Total Synthesis

Regio- and Stereocontrolled Total Synthesis of Benanomicin B**

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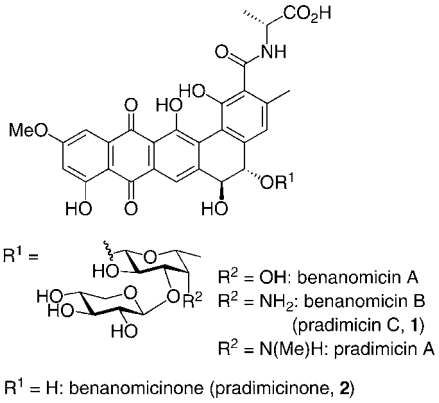
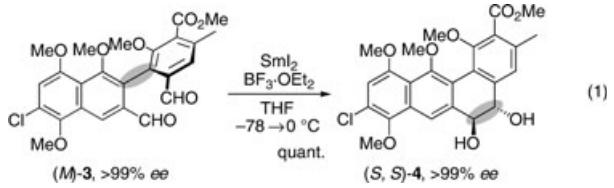
In memory of Tsuguo Mizuochi

Benanomicin/pradimicin antibiotics (BPAs) constitute a class of natural products with a unique structure consisting of a benzo[*a*]naphthacene core, an amino acid, and a disaccharide.[1] Their potent antifungal and anti-HIV activity is attributed to the specific, Ca^{2+}-mediated binding of BPAs to the mannose-rich oligosaccharides presented on the fungi or virus surfaces.[2] Stimulated by these intriguing biological properties and structural novelty, we initiated a synthesis study of BPAs.

In a previous synthesis study we reported the stereoselective synthesis of the common aglycon benanomicinone (pradimicinone, **2**)[3] by exploiting the complete transfer of



the axial chirality into the central chiralities in the pinacol cyclization of biaryl dicarbaldehyde (*M*)-**3** into the *trans*-1,2-diol (*S*,*S*)-**4** [Eq. (1)].



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Two additional issues must be addressed en route to the fully controlled total synthesis (Figure 1): a) introduction of the sugar moiety into the aglycon in a regioselective manner, and b) stereoselective access to the chiral, nonracemic biaryl

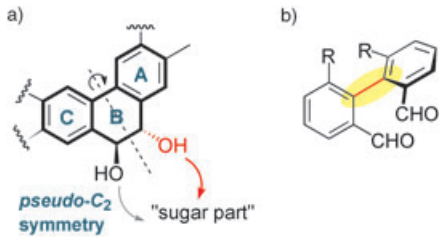
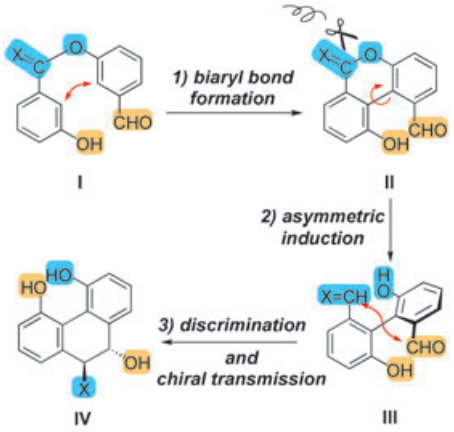


Figure 1. Tactical issues for the total synthesis of BPAs. a) regioselective introduction of the sugar moiety and b) stereocontrol of the axial chirality.

dicarbaldehyde (*M*)-**3**, as the key cyclization precursor. Conjugation of the disaccharide was an intriguing challenge, because of the local pseudo-C_2 symmetry of the 1,2-diol on the B ring. Although a subsidiary issue, the enantioselective synthesis of (*M*)-**3** was a serious bottleneck in the sequence of our synthesis. Herein, we describe clean solutions to these problems, which have culminated in the first total synthesis of benanomicin B (**1**).

