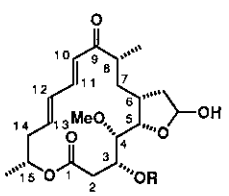
A STEREOCONTROLLED SYNTHESIS OF THE 16-MEMBERED RING MACROLIDE AGLYCONES, NIDDANOLIDE, CARBONOLIDE B, AND PLATENONOLIDE W_1[1]

Noriyuki Nakajima, Kouichi Ueto, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

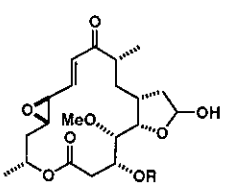
Abstract — The aglycones of the 16-membered ring macrolide antibiotics, niddanolide, carbonolide B, and platenonolide W_1, were synthesized via the Yamaguchi esterification of the C1-C10 segment and the C11-C15 segment, prepared stereoselectively from D-glucose, followed by an intramolecular Wittig-Horner 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.

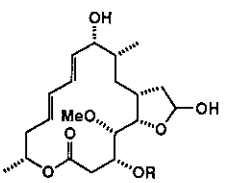
For the stereoselective synthesis of these aglycones it seems promising that type I aglycones are first synthesized and then reduced and/or oxidized to yield type II, III, and IV aglycones, although conformational control of the 16-membered ring of type I compounds is presumably essential. Recently, 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 W_1 (3). Although there are two excellent precedents for the synthesis of carbomycin B itself[3] 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.



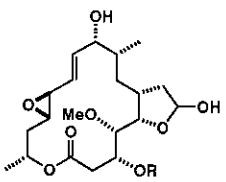
I
1: R=H Niddanolide
2: R=COMe Carbonolide B
3: R= COEt Platenonolide W_1



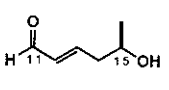
II



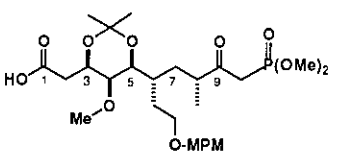
III



IV

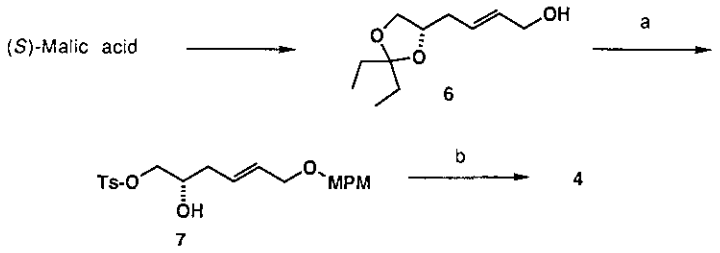


4
Segment 1



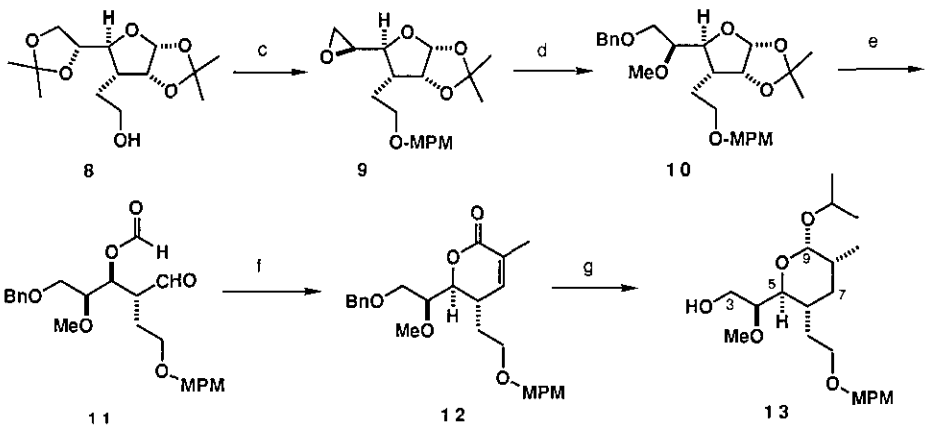
5
Segment 2

Segment 1 (**4**) was readily synthesized from (S)-malic acid via 6[5] and 7 by a series of conventional reactions.



