Natural Products Synthesis

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Synthesis of the Pluramycins 2: Total Synthesis and Structure Assignment of Saptomycin B**

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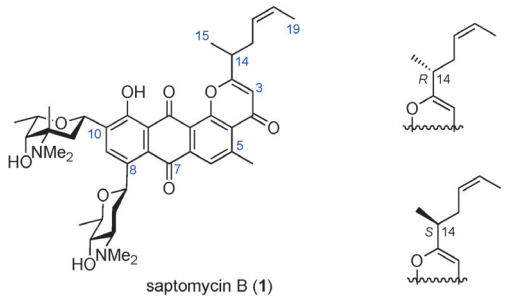
Dedicated to Professor Dieter Seebach and Dr. Shinichi Kondo

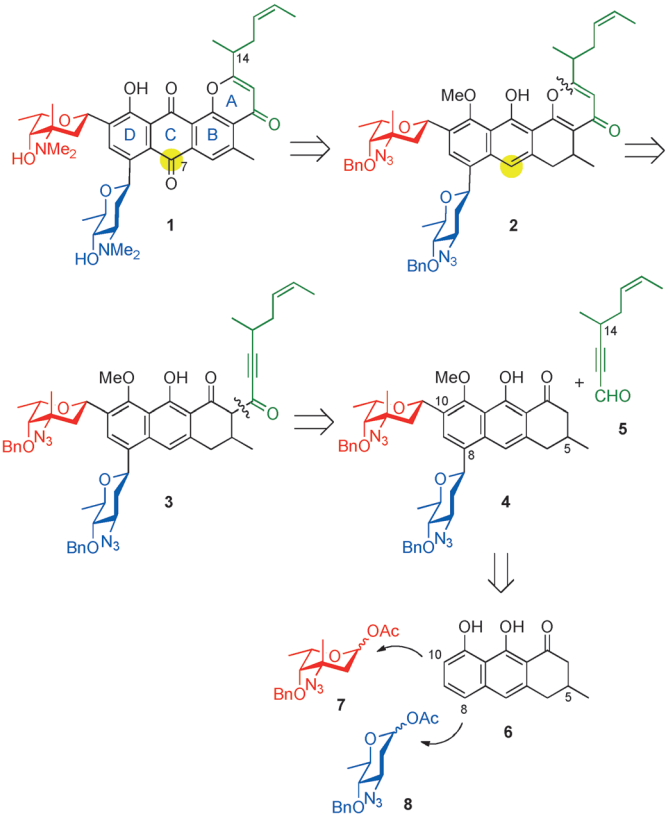
Abstract: *A concise, highly convergent total synthesis of saptomycin B, a member of the pluramycin class of antitumor antibiotics, is reported. The target compound was assembled from four building blocks (a tricyclic platform, two sugars, and an alkynal) in 15% yield through 10 synthetic operations. The key steps included the regioselective installation of two amino sugars (*L*-vancosamine and* D*-angolosamine) on the tricycle and the efficient construction of the tetracyclic skeleton by an aldol reaction followed by formation of the pyranone. The unknown configuration at C14 was assigned as R.*

Saptomycin B (**1**) was isolated from *Streptomyces* sp. HP530 from a soil sample collected in Chiba, Japan, by Sapporo Breweries researchers.[1a] It shows in vitro and in vivo antitumor activity against human and murine tumor cell lines. This compound belongs to the pluramycin family of antibiotics,[2] which share a common bis-*C*-glycoside chromophore with a distinctive six-carbon-atom side chain in which the configuration at C14 was previously unspecified.[1b]



Although this class of natural products has attracted much interest from the synthetic community owing to the intriguing bioactivity and challenging structures, synthetic endeavors had long been hampered until the recent total synthesis of a congener, isokidamycin, by Martin and co-workers.[3] In connection with our long-standing synthetic interest in the aryl *C*-glycosides,[4] we are now pleased to report the first total synthesis of saptomycin B (**1**) and the assignment of the C14 configuration.

The basis of our synthetic plan was the viability of the bis-C-glycosylation of anthrone platforms with rigorous regio- and stereochemical control.[5] Scheme 1 shows our retrosynthetic analysis of **1**. Anthrol **2** was envisaged as the immediate precursor on the assumption of the late-stage introduction of the C7 carbonyl group. We reasoned that the introduction of this carbonyl group at a late stage of the synthesis would be favorable in view of the pronounced photolability of anthra-



Scheme 1. Synthetic plan for saptomycin B (**1**). Bn = benzyl.

