) ready for further manipulation.[12] Thus, an efficient route to the C(11)-C(17) portion was exploited by the stereospecific rearrangement followed by the stereoselective reduction.

For the macrolide formation, we planned to apply the carbocyclization strategy[13] to pursue an expeditious access to the target. Thus, the stereodefined lactone 3, previously described as the key intermediate in the synthesis of 1,[2] was treated with $LiCH_2PO(OMe)_2$ to afford lactol 12, which was then treated with MPMCl in the presence of KH to give the acyclic compound 13 in 80% yield. This shortcut access to the open-form phosphonate was recently suggested by Hoffmann using LDA or t-BuOK - R_3SiCl.[14] In the present case, however, the alkoxide trapping was carried out with a weaker elecrophile (MPMCl), which required the use of a stronger base KH.[15] Nonetheless, the reaction proceeded cleanly, and more importantly, without any epimerization of C(8) retaining the requisite stereochemistry of the target. Considering that similar conversions have been conventionally done via multisteps,[16] this shortcut protocol will find general utility. Acid hydrolysis of acetal 13 followed by oxidation gave



carboxylic acid 14, which was coupled with alcohol 11 by the Yamaguchi method.[17] Ester 15 contained 10-15% of undefined by-product(s), which were inseparable by repeated chromatography causing a sizable loss of the material.[18] Thus, after a single chromatography, cyclization of 15 was carried out under the standard conditions[13] to obtain the pure cyclized product 17 (35% based on crude 15) after purification on silica-gel TLC. Finally, removal of the MPM groups[11] gave mycinolide IV which was fully identical with the natural sample.[19]

In summary, the first total synthesis of mycinolide IV was achieved, which is simple and straightforward by virtue of the new rearrangement-based methodology.

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9) ^{13}C NMR ($CDCl_3$) δ -1.5, 0.4, 10.5, 18.0, 26.9, 50.6, 63.6, 65.4, 67.5, 74.1, 94.6, 140.6, 142.4.

10) For the model study, see K. Suzuki, M. Shimazaki, and G. Tsuchihashi, Tetrahedron Lett., in press.

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15) Lactol 12 was treated with KH (3 eq. / THF, 0 ^{o}C) followed by MPMCl (2 eq., 12 h). $(Me_3Si)_2NK$ led to lower yield of 13, and no reaction occurred with t-BuOK.

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18) The side reaction is presumably the isomerization of the enoate moiety. Esterification of α,β-unsaturated acids is often accompanied by E/Z isomerization, deconjugation, Michael reaction etc: P. A. Bartlett and F. R. Green III, J. Am. Chem. Soc., 100, 4858 (1978); S. Shoda and T. Mukaiyama, Chem. Lett., 1980, 391; W. R. Roush and T. A. Blizzard, J. Org. Chem., 49, 1772 (1984).

19) $[\alpha]_D^{27}$ +23^{o} (c 0.2, MeOH); mp 222-223 ^{o}C (acetone); ^{13}C NMR ($CDCl_3$) δ 9.7, 17.3, 17.7, 19.3, 25.4, 31.6, 33.8, 40.5, 44.7, 51.6, 62.2, 73.5, 80.2, 121.1, 123.4, 134.1, 140.6, 141.7, 151.3, 166.1, 203.3; HRMS: m/z 364.2245 (364.2247 calcd for $C_{21}H_{32}O_5$, M^+). The ^{1}H NMR and IR spectra of 2 were also fully superimposable with those of the authentic sample by direct comparison.

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