Scheme 1 features three key points in our strategy; 1) construction of sterically encumbered biaryl structure **II**



Scheme 1. Overview of our synthesis strategy.

by formation of an internal C–C bond in the tethered derivative **I**; 2) The asymmetric cleavage of the C–O tether in **II** by employing a chiral agent to give the axially chiral biaryl **III**; and 3) Reconnection at two carbonyl groups to give the tricyclic product **IV**. A special requirement for the third stage was the capability of an axial-to-central chirality transfer with concomitant discrimination of the two oxy functions.

The first task was to prepare optically pure **8** as a key precursor for the pinacol cyclization (Scheme 2). We applied an asymmetric ring opening of biaryl lactones pioneered by Bringmann et al. for introducing the biaryl chirality.[4] The substrate for this purpose, the biaryl lactone **7**, was prepared

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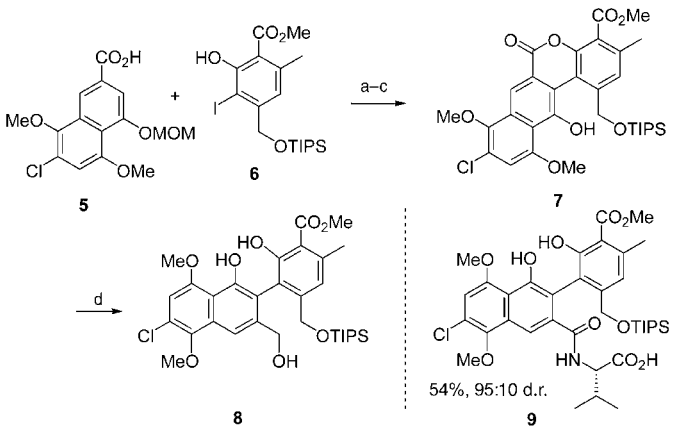
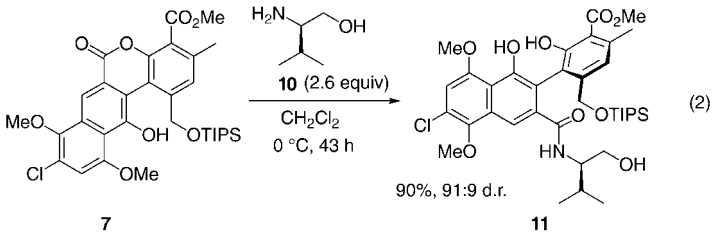


Scheme 2. Preparation and the ring-opening reaction of **7**. a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 25 °C, 20 min (99 %). b) CF_3CO_2H, CH_2Cl_2, 25 °C, 4 h (96 %). c) $Pd(OAc)_2$ (30 mol %), PPh_3 (60 mol %), $tBuCO_2Na$ (3 equiv), DMA, 110 °C, 20 min (60 %). d) L-valine (3.3 equiv), $NaBH_4$ (3.0 equiv), THF, (8 %, 2 % *ee*). DMAP = 4-*N*,*N*-dimethylaminopyridine, DMA = *N*,*N*-dimethylacetamide.

in high yield by the Yamaguchi esterification[5] of carboxylic acid **5**[3b] with phenol **6**[6] followed by the Pd-mediated cyclization.[3b,7]

Initial attempts were centered at the enantioselective reduction of **7** with $NaBH_4$ by using stoichiometric amounts of various chiral modifiers,[8–10] all of which resulted in disappointing enantioselectivities. Unexpectedly, however, we obtained an important hint when L-valine was employed: thus, although the reaction itself was not very effective (8 % yield and 2 % *ee*), a sizable amount of a highly polar by-product was noted, which was proved to be the amide **9**—the direct adduct of the amino acid. An important observation was that amide **9** was highly enriched in one of the diastereomers (90:10 d.r.).