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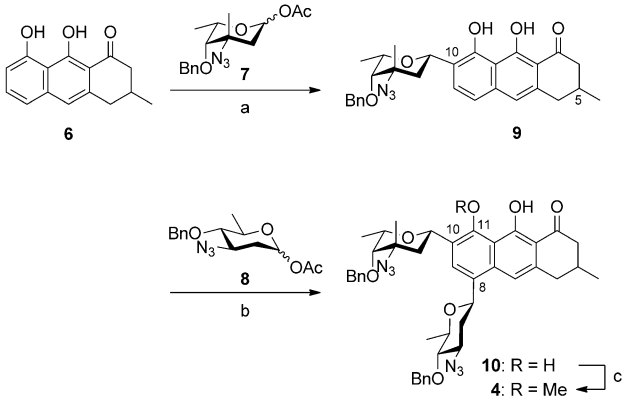
quinone *C*-glycosides.[6] For the sake of simplicity, an azide functional group was selected as the surrogate for both nitrogen functionalities to enable the simultaneous development of the dimethylamino groups.[7] The γ-pyrone in **2** would be accessible from alkynone **3** by 6-*endo* cyclization.[8] Alkynone **3** was dissected into the bis-*C*-glycosyl anthrone **4** and the chiral, nonracemic alkynal **5**, which incorporates part of the A ring and the side chain. We planned to prepare alkynal **5** in both enantiomeric forms for the assignment of the C14 configuration. Finally, the bis-*C*-glycosyl anthrone **4** would be obtained from anthrone **6** by the stepwise installation of two sugar moieties, *N*,*N*-dimethyl-L-vancosamine at C10 and D-angolosamine at C8. The two differences from the model study[5] are: 1) Both glycosyl donors, **7** and **8**,[9] possess azido functionalities as equivalents of the dimethylamino groups, and 2) anthrone **6** has an extra methyl group at C5, which should not be a problem. The successful realization of this synthetic plan is presented below.

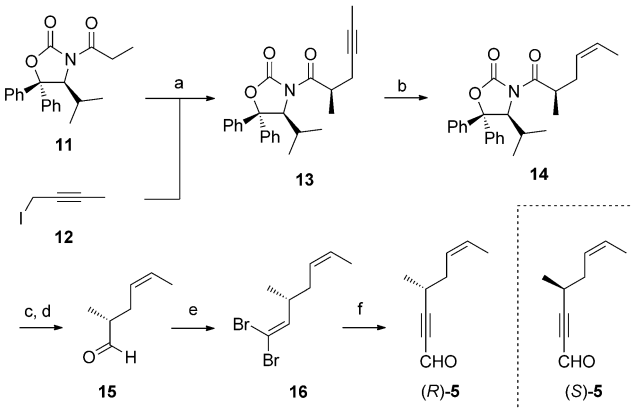
The first stage of the successful synthetic route to **1** was the stepwise, regiocontrolled installation of two amino sugars on the racemic tricycle **6**[10] (Scheme 2). Upon the reaction of



Scheme 2. Bis-C-glycosylation of tricycle **6**: a) $Sc(OTf)_3$ (30 mol%), Drierite, $ClCH_2CH_2Cl$, −30→−10°C, 3 h (82%); b) $Sc(OTf)_3$ (50 mol%), Drierite, $ClCH_2CH_2Cl$, −30→28°C, 12 h (96%); c) CH_3I, NaH, TBAI, DMF, 0°C, 5 h (99%). DMF = *N*,*N*-dimethylformamide, TBAI = tetrabutylammonium iodide.

