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First Total Synthesis of Mycinamicin IV and VII. Successful Application of New Glycosidation Reaction

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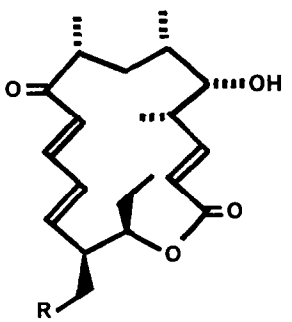
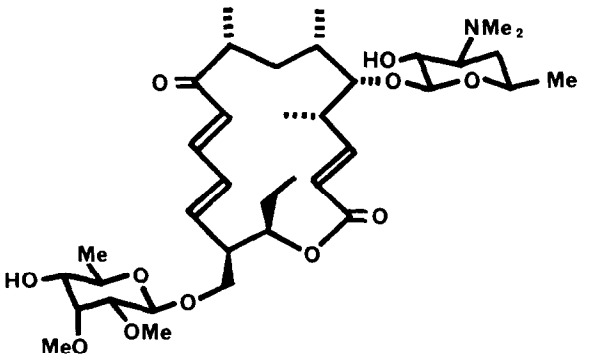
Summary: *First total synthesis of mycinamicin IV via mycinamicin VII is described. New glycosidation reaction using Cp_2MCl_2-$AgClO_4$ (M=Zr, Hf) was effectively applied to the selective introduction of β-D-mycinosyl and β-D-desosaminyl linkages.*

Mycinamicins constitute a novel class of macrolide antibiotics with strong antibacterial activities, produced by Micromonospora griseorubida sp. nov.[1] We have synthesized the aglycons,[2] mycinolide IV (1)[2a] and protomycinolide IV (2)[2b] by way of the rearrangement-based acyclic stereocontrol. To complete the synthesis, we turned our attention to the glycosylation of 1.

Glycosidation of macrolides is undoubtedly an important problem, since the biological activities depend heavily on the sugar portion. However, only a few successful examples have been recorded in *the synthesis of the full structures armed with the sugar(s)*,[3] which is in sharp contrast with the vast number of successes in aglycon synthesis.[4] The problem resides in that the classical methods are unready to glycosylate the macrocyclic aglycons with the low reactivity and yet the high chemical sensitivity.[5,6]

We found a novel activation system for glycosyl fluorides, Cp_2MCl_2-$AgClO_4$ (M=Zr, Hf),[7] having a promising potentiality. Herein, we wish to describe the first total synthesis of mycinamicin IV (3), via mycinamicin VII, which definitely demonstrates the efficiency of new glycosidation reaction.

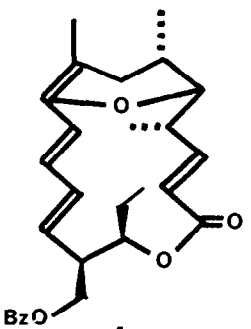




1 R = OH **Mycinolide IV**
2 R = H **Protomycinolide IV**

3 **Mycinamicin IV**

The order of two glycosidations was chosen that the D-desosamine is introduced first (to the C(5)-OH) followed by the D-mycinose (to the C(21)-OH). Thus, mycinolide IV (1)[2a] was benzoylated under the strictly-controlled conditions to give selectively mono-protected aglycon 5 in 96 % yield. The first glycosidation to 5, however, posed an extremely hard problem, which was not only due to the low reactivity by the sterically crowded nature of the C(5) hydroxyl group but also due to its propensity to internally cyclize to the C(9) carbonyl group even under weakly acidic conditions to result in the formation of bicylic enol ether 4.[8,9]



4

On this occasion, our new glycosidation protocol[7] worked well. The reaction of 5 with the fluoride 10 in the presence of Cp_2HfCl_2-$AgClO_4$ in CH_2Cl_2 at 0-5 °C proceeded smoothly to afford 6 in 72 % yield with the ratio of α/β=1/6.[10] Central to this successful joining is the rapidity of the reaction which can exclude the competing cyclic dehydration. Actually, attempted reactions by employing some other methods[6a,b] were considerably slower, which led to the formation of 4 in variable yields.

After the anomers were separated (basic Al_2O_3 TLC),[11] the two protecting groups of 6 were once detached to afford 7 in 75 % yield. Compound 7 is mycinamicin VII,[1c] one of the minor components in the mycinamicin macrolides, which was fully identical to the natural sample [$[\alpha]_D^{29}$ +51° (c 0.51, DMSO), lit. $[\alpha]_D^{22}$ +50.1° (c 0.5, DMSO)].[1c,8] Subsequent treatment of 7 with methyl chloroformate without additional base cleanly afforded the alcohol 8, selectively protected at the sugar portion, ready for the second glycosidation.

