HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 1240 - 1253. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 8th August, 2014, Accepted, 10th September, 2014, Published online, 18th September, 2014
DOI: 10.3987/COM-14-S(K)106

TOWARD THE PLURAMYCINS: ROUTE EXPLORATION FROM DIHYDROXYANTHRONE TRICYCLIC PLATFORM TO AN AGLYCON, SAPTOMYCINONE B

Kei Kitamura,[1] Yoshio Ando,[1] Yoshihiko Maezawa,[1] Takashi Matsumoto,[2]* and Keisuke Suzuki[1]*

[1]Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan. [2] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
e-mail: ksuzuki@chem.titech.ac.jp, tmatsumo@toyaku.ac.jp

Dedicated to Professor Isao Kuwajima on occasion of his 77th birthday

Abstract – In connection with the total synthesis of the pluramycin-class antibiotics, we recently found dihydroxyanthrone derivatives to be suitable platforms for the installation of bis-*C*-glycosides. As a basis for the total synthesis, we explored viable routes to construct the characteristic tetracyclic skeleton. By setting saptomycinone B (**5**) as a model target, anthrone **6** was combined with the side chain moiety to access key intermediate **9**, from which two viable routes have been developed. One of the routes has been exploited in the realization of our recent total synthesis of saptomycin B (**4**).

INTRODUCTION

The pluramycins constitute a family of antibiotics featured by the polyketide-derived anthrapyranotrione chromophore containing two amino *C*-glycosides.[1] Pluramycin A (**1**), reported in 1956 by Umezawa and Kondo et al., is the first member of this class, which was isolated from a terrestrial *Streptomyces* sp.[2] Since then, many related compounds have appeared, including kidamycin (**2**),[3] hedamycin (**3**),[4] and saptomycin B (**4**)[5] (Figure 1). The potent antitumor activity exhibited by several of these compounds has

proven to be relevant to specific DNA alkylation, where the two amino sugars play a significant role in sequence recognition.[6]

In addition to such biological importance, the challenging structural features have attracted significant interests from the synthetic communities. Two major synthetic challenges include, (1) selective construction of the highly oxygenated tetracycle, and (2) installation of two *C*-glycosides, D-angolosamine at C8 and *N*,*N*-dimethyl-L-vancosamine at C10.

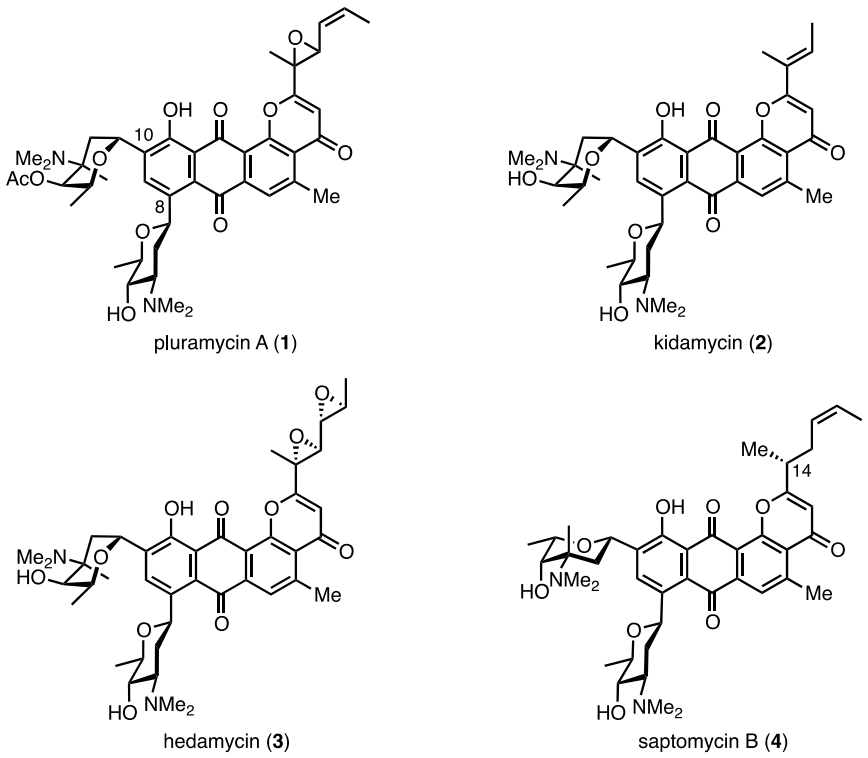


Figure 1. Pluramycin-class antibiotics

Initially described here are overviews of the previous aglycon synthesis,[7] bis-*C*-glycoside synthesis[8] and our own approaches.