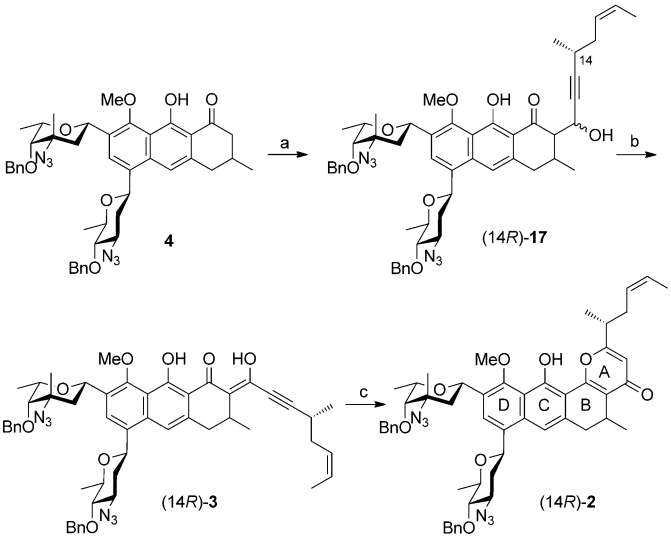
the L-vancosaminyl acetate **7** with anthrone **6** (2 equiv) in the presence of $Sc(OTf)_3$ (30 mol%; Drierite, 1,2-dichloroethane, −30→−10°C, 3 h), the mono-C-glycoside **9** was obtained in 82% yield as a 1:1 mixture of diastereomers at C5. The regioselectivity of *C*-glycoside formation was assigned by an NOE study, and the β configuration was established on the basis of ^1H NMR spectroscopy ($J_{1,2}$).[11] The *C*-glycoside **9** was combined with the D-angolosaminyl acetate **8** (2 equiv; $Sc(OTf)_3$, Drierite, −30→28°C, 12 h) to give the bis-*C*-glycoside **10** in 96% yield. The anomeric configurations of the *C*-glycoside moieties were both β.[11] Methylation of **10** with CH_3I and NaH (DMF, catalytic TBAI) protected the C11 phenol group to give anthrone **4**.

Alkynal **5** was prepared in both enantiomeric forms by asymmetric alkylation with the Seebach auxiliary (Scheme 3).[12] The lithium enolate derived from (*S*)-**11** was combined with propargyl iodide **12** to give amide **13** in 95% yield (d.r. > 99:1). The newly formed stereogenic center was verified by X-ray crystallographic analysis.[11] Semihydrogenation of **13** gave the *Z* alkene **14** (93% yield). Next, removal of the chiral auxiliary in **14** ($LiAlH_4$) and oxidation with TPAP[13] gave the corresponding aldehyde **15**, which was subjected to a Corey–Fuchs reaction[14] to give dibromide **16** in 84% overall yield in three steps. The treatment of **16** with *n*BuLi followed by DMF gave alkynal (*R*)-**5** (99% *ee*) in 80% yield.[15] For comparative purposes, the enantiomeric aldehyde (*S*)-**5** was prepared from (*R*)-**11** by the same protocol.

