

A STEREOCONTROLLED SYNTHESIS OF THE 16-MEMBERED RING MACROLIDE AGLYCONES, NIDDANOLIDE, CARBONOLIDE B, AND PLATENONOLIDE W₁¹

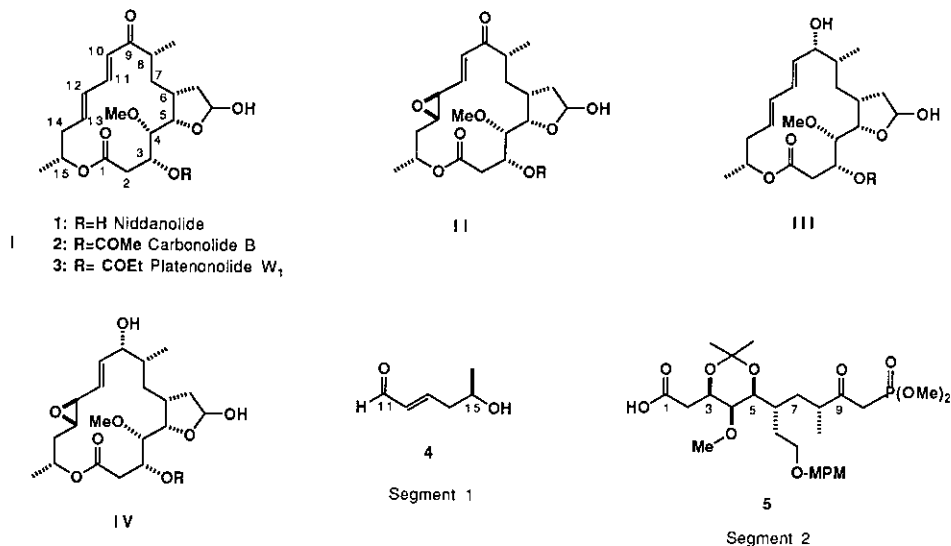
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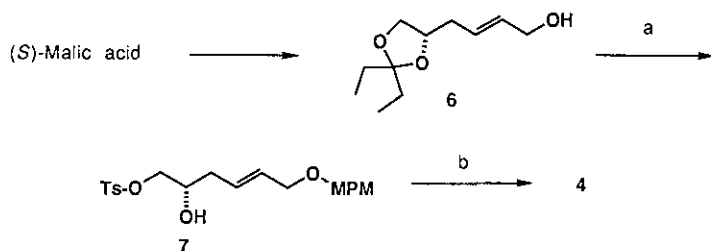
Abstract — The aglycones of the 16-membered ring macrolide antibiotics, niddanolide, carbonolide B, and platenonolide W₁, were synthesized via the Yamaguchi esterification of the C1-C10 segment and the C11-C15 segment, prepared stereoselectively from D-glucose, followed by an intramolecular Wittig-Horner type cyclization.

Among a great number of macrolide antibiotics isolated mainly from *Streptomyces* since the first discovery of pikromycin in 1950, the 16-membered macrolides represented by carbomycins, leucomycins, spiramycins, and maridomycins form the largest group, and their aglycones are classified into four types I, II, III, and IV according to their oxidation levels.

For the stereoselective synthesis of these aglycones it seems promising that type I aglycones are first synthesized and then reduced and/or oxidized to yield type II, III, and IV aglycones, although conformational control of the 16-membered ring of type I compounds is presumably essential. Recently, we reported highly stereoselective syntheses of typical macrolide aglycones such as methynolide, pikronolide, and tylonolide via the macrocyclization using the Wittig-Horner reaction.² This methodology was now applied to the synthesis of type I aglycones, niddanolide (1), carbonolide B (2), and platenonolide W₁ (3). Although there are two excellent precedents for the synthesis of carbomycin B itself³ and 2,⁴ this report may provide an additional and improved synthetic method, in which 1, 2, and 3 were synthesized via the ester coupling between segment 1 and segment 2 followed by the intramolecular Wittig-Horner cyclization.