Previous aglycon synthesis: Various strategies have emerged for the construction of the tetracyclic aglycon.[7] Figure 2 shows a rough classification of these approaches by focusing on the last ring to be formed. The type-1 approach is featured by the formation of the pyranone (the A-ring) at the final stage onto the B/C/D tricyclic system. This approach has been applied to the syntheses of kidamycinone,[7a,b] espicufolin,[7d] indomycinones,[7e–g] and the related aglycons.[7h–k] Alternatively, the type-2 approach features the annulation of the D-ring onto the A/B/C ring system by Diels–Alder reaction.[7c,l] Unfortunately, these approaches are not strategically compatible with the installation of the bis-*C*-glycoside structure as stated below, and have not been exploited in the synthesis of the full structure of natural products.

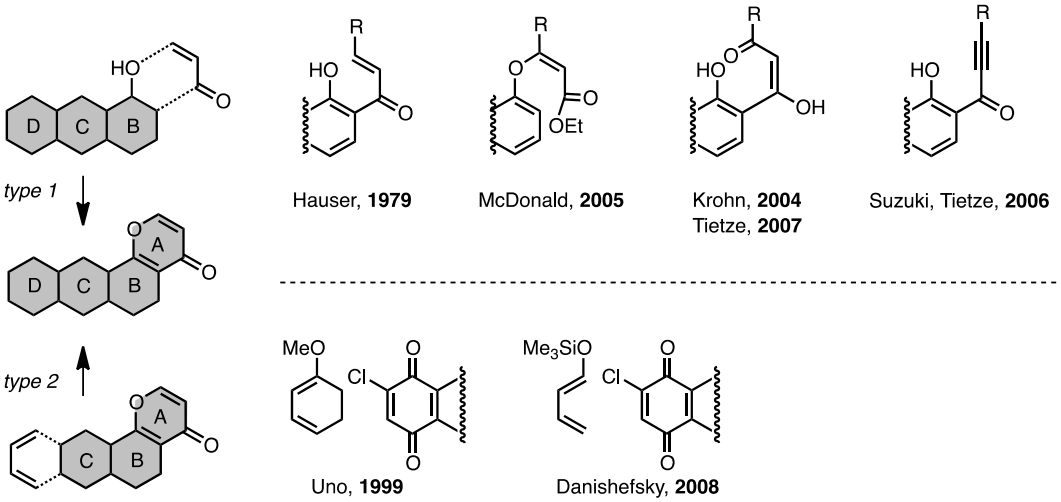


Figure 2. Classification of aglycon synthesis

Bis-C-glycoside synthesis: Studies toward the installation of the two *C*-glycosides have also been reported, which are roughly classified into two categories, *early* or *late*, by the timing of the bis-*C*-glycosylation (Figure 3).[8] The early-stage approach uses mono- or bicyclic compounds as *C*-glycosyl acceptors. For example, we reported resorcinol derivative **I** as a monocyclic platform, enabling the installation of two sugars by repeated *O*→*C* glycoside rearrangement.[8d] Parker used naphthoquinone **II** as a bicyclic platform to accept two glycal anions followed by dienone–phenol rearrangement.[8a] Unfortunately, such approaches inevitably need long subsequent steps, and to date, no total syntheses using this strategy have been completed.

By contrast, the late-stage approach, if viable, is ideal in terms of its convergency and simplicity. However, the critical difficulty is the regiochemical control, e.g., McDonald used a pyranoanthracene **IV** as a glycosyl acceptor with an extra phenol to secure the regiochemical control and enhance the reactivity.[8c] Unfortunately, yields were low, and further conversion to the target has not been reported.

Martin employed a unique approach in his first synthesis of isokidamycin,[9] through the *C*-glycosylation of a furan derivative followed by intramolecular benzyne cycloaddition and the late-stage introduction of the second sugar.