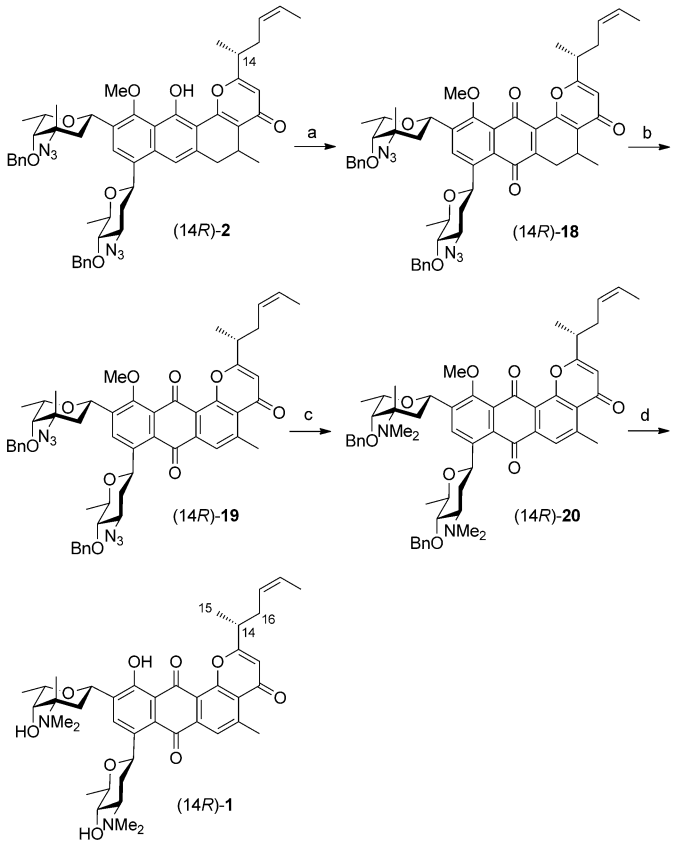


Scheme 3. Synthesis of the enantiomeric alkynals (*R*)- and (*S*)-**5**: a) LDA, **12**, THF, −78°C→RT, 10 h (95%, d.r. > 99:1); b) H_2 (balloon), Lindlar catalyst, quinoline, EtOAc, room temperature, 5 h (93%); c) $LiAlH_4$, Et_2O, 0°C, 1 h; d) TPAP (5 mol%), NMO, MS (4 Å), CH_2Cl_2, 0°C→RT, 2 h; e) CBr_4, PPh_3, Zn, CH_2Cl_2, room temperature, 3 h (84% from **14**); f) *n*BuLi, THF, −78→−20°C; DMF, −78→0°C, 2 h (80%). LDA = lithium diisopropylamide, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, MS = molecular sieves.

The bis-*C*-glycoside **4** was treated with LDA (−78→0°C) and combined with the *R* alkynal **5** at −78°C to afford aldol



Scheme 4. Formation of the A ring: a) LDA, −78→0°C, 1 h, then (*R*)-**5**, −78°C, 1 h (89%); b) IBX, DMSO, CH_2Cl_2, room temperature, 3 h (81%); c) K_2CO_3, MeOH, room temperature, 6 h (96%). IBX = 2-iodoxybenzoic acid, DMSO = dimethyl sulfoxide.



Scheme 5. Completion of the total synthesis of (14*R*)-**1**: a) PhI(OCOCF$_3$)$_2$, H$_2$O, MeCN, 0 °C, 1 h; b) DBU, MeCN, 0 °C, 30 min, then air, room temperature, 1 h (67% from (14*R*)-**2**); c) PMe$_3$, CH$_2$Cl$_2$, room temperature, 4 h; 37% aqueous HCHO, NaBH$_3$CN, AcOH, MeCN, 0 °C→RT, 2 h (65%); d) BBr$_3$, CH$_2$Cl$_2$, −90 °C, 1 h (62%). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

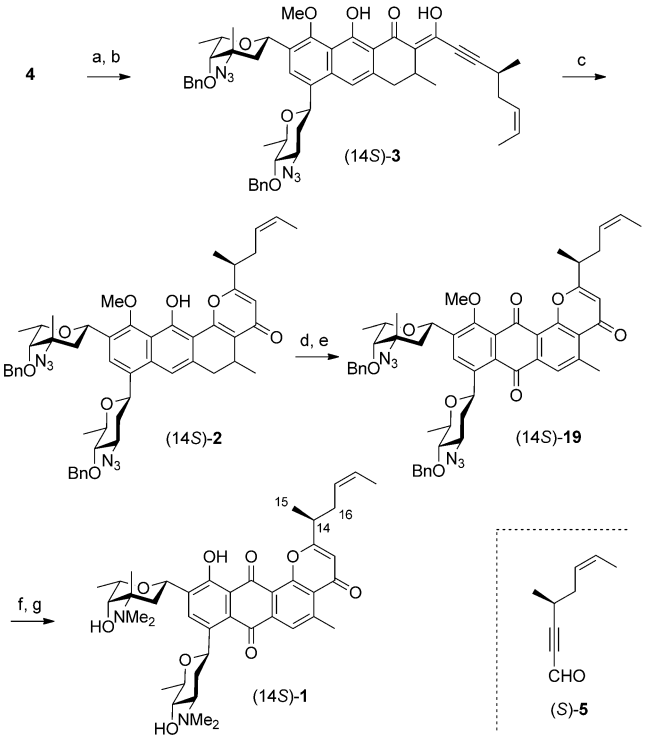
(14*R*)-**17** in 89% yield (Scheme 4). The oxidation of (14*R*)-**17** with IBX[16] gave 1,3-diketone (14*R*)-**3** in 81% yield without affecting the aromatic system. The ^{1}H NMR spectrum suggested that (14*R*)-**3** mostly existed in the tautomeric form shown. The key A-ring annulation occurred cleanly in 96% yield upon the treatment of (14*R*)-**3** with K$_2$CO$_3$ (MeOH, room temperature). On this occasion, the 5-*exo* cyclization did not compete.[8] The use of methanol as the solvent was crucial to attain a reasonable reaction rate.

