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[12] Both enantiomers of **6** proved to have an enantiomeric excess of greater than 99% *ee* by derivatization with (*S*)-(+)-methoxy(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl) and assay by ^{1}H NMR spectroscopy (400 MHz) and HPLC (SUMICHIRAL OA-2000): J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549.

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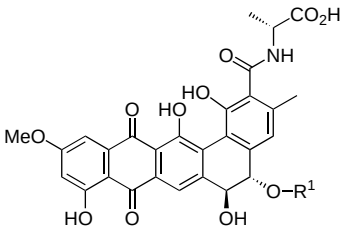
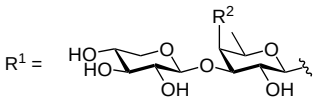
Total Synthesis of Pradimicinone, the Common Aglycon of the Pradimicin–Benanomicin Antibiotics**

Mitsuru Kitamura, Ken Ohmori, Toshihisa Kawase, and Keisuke Suzuki*

The pradimicin–benanomicin antibiotics[1] constitute an emerging class of natural products with a unique structure consisting of a benzo[*a*]naphthacenequinone core, an amino acid, and a disaccharide. The important biological activities shown by these compounds, antifungal and anti-HIV, are attributed to the potentially specific binding to oligosaccharides of fungi or viral surfaces.[1, 2] Stimulated by the unique structure and the significant bioactivities, we initiated a synthetic study of these compounds.[3] Herein, we report the first total synthesis of pradimicinone (benanomicinone, **1**), the common aglycon of these antibiotics, based on the chiral transmission approach.[4]





R^2 = N(Me)H: pradimicin A
R^2 = NH_2: pradimicin C, benanomicin B
R^2 = OH: benanomicin A
R^1 = H
pradimicinone, benanomicinone **1**

Scheme 1 outlines the synthesis plan. Disconnection of the D-alanine moiety from **1** leads to an intact pentacycle, which can presumably be obtained from the simpler tetracyclic haloquinone **II** (X = halogen) by Diels–Alder reaction with siloxydiene **I**.[5] Given that the key pinacol-forming reaction[4] worked well, the diol could be derived from dialdehyde **III**. Formal rotation of the molecule around the biphenyl axis as in **III′** suggests tetracyclic lactone **IV** as a precursor. As another key step, the sterically encumbered biaryl bond could hopefully be formed by the Pd-catalyzed internal C–C bond formation[6] of ester **V**, which in turn could

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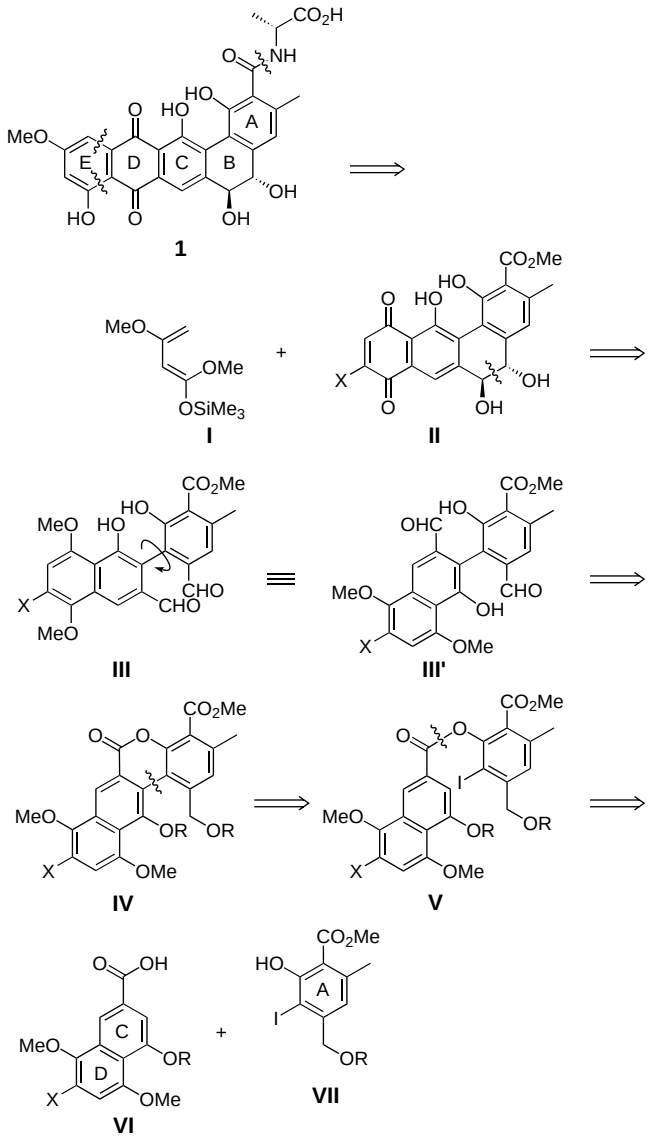
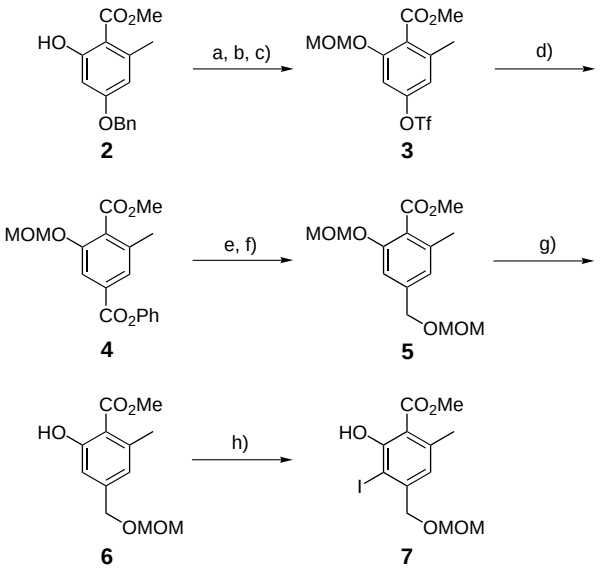