Without the advantage of the neighboring participation, the main issue in the formation of β-mycinosyl linkage lies in the stereocontrol. Here again, our new protocol worked efficiently under the conditions found in the extensive model study.[7] Namely, the reaction of alcohol 8 with fluoride 11 in the presence of Cp_2ZrCl_2-$AgClO_4$ in benzene proceeded smoothly to furnish glycoside 9 in 86 % yield with an excellent selectivity in favor of the desired β-anomer (α / β = 1 / 26).[12] After the α-anomer was removed chromatographically, the hydrolytic cleavage of the protecting groups of 9 uneventfully afforded mycinamicin IV (3) [$[\alpha]_D^{29}$ +2.8° (c 1.5, MeOH), lit.[1a] $[\alpha]_D^{25}$ +2.7° (c 1.0, MeOH)] which was identical in full respects to the authentic sample.[8,13]

In summary, the first total synthesis of mycinamicin IV (3) and VII (7) was accomplished. The synthesis not only records a flexible and stereoselective access to the mycinamicin-class macrolide antibiotics but also shows the promising potentiality of the new glycosidation reaction.

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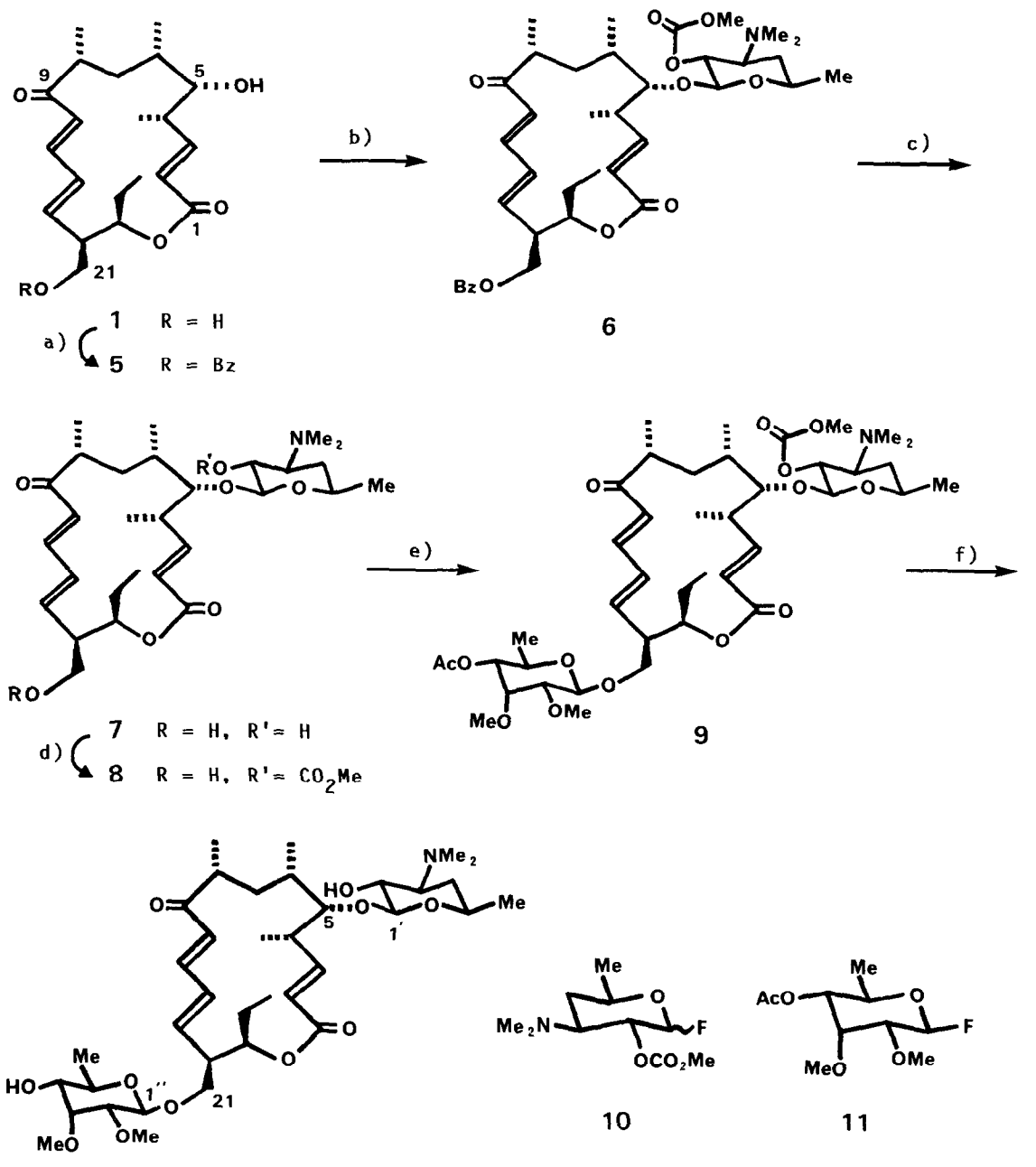