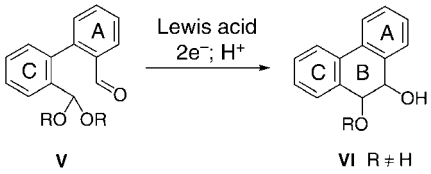
Encouraged by this finding, we decided to pursue a diastereoselective ring-opening reaction, and optimization experiments showed that D-valinol (**10**) was an excellent chiral nucleophile, which afforded amide alcohol **11** in 90 % yield with 91:9 diastereoselectivity [Eq. (2)].[11] Purification of



(2)

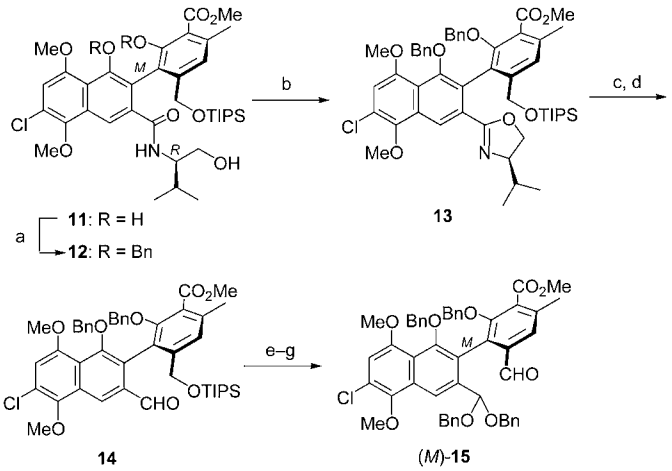
the major diastereomeric product by column chromatography (silica gel, hexane/EtOAc = 1/2) gave single crystals that were suitable for X-ray crystallographic analysis.[12] This analysis proved the compound had the requisite *M* configuration around the biaryl axis.

Now the stage was set for the pivotal stage: construction of the B-ring diol with discrimination of the two oxy functions, for which we planned the semipinacol cyclization of acetal-aldehyde **V** [Eq. (3)]. Activation of the acetal with Lewis acid followed by a net two-electron reduction would hopefully give the mono-masked diol **VI**.[13]



(3)

With this strategy in mind, we envisioned the acetal-aldehyde (*M*)-**15** as the key substrate, which was readily available from the lactone ring-opening product **11** (Scheme 3). After selective benzylation of two of the phenol

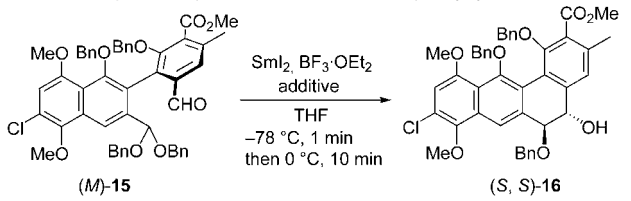


Scheme 3. a) BnBr, Cs_2CO_3, DMF, 0 °C → RT, 70 min (97 %). b) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 20 min (quant.). c) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, RT, 1 h. d) L-Selectride, 0 °C, 20 min; SiO_2, RT, 17 h (96 % from **13**). e) BnOTMS, TMSOTf, toluene, −15 °C, 6 h. f) nBu_4NF, THF, 0 °C, 1 h. g) MnO_2, CH_2Cl_2, RT, 16 h (94 % from **14**). TIPS = triisopropylsilyl; Bn = benzyl, Tf = trifluoromethanesulfonyl, L-selectride = lithium tri-*sec*-butylborohydride, TMS = trimethylsilyl.

groups in **11**, the hydroxyamide moiety in the product **12** was converted into an oxazoline functionality by treatment with PPh_3 and I_2 to give **13** in high yield. After N-methylation of **13**, reduction and exposure to silica gel gave the corresponding aldehyde **14** cleanly in 96 % yield.[14] Conversion of **14** into the corresponding dibenzyl acetal[15] followed by detachment of the silyl group and oxidation afforded the enantiopure acetal-aldehyde (*M*)-**15** for the key cyclization.