Scheme 1. Retrosynthesis of pradimicinone (benanomicinone, **1**).

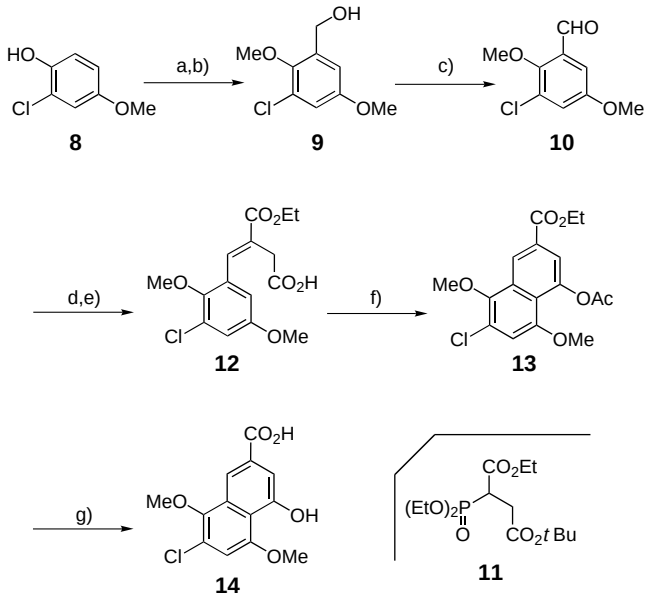
be derived from naphthalene carboxylic acid **VI** and phenol **VII**.

Synthesis of the A ring fragment **7** (Scheme 2) began with the orsellinic acid derivative **2**,[7] which, after conversion into triflate **3** in three steps, was carbonylated in the presence of phenol to afford phenyl ester **4**.[8] Selective reduction of the phenyl ester moiety in **4** was nicely achieved with $NaBH_4$ without touching the methyl ester moiety to give the alcohol, which was protected to give the bis-MOM ether **5**. Acid treatment allowed selective removal of the MOM protection of the phenol to give **6**, and its iodination gave iodophenol **7**.[7]

Synthesis of the CD ring fragment started with the known compound **8** (Scheme 3).[9] Regioselective hydroxymethylation[10] of **8** and methylation of the phenol gave benzyl alcohol **9**, which was oxidized to aldehyde **10**. Wittig–Horner reaction with use of phosphonate **11**[11] gave the corresponding unsaturated ester, whose *tert*-butyl ester was hydrolyzed with acid to give unsaturated acid **12**. Treatment of **12** with acetic anhydride/sodium acetate gave naphtyl acetate **13**,[12] which was hydrolyzed to naphthol **14**.