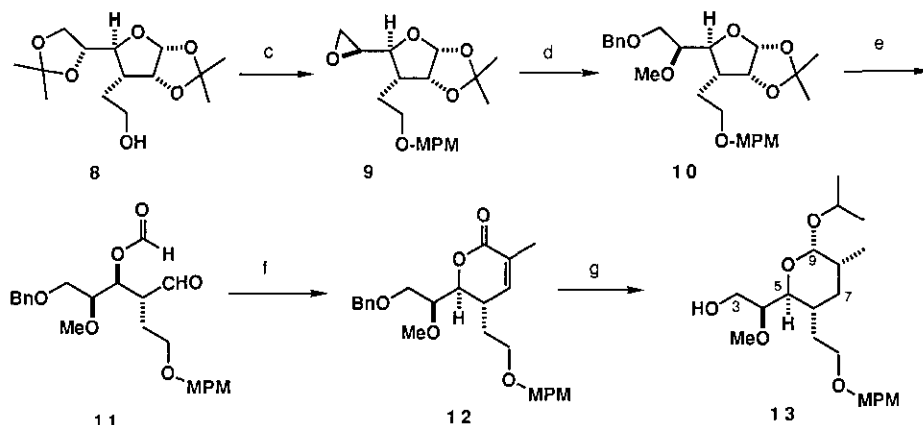


Segment 1 (4) was readily synthesized from (*S*)-malic acid via 6⁵ and 7 by a series of conventional reactions.



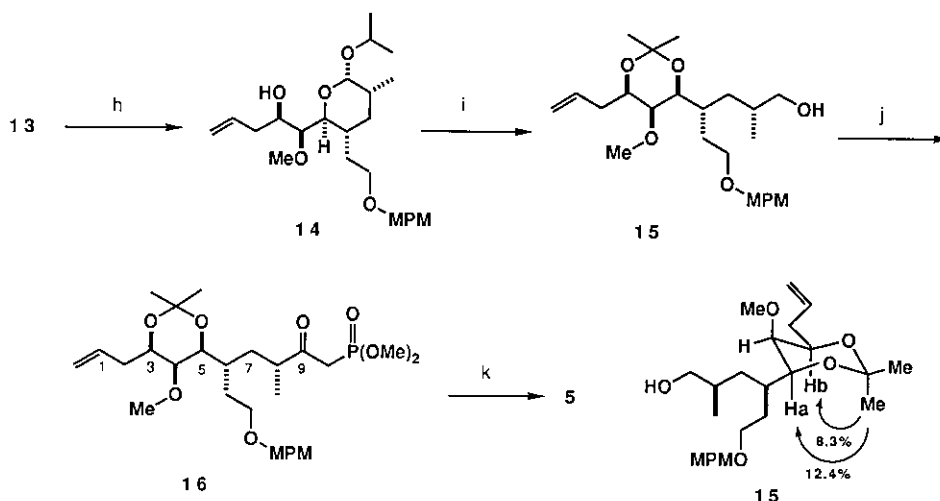
(a) 1) MPMCl, NaH, DMSO-THF (4:3) (94%); 2) 1% H₂SO₄-MeOH; 3) TsCl, Py., CH₂Cl₂ (70%, 2 steps). (b) 1) LiAlH₄, ether, (94%); 2) DDQ, CH₂Cl₂-H₂O; 3) MnO₂, CH₂Cl₂ (74%, 2 steps).

Since the configuration at C3-C8 is identical to that at the same positions of tylosolide, the methodology employed in the synthesis of segment 2 of tylosolide^{2c,f} was directly applicable to the synthesis of **5**, which has only a difference, a methoxy group at C4 instead of a methyl group. The alcohol (**8**),^{2c,f} easily synthesized from D-glucose, was first protected with a 4-methoxybenzyl (MPM) group⁶ and then converted to the epoxide (**9**) in the usual way in order to invert the configuration at C5 (based on D-glucose). Ring opening with sodium benzyl oxide and subsequent methylation gave **10** in excellent yield. The acetonide of **10** was cleaved in the usual way,⁷ and the resulting aldehyde (**11**) was treated with a Wittig-Horner reagent of the sodium salt of trimethyl 1-phosphonopropionate to give the (Z)- α,β -unsaturated ester,⁸ which, without purification, was converted to the lactone (**12**) by treatment with potassium carbonate. In order to increase the stereoselectivity of the reduction of the double bond of **12**, the lactone was converted to the anomerically pure δ -lactolide via reduction with DIBAL followed by isopropyl protection of the resulting lactol. Selective hydrogenation of the benzyl (Bn) group and the C7-C8 double bond, not of the MPM group, was achieved by use of Raney nickel (W2) catalyst. The stereoselectivity at C8 was 9 : 1.