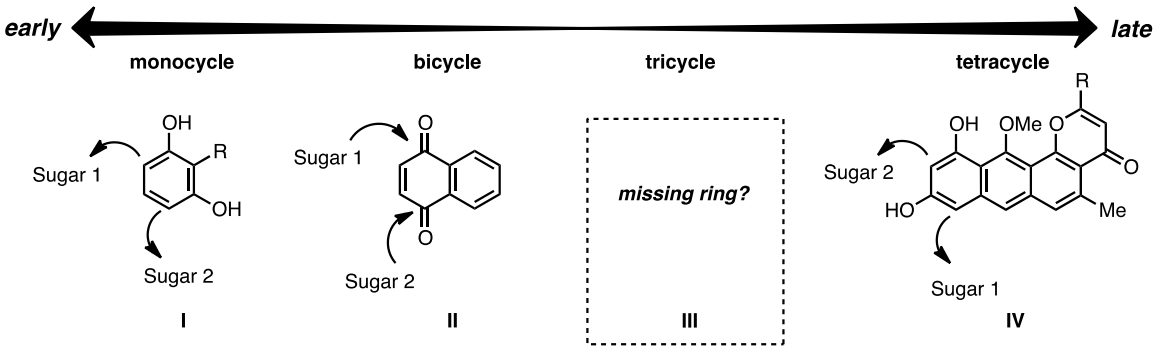
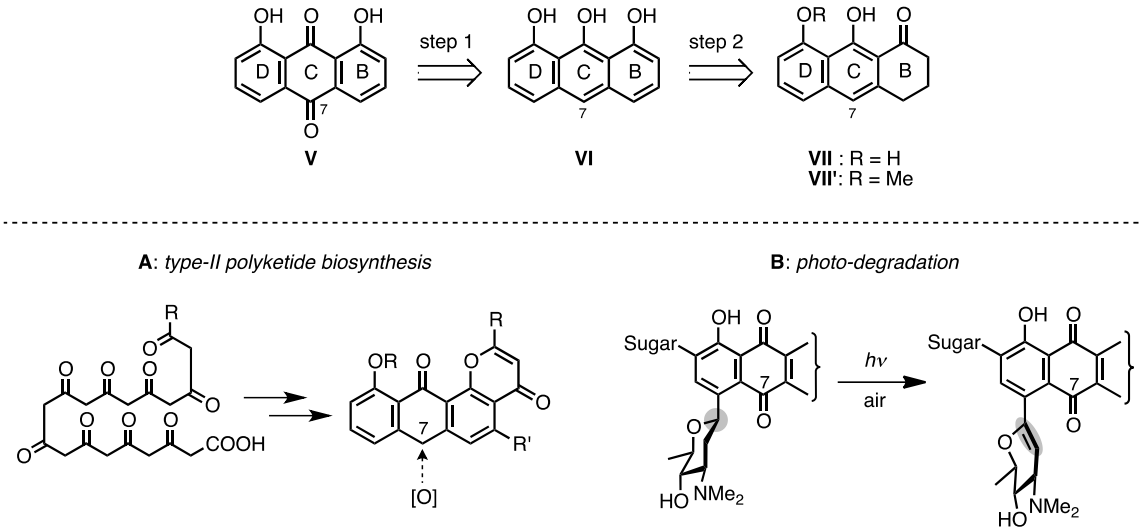


Figure 3. Platforms for installing bis-*C*-glycoside

Our previous study and a turning point: Our synthetic endeavor toward the pluramycins had been unfruitful for a long time. Despite resorcinol derivative **I** (vide supra) allowing installation of the two requisite *C*-glycosides, the corresponding advanced intermediates were unexpectedly resistant to seemingly trivial transformations. After long struggle, we decided to explore any other timings for the bis-*C*-glycosylation. It occurred to us that the *tricycle* was a "missing ring" in the synthetic strategies explored to date, and indeed, this naive idea gave us a breakthrough.

Among the possible tricycles envisioned, we focused particularly on dihydroxyanthrones **VII** and **VII'** as potential platform to install bis-*C*-glycoside by the following two-step deduction (Scheme 1). Starting from the intact B/C/D ring system **V**, we envisaged to remove the C7 carbonyl in a retrosynthetic fashion, leading to anthracene **VI** (step 1). This idea was inspired by the type-II polyketide biosynthesis (see **A**, Scheme 1),[1,11] which, we hoped, would benefit us in two ways: (1) Anthracene **VI**, π-electron rich, would provide good opportunities for the installation of the two sugars by electrophilic aromatic substitutions (cf. quinone **V**). (2) This retrosynthetic strategy involves the late stage installation of the C7 carbonyl, which would help minimizing the possible photo-degradation associated with the pluramycins (see **B**, Scheme 1).[1a,12] Furthermore, the B-ring in **VI** was modified to *non-aromatic* as in **VII** and **VII'** (step 2), expecting two additional benefits, (1) any undesired *C*-glycosylation at the B-ring could be avoided, and (2) the ketone could function as a handle to form the A-ring.