Keys: a) PhCOCl (1.2 equiv.) / pyridine-CH_2Cl_2 (1:1), 0 °C, 1 hr (96 %); b) **10** (3 equiv.), Cp_2HfCl_2 (5 equiv.), $AgClO_4$ (5 equiv.) / CH_2Cl_2, 0-5 °C, 2 hr (72 %); c) Et_3N-H_2O-MeOH (1:1:5), 70 °C, 3 hr (75 %); d) $ClCO_2Me$ (2 equiv.) / CH_2Cl_2, 0 °C, 1 hr (quant.); e) **11** (3 equiv.), Cp_2ZrCl_2 (5 equiv.), $AgClO_4$ (5 equiv.) / C_6H_6, rt, 1hr (86 %); f) Et_3N-H_2O-MeOH (1:1:5), rt, 16 hr (73 %).

References and Notes

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4) Review: S. Masamune and P. A. McCarthy, in "Macrolide Antibiotics", S. Ōmura Ed., Academic, Orlando, pp 127-198 (1984); I. Paterson and M. M. Mansuri, Tetrahedron, 41, 3569 (1985).

5) To evade these difficulties, an intriguing strategy was proposed, that is, the glycosidation is executed at the fragment stage before the macrocyclization, which, however, causes an inevitable loss of convergence and flexibility of the synthetic scheme: K. C. Nicolaou, M. R. Pavia, and S. P. Seitz, J. Am. Chem. Soc., 104, 2027, 2030 (1982).

6) Considerable progress has recently been made in glycosidation chemistry. For use of glycosyl fluorides; a) T. Mukaiyama, Y. Murai, and S. Shoda, Chem. Lett., 1981, 431; b) S. Hashimoto, M. Hayashi, and R. Noyori, Tetrahedron Lett., 25, 1379 (1984). For other approaches; K. C. Nicolaou, D. P. Papahatjis, and S. P. Seitz, J. Am. Chem. Soc., 105, 2430 (1983); R. R. Schmidt, Angew. Chem., Int. Ed. Engl., 25, 212 (1986).

7) See the preceding communications in this issue.

8) All new compounds were fully characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), IR and high-resolution MS (EI In-beam).

9) HRMS: m/z 450.2407 (450.2404 calcd for $C_{28}H_{34}O_5$, M^+). For the related behavior in the erythromycin series, see T. J. Perun, J. Org. Chem., 32, 2324 (1967).

10) Decrease of the ratio above 0 °C was already found in model study (ref. 7). In this case, however, no reaction occurred at lower temperature. Further optimization is in progress.

11) β-6: $[\alpha]_D^{27}$ +34° (c 1.4, $CHCl_3$), NMR (δ, $CDCl_3$): H(1') 4.33 (d, J=7.3 Hz); C(1') 102.6; IR (neat) 1750, 1720, 1680, 1650, 1635, 1595 cm^{-1}; HRMS: m/z 683.3657 (683.3665 calcd for $C_{38}H_{53}O_{10}N$, M^+); Rf 0.58 (hexane/Et_2O=1/9, Al_2O_3 Merck #5713). α-6: $[\alpha]_D^{27}$ +40° (c 0.25, $CHCl_3$); NMR: H(1') 5.10 (d, J=3.9 Hz); IR (neat) 1750, 1720, 1680, 1650, 1635, 1595cm^{-1}; HRMS: m/z 683.3670 (683.3666 calcd for $C_{38}H_{53}O_{10}N$, M^+); Rf 0.50 (vide supra).

12) 9: mp: 96-101 °C; $[\alpha]_D^{26}$ +20° (c 1.8, $CHCl_3$); NMR (δ, $CDCl_3$): H(1') 4.32 (d, J=7.8 Hz), H(1") 4.64 (d, J=7.8 Hz); C(1') 102.6, C(1") 101.0; IR (KBr) 1755, 1725, 1680, 1650, 1630, 1595 cm^{-1}; HRMS: m/z 795.4391 (795.4440 calcd for $C_{41}H_{65}O_{14}N$, M^+).

13) Mp: 174-175 °C (acetone-hexane) [lit[1a] 174-176 °C]; HRMS: m/z 695.4246 (695.4241, calcd for $C_{37}H_{61}O_{11}N$, M^+).

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