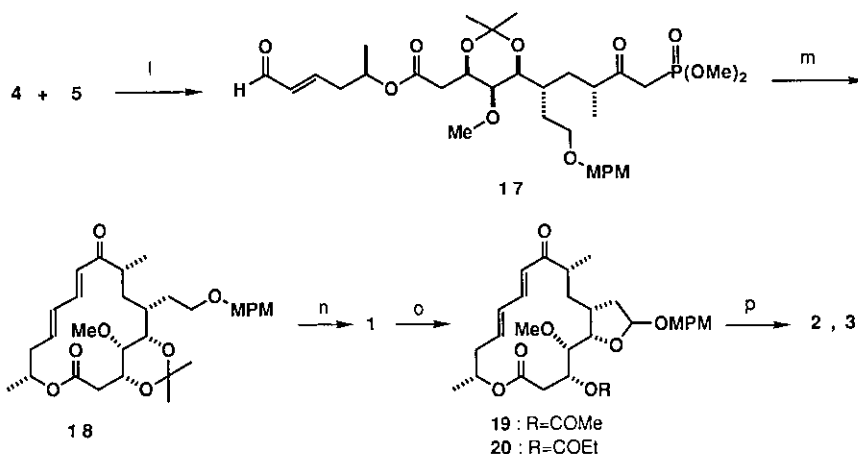
(c) 1) MPMCl, NaH, DMF-THF (97%); 2) 2% H₂SO₄-MeOH; 3) TBDMSCl, imidazole, CH₂Cl₂ (64%, 2 steps); 4) MsCl, Py. (98%); 5) 1N HCl, THF (91%); 6) K₂CO₃, MeOH (96%). (d) 1) BnOH, NaH, DMF (98%); 2) MeI, NaH, DMSO, THF (100%). (e) 1) 3N H₂SO₄, dioxane, rt, 48 h; 2) NaIO₄, H₂O, MeOH [36% (100% based on consumed **10**), 2 steps]. (f) 1) MeO₂CCHMePO(OMe)₂, NaH, THF, -90°C; 2) K₂CO₃, MeOH (65%, 2 steps). (g) 1) DIBAL, toluene; 2) CSA, iPrOH (75%, 2 steps); 3) Raney Ni-W2, H₂, EtOH (83%).

The final chiral center at C3 was constructed as follows. Swern oxidation of **13** gave the aldehyde, which was treated with allyltributyltin in the presence of magnesium bromide at -60°C.⁹ A



(h) 1) DMSO, (COCl)₂, CH₂Cl₂ (96%); 2) CH₂=CHCH₂SnBu₃, MgBr₂·Et₂O, CH₂Cl₂, -60°C (87%). (i) 1N HCl, THF (80%); 2) NaBH₄, CaCl₂, EtOH (91%); 3) Me₂C(OMe)₂, CSA, benzene (90%). (j) 1) DMSO, (COCl)₂, CH₂Cl₂ (91%); 2) MePO(OMe)₂, nBuLi, THF (99%); 3) PDC, DMF (87%). (k) KMnO₄, NaIO₄, NaHCO₃, acetone (80%).

chelation-controlled addition readily occurred almost completely stereoselectively (72 : 1) to give 14,¹⁰ whose configuration was confirmed after conversion of 14 to 15 via three reactions, acid-hydrolysis, reduction with calcium borohydride, and protection with an isopropylidene group. In the nmr spectrum of 15, NOR from the axial methyl group of the isopropylidene group to H_a (12.4%) and H_b (8.3%) was clearly observed. Swern oxidation of 15 gave the aldehyde, which was treated with the lithio derivative of dimethyl methanephosphonate and then pyridinium dichromate (PDC) to give the β-keto phosphonate (16). Oxidation of the terminal olefin of 16 was carried out under Lemieux-von Rudloff's conditions,¹² and segment 2 (5) was isolated in good yield.