Scheme 2. Synthesis of the A ring fragment **7**. a) MOMCl, iPr$_2$NEt/CH_2Cl_2, 40 °C, 4 h; b) H_2, $Pd(OH)_2$/EtOAc, 24 h; c) Tf_2O, iPr$_2$NEt/CH_2Cl_2, −78 °C, 30 min (3 steps, 96 %); d) CO, PhOH, Et_3N, $Pd(OAc)_2$, DPPF/DMF, 60–80 °C, 3 h (quant.); e) $NaBH_4$/1,4-dioxane, MeOH, 0 °C → room temperature, 2.5 h (85 %); f) MOMCl, iPr$_2$NEt/CH_2Cl_2, 3 h (88 %); g) CF_3CO_2H/CH_2Cl_2, 0 °C, 3 h (99 %); h) I_2, $Hg(OAc)_2$/CH_2Cl_2, 0 °C, 1 h (99 %). Bn = benzyl; MOM = methoxymethyl; DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene; Tf = trifluoromethanesulfonyl.



Scheme 3. Synthesis of the CD ring fragment **14**. a) $(HCHO)_n$, Me_2AlCl/CH_2Cl_2, 0 °C, 4.5 h; b) MeI, K_2CO_3/acetone, reflux, 13 h (91 %); c) MnO_2/CH_2Cl_2, 40 °C, 17 h (90 %); d) **11**, NaH/THF; e) CF_3CO_2H, H_2O, 1 h; f) Ac_2O, NaOAc, reflux, 1 h (3 steps, 76 %); g) NaOH (aq)/THF, EtOH, 70 °C, 1 h; H_3O^+ (87 %).

Union of the A and CD ring fragments, **7** and **14**, was effected by the ester formation with a water-soluble carbodiimide (Scheme 4). After considerable efforts to optimize the reaction conditions, we were delighted to observe that the Pd-catalyzed internal cyclization of ester **15** proceeded smoothly and regioselectively in the presence of sodium pivaloate[6b] to give tetracycle **16**. Because the product was prone to

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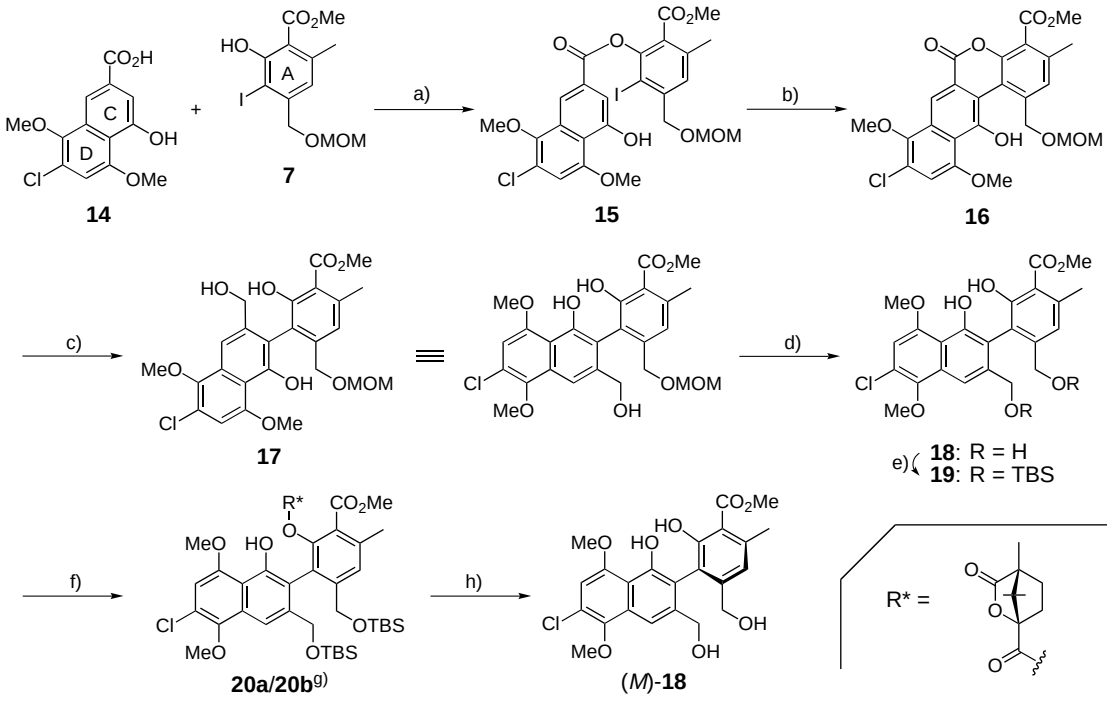