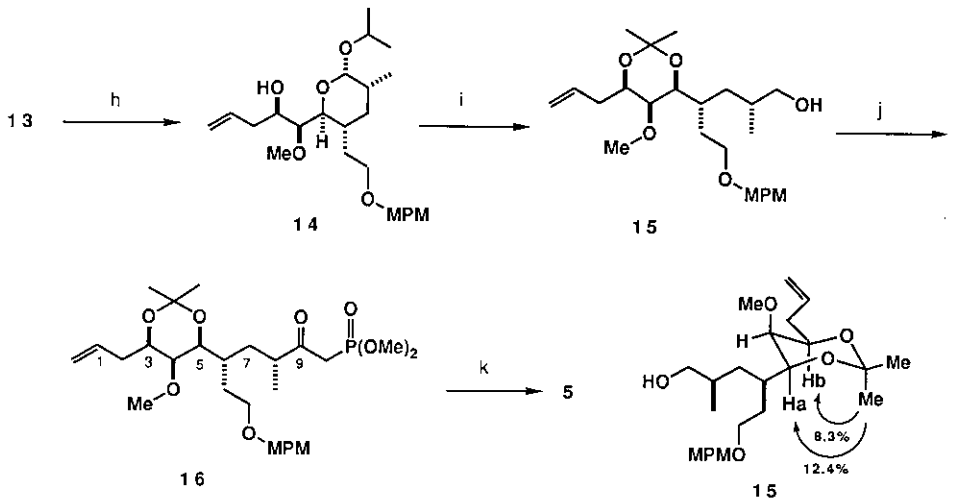
(a) 1) MPMCl, NaH, DMSO-THF (4:3) (94%); 2) 1% H_2SO_4-MeOH; 3) TsCl, Py., CH_2Cl_2 (70%, 2 steps). (b) 1) $LiAlH_4$, ether, (94%); 2) DDQ, CH_2Cl_2-H_2O; 3) MnO_2, CH_2Cl_2 (74%, 2 steps).

Since the configuration at C3-C8 is identical to that at the same positions of tylonolide, the methodology employed in the synthesis of segment 2 of tylonolide[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) group[6] 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.