(l) Cl₃C₆H₂COCl, DMAP, toluene, 1.5 h, rt (78%). (m) K₂CO₃, 18-crown-6, toluene, rt, 17 h (57%). (n) 1) DDQ, CH₂Cl₂-H₂O (84%); 2) DMSO, (COCl)₂, CH₂Cl₂ (95%); 3) 1N HCl-THF (1: 3) (84%). (o) 1) MPMOH, CSA (93%); 2) for 19, Ac₂O, TEA, DMAP (98%); for 20 (EtCO)₂O, TEA, DMAP (75%). (p) 80%-TFA, 0°C (2, 92% ; 3, 97%).

Esterification of 4 and 5 was carried out by the Yamaguchi method,¹³ and the resulting ester (17) was subjected to the intramolecular Wittig-Horner type cyclization by Nicolaou's method¹⁴ using powdered potassium carbonate and 18-crown-6 in toluene at room temperature to give the 16-membered dienone (18).¹⁵ Removal of the MPM group by DDQ oxidation⁶ followed by Swern oxidation gave the aldehyde, and the remaining isopropylidene protection was removed with hydrochloric acid to give niddanolide (1)¹⁶ in good yield. After protection of the hemiacetal with an MPM group, acetylation of the C3-hydroxy group gave 19. Similarly, treatment with propionic anhydride gave 20. Removal of the MPM protecting group of 19 and 20 under acidic conditions readily afforded carbonolide B (2)¹⁷ and platenonolide W₁ (3),¹⁸ respectively, in excellent yields.

REFERENCES AND NOTES

- Chiral synthesis of polyketide-derived natural products. 29. For part 28, see: K. Horita, I. Noda, K. Tanaka, T. Miura, and O. Yonemitsu, Heterocycles, 1990, **30**, 321.
- a) Y. Oikawa, T. Tanaka, and O. Yonemitsu, Tetrahedron Lett., 1986, **27**, 3647; b) N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, J. Am. Chem. Soc., 1986, **108**, 4645; c) T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, Tetrahedron Lett., 1986, **27**, 3651; d) T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada, and O. Yonemitsu, Chem. Pharm. Bull., 1987, **35**, 2203; e) N. Nakajima, T. Tanaka, T. Hamada, Y. Oikawa, and O. Yonemitsu, ibid., 1987, **35**, 2228; f) T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, ibid., 1987, **35**, 2209, 2219.
- K. Tatsuta, Y. Amemiya, S. Maniwa, and M. Kinoshita, Tetrahedron Lett., 1980, **21**, 2837.
- K. C. Nicolaou, S. P. Seitz, and M. R. Ravia, J. Am. Chem. Soc., 1981, **103**, 1222.
- a) S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe, and Y. Ito., J. Org. Chem., 1984, **49**, 2837; b) Cf. Y. Guindon, C. Yoakim, M. A. Bernstein, and H. E. Monton, Tetrahedron Lett., 1985, **26**, 1185.
- K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, Tetrahedron, 1986, **42**, 3021.
- When the acid-treatment of 10 was further continued, the MPM group was also cleaved very slowly to drop the yield of 11.
- The Z, E ratio of the α,β -unsaturated ester was only 3.5 : 1, but the E-ester (19%) was easily removed when the lactone (12) was purified by a column chromatography.
- G. E. Keck and E. P. Boden, Tetrahedron Lett., 1984, **25**, 265, 1879.
- Allylmagnesium bromide at -90°C also gave 14, but the stereoselectivity at C3 was only 4 : 1. Allyltrimethylsilane in the presence of titanium tetrachloride¹¹ gave 14 highly stereoselectively (60 : 1), but concomitant loss of the MPM group was unavoidable, and the yield of 14 was only 22%.
- a) H. Sakurai, Pure Appl. Chem., 1982, **54**, 1; b) A. Hosomi and H. Sakurai, Tetrahedron Lett., 1976, 1295.
- R. U. Remiex and E. von Rudloff, Can. J. Chem., 1955, **33**, 1701, 1710.
- J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 1979, **52**, 1989.
- K. C. Nicolaou, M. R. Pavia, and S. P. Seitz, J. Am. Chem. Soc., 1982, **104**, 2030.
- The cyclization proceeded more rapidly at 80°C and was completed in 3 h, but the yield of 18 was 30-40%.
- 1 is a 2 : 1 isomeric mixture with respect to the hemiacetal position.
- 2 is a 3 : 1 isomeric mixture with respect to the hemiacetal position.
- 3 is a 2.3 : 1 isomeric mixture with respect to the hemiacetal position.

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