Scheme 4. Synthesis of optically active tetraol (*M*)-**18**. a) EDCI, DMAP/CH_2Cl_2, 3 h (78%); b) $Pd(OAc)_2$ (30 mol%), PPh_3 (60 mol%), *t*$BuCO_2Na$ (3 equiv)/*N*,*N*-dimethylacetamide, 110 °C, 1.5 h; c) $NaBH_4$, THF, MeOH, −40 °C, 3 h (2 steps, 86%); d) 6 M HCl/DME, 50 °C, 3 h (93%); e) TBSCl, imidazole/DMF, 0.5 h (84%); f) (−)-(1*S*,4*R*)-camphanoyl chloride, DMAP, pyridine, 20 h; g) silica gel for separation (**20a** (more polar): 38%, **20b** (less polar): 40%); h) HF (aq)/CH_3CN (aq), 45 min; K_2CO_3/MeOH, 19 h (97% from **20a**). EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP = 4-dimethylaminopyridine; DME = 1,2-dimethoxyethane, TBS = *tert*-butyldimethylsilyl.

hydrolysis during purification on silica gel, we opted to reduce the crude material with $NaBH_4$ to obtain alcohol **17**.[13]

After detachment of the MOM protection, tetraol **18** was resolved in the following manner: The primary hydroxyl groups were protected as TBS ethers to give **19**, which was treated with (−)-(1*S*,4*R*)-camphanoyl chloride to give diastereomeric mono-esters **20**. Separation of the diastereomers by chromatography (SiO_2, hexane/EtOAc 7/3) gave more polar **20a** ($R_f = 0.34$; 38%) and less polar **20b** ($R_f = 0.42$; 40%). The former diastereomer was converted in two steps into enantiopure tetraol (*M*)-**18**, which was employed for the total synthesis.[14]

Scheme 5 shows the key cyclization of enantiopure dialdehyde (*M*)-**21**, derived from tetraol (*M*)-**18**. We were delighted to observe, upon treatment of dialdehyde (*M*)-**21** with SmI_2 (0 °C, THF), the quantitative formation of the *trans*-diol **22** as the sole product,[4] which was proven to be enantiomerically pure.[15] For elaborating the tetracycle to the pentacyclic full carbon skeleton, the diols were protected as diacetate, and oxidation with $Ce(NH_4)_2(NO_3)_6$ (CAN) gave chloroquinone **23** quantitatively. Diels–Alder reaction of **23** with siloxydiene **24**[5a] proceeded in a fully regiocontrolled manner to give the pentacycle, where the chloro group was important in order for the regioselective cycloaddition and the smooth aromatization to occur. Selective hydrolysis of the silyl acetal with acidic SiO_2 followed by elimination of HCl with K_2CO_3 gave naphthacenequinone **25** in 90% yield. Selective removal of the methyl ether groups proximal to the carbonyl groups was nicely achieved by treatment with BCl_3, and saponification gave the fully functionalized aromatic **27**. Condensation of acid **27** with D-alanine methyl ester by using a benzotriazole derivative (BOP) gave pradimicinone methyl ester (**28**) in 80% yield (from **26**); the sample was fully indistinguishable from an authentic specimen.[16, 17] Final saponification gave pradimicinone (**1**), which was again consistent with an authentic specimen.[16, 17]

Currently we are studying the glycosylation of **28**, aiming at the total synthesis. Also under study is the refinement of the synthetic scheme, particularly the asymmetric synthesis without resort to resolution.[13]