The initial attempts at the semipinacol cyclization of (*M*)-**15** by using SmI_2 and $BF_3{\cdot}OEt_2$ suffered from not only modest yields, but also the lack of reproducibility (Table 1).[16] The yields widely fluctuated in the range 10–50 %, even by a slight change in reaction parameters (temperature, reaction time, amounts of reducing agent, and Lewis acid). After extensive effort, we finally found that the presence of a suitable proton source was the key to secure the reproducibility. A clean reaction occurred in the presence of H_2O to give semipinacol

Table 1: Semipinacol cyclization of acetal-aldehyde (*M*)-**15**.[a]



Entry	Additive[b]	Yield [%]	*trans*/*cis*	*ee* [%]
1	none	0–50	>99/<1	>99
2	H_2O	82	>99/<1	>99
3	MeOH	95	>99/<1	>99

[a] 2.5 equiv of SmI_2, 3.0 equiv of $BF_3{\cdot}OEt_2$. [b] 1.0 equiv.

16 in 82% yield; furthermore, methanol proved to be even more effective (95% yield). The reaction proceeded with stereochemical integrity, namely it was *trans*-selective and with complete chiral transmission, and (*M*)-**15** (>99% *ee*) was cleanly converted into (*S*,*S*)-**16** (>99% *ee*).[17]

Having finally overcome two major synthetic hurdles, the stage was set for the introduction of the amino acid and the sugar moieties (Scheme 4). Thus, tetracycle **16** was saponified, and condensed with D-alanine methyl ester by using the benzotriazole derivative BOP to give the corresponding amide **17** in excellent yield. The metallocene-based activator $[Cp_2HfCl_2]/2\,AgOTf$,[18] allowed the coupling of glycosyl fluoride **18**[19] with the acceptor **17** to give the β-glycoside **19** in 72% yield along with its α-anomer in 9% yield.

After oxidation of **19** by $Ce(NH_4)_2(NO_3)_6$ (CAN), the resulting chloroquinone **20** was subjected to a Diels–Alder reaction with siloxydiene **21**,[3b,20] from which pentacycle **22** was obtained in a fully regiocontrolled manner, thus completing the full carbon framework. Removal of the four acyl groups and hydrolysis of the methyl ester moiety in **22** was achieved by treatment with 1M NaOH to give **23**. Final hydrogenolysis of **23** in the presence of aqueous HCl gave benanomicin B hydrochloride (**1**·HCl), which was fully identical with an authentic sample.[21]

In conclusion, the first total synthesis of benanomicin B (**1**) was achieved based on a chiral transmission strategy. Stereoselective incorporation of valinol into lactone **7** effectively gave the axially chiral product **11**. The semipinacol cyclization of acetal-aldehyde (*M*)-**15** successfully provided the semiprotected *trans*-diol (*S*,*S*)-**16**, which allowed the selective introduction of the sugar moiety, thus enabling access to **1**.

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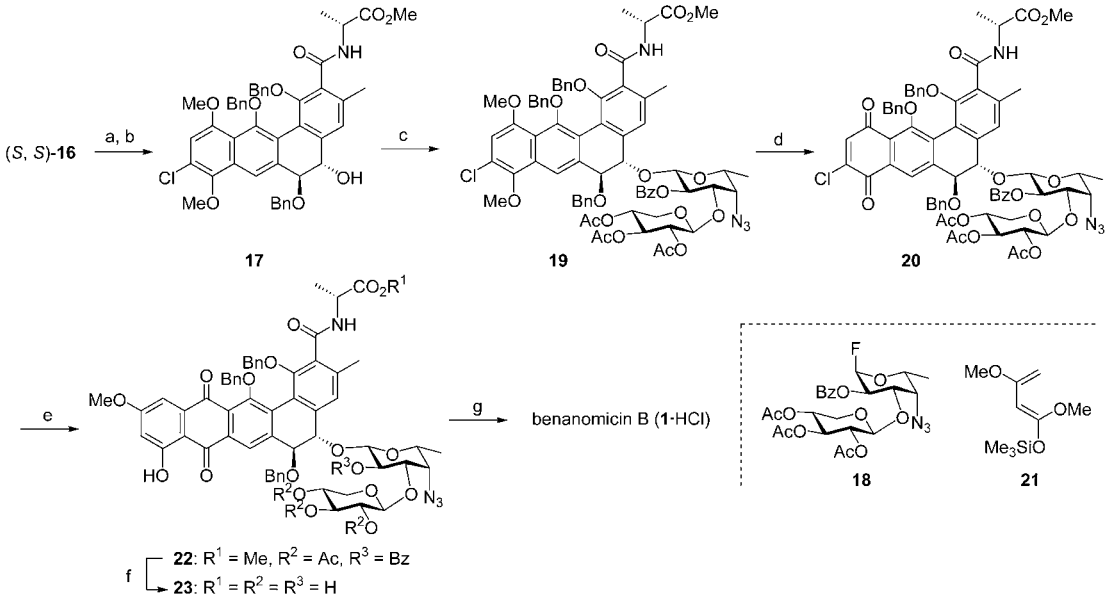