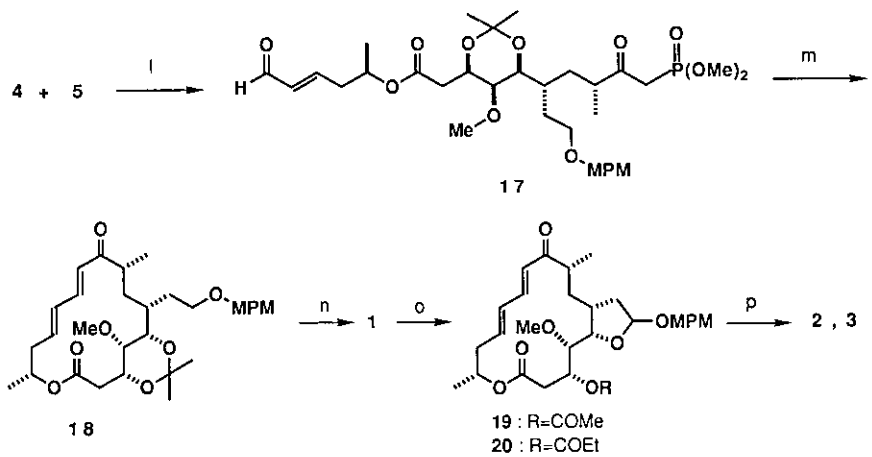
(c) 1) MPMCl, NaH, DMF-THF (97%); 2) 2% H_2SO_4-MeOH; 3) TBDMSCl, imidazole, CH_2Cl_2 (64%, 2 steps); 4) MsCl, Py. (98%); 5) 1N HCl, THF (91%); 6) K_2CO_3, MeOH (96%). (d) 1) BnOH, NaH, DMF (98%); 2) MeI, NaH, DMSO, THF (100%). (e) 1) 3N H_2SO_4, dioxane, rt, 48 h; 2) $NaIO_4$, H_2O, MeOH [36% (100% based on consumed **10**), 2 steps]. (f) 1) $MeO_2CCHMePO(OMe)_2$, NaH, THF, -90°C; 2) K_2CO_3, MeOH (65%, 2 steps). (g) 1) DIBAL, toluene; 2) CSA, iPrOH (75%, 2 steps); 3) Raney Ni-W2, H_2, 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, $(COCl)_2$, CH_2Cl_2 (96%); 2) CH_2=$CHCH_2SnBu_3$, $MgBr_2 \cdot Et_2O$, CH_2Cl_2, -60°C (87%). (i) 1N HCl, THF (80%); 2) $NaBH_4$, $CaCl_2$, EtOH (91%); 3) $Me_2C(OMe)_2$, CSA, benzene (90%). (j) 1) DMSO, $(COCl)_2$, CH_2Cl_2 (91%) 2) $MePO(OMe)_2$, nBuLi, THF (99%); 3) PDC, DMF (87%). (k) $KMnO_4$, $NaIO_4$, $NaHCO_3$, 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**, NOE 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) $Cl_3C_6H_2COCl$, DMAP, toluene, 1.5 h, rt (78%). (m) K_2CO_3, 18-crown-6, toluene, rt, 17 h (57%). (n) 1) DDQ, CH_2Cl_2-H_2O (84%); 2) DMSO, $(COCl)_2$, CH_2Cl_2 (95%); 3) 1N HCl-THF (1: 3) (84%). (o) 1) MPMOH, CSA (93%); 2) for **19**, Ac_2O, 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 method[14] 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 oxidation[6] 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 W_1 (3),[18] respectively, in excellent yields.

REFERENCES AND NOTES

1. 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.
2. 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.
3. K. Tatsuta, Y. Amemiya, S. Maniwa, and M. Kinoshita, Tetrahedron Lett., 1980, **21**, 2837.
4. K. C. Nicolaou, S. P. Seitz, and M. R. Ravia, J. Am. Chem. Soc., 1981, **103**, 1222.
5. 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.
6. K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, Tetrahedron, 1986, 42, 3021.
7. When the acid-treatment of **10** was further continued, the MPM group was also cleaved very slowly to drop the yield of **11**.
8. 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 lcatone (**12**) was purified by a column chromatography.
9. G. E. Keck and E. P. Boden, Tetrahedron Lett., 1984, **25**, 265, 1879.
10. Allylmagnesium bromide at -90°C also gave **14**, but the stereoselectivity at C3 was only 4 : 1. Allyltrimethylsilane in the presence of titanium tetrachloride[11] gave **14** highly stereoselectively (60 : 1), but concomitant loss of the MPM group was unavoidable, and the yield of **14** was only 22%.
11. a) H. Sakurai, Pure Appl. Chem., 1982, **54**, 1; b) A. Hosomi and H. Sakurai, Tetrahedron Lett., 1976, 1295.
12. R. U. Remiex and E. von Rudloff, Can. J. Chem., 1955, 33, 1701, 1710.
13. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 1979, **52**, 1989.
14. K. C. Nicolaou, M. R. Pavia, and S. P. Seitz, J. Am. Chem. Soc., 1982, **104**, 2030.
15. The cyclization proceeded more rapidly at 80°C and was completed in 3 h, but the yield of **18** was 30-40%.
16. 1 is a 2 : 1 isomeric mixture with respect to the hemiacetal position.
17. 2 is a 3 : 1 isomeric mixture with respect to the hemiacetal position.
18. 3 is a 2.3 : 1 isomeric mixture with respect to the hemiacetal position.

Received, 18th September, 1989