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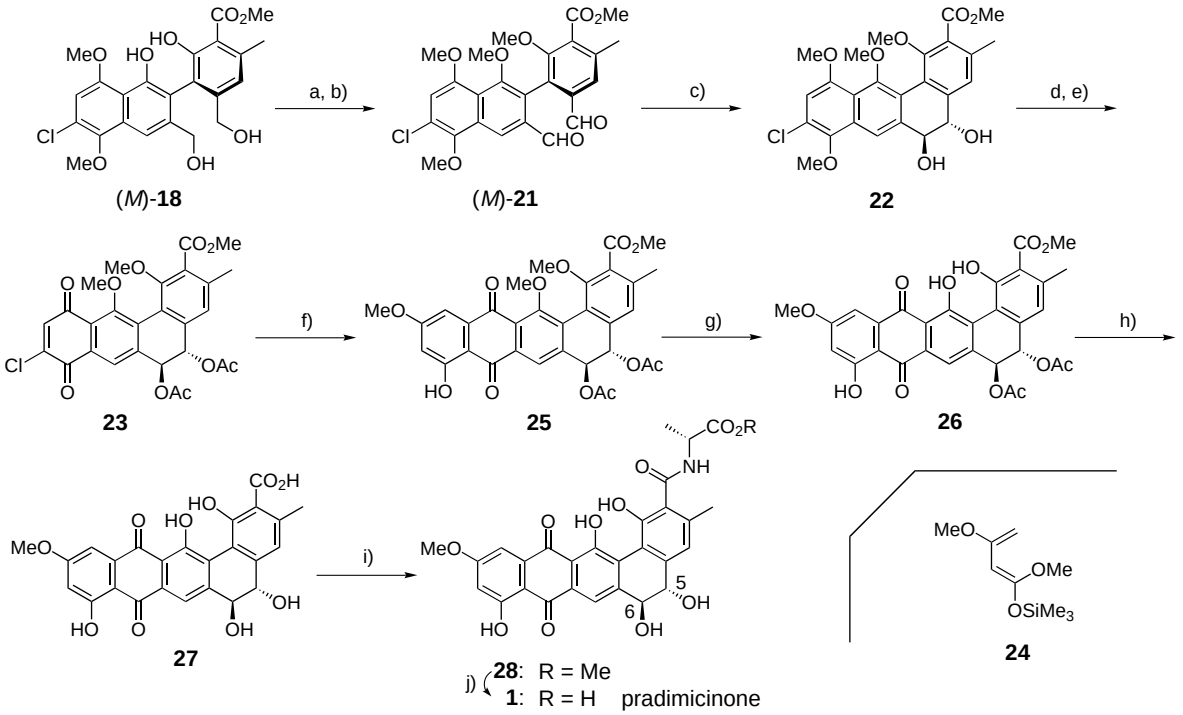

Scheme 5. Total synthesis of pradimicinone (**1**). a) MeI, K_2CO_3/acetone, 40 °C, 11 h (81 %); b) MnO_2/CH_2Cl_2, 24 h (79 %); c) SmI_2/THF, 0 °C, 5 min (quant.); d) Ac_2O, DMAP/pyridine, 0.5 h (quant.); e) $Ce(NH_4)_2(NO_3)_6/CH_3CN$, H_2O, 0 °C, 5 min (quant.); f) **24**/THF, 0 °C → room temperature, 2 h; SiO_2, 12 h, then K_2CO_3/CH_2Cl_2, THF, 4 h (90 %); g) BCl_3/CH_2Cl_2, −10 °C, 30 min (99 %); h) 2 M NaOH (aq), 70 °C, 2 h; H_3O^+; i) D-Ala-OMe · HCl, BOP, Et_3N/DMF, 1.5 h (2 steps, 80 %); j) 0.1 M NaOH, 15 min; H_3O^+ (quant.). BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

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[14] That the diastereomer **20a** has the requisite chirality (*M*) was judged by the CD spectra of the two enantiomers of **18**, derived from **20a** and **20b**, respectively.

[15] Determined by HPLC analysis (DAICEL CHIRALCEL OD-H (25 cm, 0.46 cm diameter), hexane/*i*PrOH 9/1).

[16] Prepared by the degradation of benanomicin A,[1] kindly provided by Meiji Seika, Ltd. The ^{1}H NMR spectra of **28** (and **1**) are highly dependent on concentration, pH, temperature, and other factors, which makes their identification difficult. However, ^{1}H NMR measurement on a mixed sample of synthetic and authentic materials fully coincided.

[17] The same sequence of conversions was also applied to racemic **18**. In the samples of **28** (and **1**) thus obtained, additional peaks in the ^{1}H NMR spectra were observed arising from the 5,6-bis-epimer (relative to the D-alanine moiety).

Enantiomerically Pure Cyclic *trans*-1,2-Diols, Diamines, and Amino Alcohols by Intramolecular Pinacol Coupling of Planar Chiral Mono-Cr(CO)$_3$ Complexes of Biaryls**

Nobukazu Taniguchi, Takeshi Hata, and Motokazu Uemura*

Enantiomerically pure 1,2-diols, diamines, and amino alcohols have found widespread use as chiral ligands in asymmetric reactions.[1] Although a reductive coupling of carbonyl or imine compounds, pinacol coupling, is the most direct way to synthesize 1,2-diols or diamines, highly stereoselective formation of these compounds is problematic.[2] We

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