Scheme 4. The final stage toward **1**. a) 5M NaOH, EtOH, in sealed tube, 100°C, 2 h. b) D-Ala-OMe·HCl, BOP, Et_3N, DMF, RT, 1 h (84% from **16**). c) **18**, $[Cp_2HfCl_2]/2\,AgOTf$, 4-Å MS, CH_2Cl_2, −78°C, 20 min then −35°C, 11 h (72% for the β anomer **19**, 9% for the α anomer). d) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0°C, 5 min. e) **21**, THF, RT, 2 h; SiO_2, RT, 12 h; K_2CO_3, CH_2Cl_2, THF, 3 h (74% from **19**). f) 5M NaOH, MeOH, 25°C, 9 h. g) H_2, Pd/C, MeOH, 1M HCl, DMF, 2 h (53% from **22**). D-Ala-OMe = D-alanine methyl ester, DMAP = 4-*N*,*N*-dimethylaminopyridine, DMA = *N*,*N*-dimethylacetamide, BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, Tf = trifluoromethanesulfonyl, MS = molecular sieves, Bz = benzoyl.

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[6] Prepared from the known orsellinic acid derivative, namely, methyl 4-hydroxymethyl-2-methoxymethoxy-6-methylbenzoate,[3b] by a three-step sequence [1) iPr$_3$SiCl, imidazole, DMF; 2) TFA, CH_2Cl_2; 3) $BnMe_3NCl{\cdot}ICl$, $NaHCO_3$, MeOH, CH_2Cl_2 (83 % over 3 steps)].

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[8] Initial attempts at the enantioselective ring opening of **7** were centered on the borane activated by chiral oxazaborolidines,[9] which uniformly led to poor enantioselectivity. Attempts were also made to use $NaBH_4$ with stoichiometric amounts of various chiral compounds, such as L-(+)-tartaric acid diethyl ester,[10a] *N*,*N*-dibenzoylcycteine,[10b] and (*S*)-(−)-1,1′-binaphthol.[10c]

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[11] The diastereomer ratio was assessed by ^{1}H NMR spectroscopic analysis ($CDCl_3$, 400 MHz).

[12] The major diastereomer of **11** gave a single crystal (EtOAc/hexane) suitable for X-ray analysis, which confirmed the stereostructure of **11**. CCDC-262629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[17] The enantiomeric purity of **15** was assessed by HPLC analysis (Daicel Chemical Industries, Ltd, CHIRALPAK AD-H (25 cm, 0.46 cm diameter), hexane/iPrOH 9/1, flow rate 0.5 mL min^{-1}, $t_R = 11.4$ min for the *M* isomer, 15.2 min for the *S* isomer). Also, **16** was analyzed (Daicel Chemical Industries Ltd, CHIRALPAK AD-H (25 cm, 0.46 cm diameter), hexane/iPrOH 8/2, flow rate 0.5 mL min^{-1}, $t_R = 14.2$ min for the *S*,*S* isomer, 23.1 min for the *R*,*R* isomer).

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[21] Although the ^{1}H NMR spectra of free benanomicin B (**1**) are highly dependent on the pH value and temperature, the mixed sample of synthetic/authentic benanomicin B hydrochloride showed fully coincided ^{1}H NMR spectra. Furthermore, all physical data (^{1}H and ^{13}C NMR, IR, HRMS (FAB), $[\alpha]_D$, and m.p.) of the synthetic material were fully identical with those of **1**·HCl.[1b]