Scheme 5 shows the final stages of the synthesis. In anticipation of the potential photoinduced degradation, all manipulations hereafter were performed in brown glassware. Tetracycle (14*R*)-**2** was carefully oxidized (PhI(OCOCF$_3$)$_2$, aqueous MeCN, 0 °C)[17] to the corresponding naphthoquinone (14*R*)-**18**, which was not isolated, but treated directly with DBU at 0 °C. Exposure to air then afforded anthraquinone (14*R*)-**19** in 67% overall yield.[18] Quinone (14*R*)-**19** was reasonably stable at room temperature when stored in the dark. Next, the two azides in (14*R*)-**19** were simultaneously converted into *N*,*N*-dimethylamino groups via the corresponding iminophosphoranes (PMe$_3$, CH$_2$Cl$_2$, 0 °C→RT), which underwent subsequent reductive dimethylation (formalin, NaBH$_3$CN, AcOH, 0 °C→RT) to give diamine (14*R*)-**20** in 65% yield.[6] Finally, the two benzyl groups and the methyl protecting group were detached by careful treatment with BBr$_3$ at −90 °C (CH$_2$Cl$_2$, 1 h) to give the final product (14*R*)-**1**. The low temperature was critical at this stage; substantial decomposition of **1** occurred even at −78 °C.

For the purification of **1**, besides shielding from light, two additional precautions were needed. The dimethylamino group in the angolosamine moiety was highly prone to oxidation by air to the corresponding *N*-oxide. Whereas chromatography on regular silica gel led to considerable loss of material, aminopropyl-modified silica gel was effective.[19] Chromatography (preparative TLC on aminopropyl-modified SiO$_2$; toluene/methanol 9:1) in the dark under argon cleanly gave (14*R*)-**1** in 62% yield as a reddish-orange powder.

The 14*S* congener of **1** was also synthesized from **4** and the enantiomeric alkynal, (*S*)-**5**. The synthesis proceeded uneventfully to give the final product in similar overall yield (Scheme 6). Careful purification (see above) gave (14*S*)-**1** as a reddish-orange powder.

The synthetic samples (14*R*)-**1** and (14*S*)-**1** were clearly distinguishable by ^{1}H NMR spectroscopy (600 MHz, CD$_3$OD),[11] thus proving their stereochemical integrity: No epimerization at C14 occurred during any of the synthetic transformations for both epimers, which were ready for comparison with the natural product.



Scheme 6. Synthesis of (14*S*)-**1**: a) LDA, THF, −78→0 °C, 1 h, then (*S*)-**5**, −78 °C, 1 h (90%); b) IBX, DMSO, CH$_2$Cl$_2$, room temperature, 3 h (84%); c) K$_2$CO$_3$, MeOH, room temperature, 6 h (89%); d) PhI(OCOCF$_3$)$_2$, H$_2$O, MeCN, 0 °C, 1 h; e) DBU, MeCN, 0 °C, 30 min, then air, room temperature, 1 h (59% from **3**); f) PMe$_3$, CH$_2$Cl$_2$, room temperature, 4 h; 37% aqueous HCHO, NaBH$_3$CN, AcOH, MeCN, 0 °C→RT, 2 h (64%); g) BBr$_3$, CH$_2$Cl$_2$, −90 °C, 1 h (73%).

Unfortunately, the natural sample is no longer available, and the only evidence available for comparison was the ^{1}H NMR spectrum ($CDCl_3$), kindly provided by Professor Abe. In $CDCl_3$, however, the peaks of (14*R*)- and (14*S*)-**1** tended to coincide, and even the ^{13}C NMR spectra (150 MHz) overlapped completely. Upon close inspection of the ^{1}H NMR spectrum, fortunately, a small but clear difference was noted in the chemical shifts of two hydrogen atoms near the stereogenic center in question (14-H and one of 16-CH_2); comparison of these signals enabled us to conclude that the configuration at C14 in the natural product is *R*.[11]

From a synthetic point of view, the route described is enabled by the efficient assembly of four building blocks, that is, tricycle **6**, glycosyl donors **7** and **8**, and alkynal **5**, in 10 synthetic operations to provide saptomycin B (**1**) in 15% chemical yield. This convergent route would enable access to various pluramycin-related natural/non-natural compounds. Further studies are currently under way.

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[19] NH_2-modified silica plates from Merck were used (HPTLC silica gel NH_2 F_{254s}).