Scheme 1. Design of tricyclic platforms for the installation of bis-*C*-glycoside

Pleasingly, tricycles **VII** and **VII'** turned out to be excellent platforms for the *installation of two sugars in complementary manners* (Figure 4).[10] Phenol **VII** allowed initial *C*-glycosylation to occur at C10 followed by C8. On the other hand, methyl ether **VII'** enabled the first *C*-glycosylation at C8, and after

demethylation, at C10. In each case, $Sc(OTf)_3$ served as a specifically effective Lewis acid, enabling stepwise, regioselective *C*-glycosylations.[13]

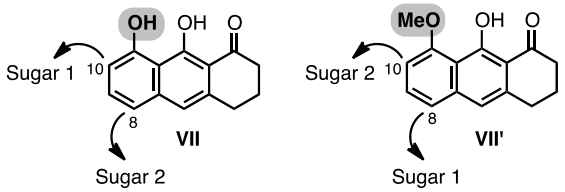


Figure 4. Complementary bis-*C*-glycosylation

With this promising basis, we re-launched the total synthesis, where prerequisite was to find the efficient conversion of tricyclic structures **VII** or **VII'** into the complete tetracyclic structure. Since the chemical reactivities and selectivities are often different with/without the *C*-glycoside(s) as pointed out previously, the conversion should be *truly efficient*. We selected saptomycin B (**4**) as our first target, and accordingly explored the possible method of converting tricycle **6**, through the union with synthon **VIII**, into its aglycon, saptomycinone B **(5)**. Herein, we disclose the results of our investigation along these lines.

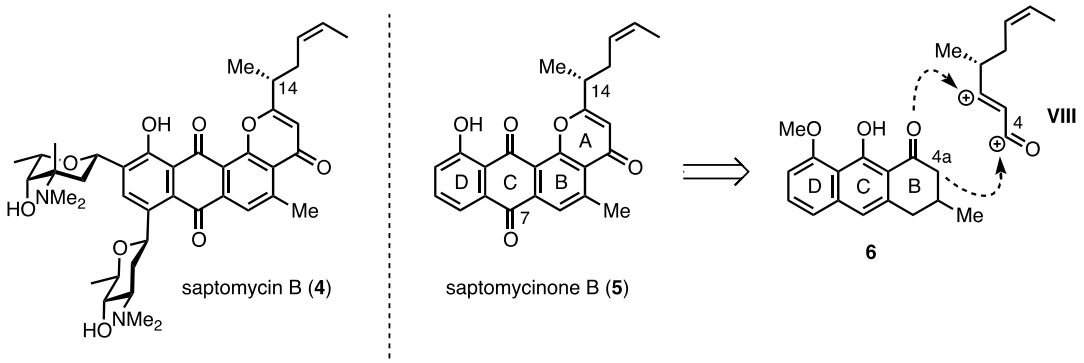
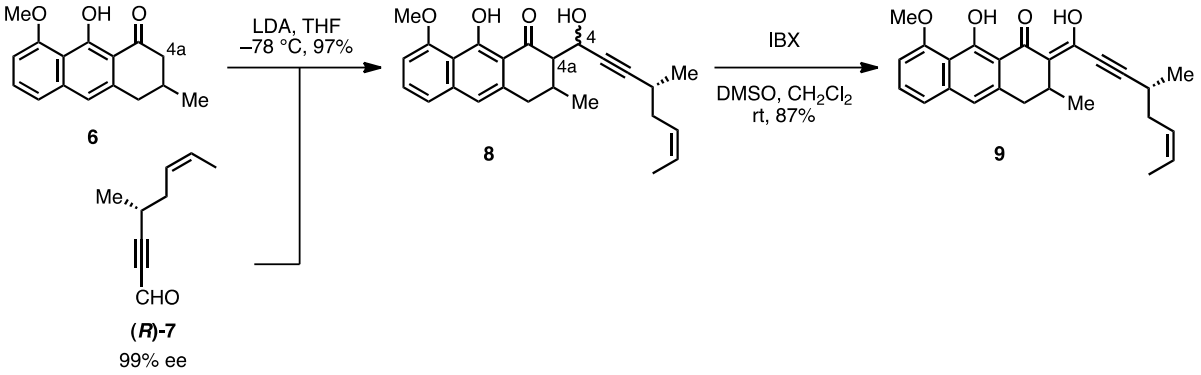


Figure 5. Toward aglycon **5** from tricycle **6**

RESULTS AND DISCUSSION

As the initial step toward annulation of the A-ring, we connected the C4–C4a bond by aldol reaction (Scheme 2). Tricycle **6**[14] was enolized (LDA, THF, –78 ºC, 0.5 h)[14b] and allowed to react with chiral, enantiopure (*R*)-aldehyde **7**,[15] giving aldol **8** in 97% yield as a diastereomeric mixture. Discovery of the most effective reagents and conditions for the subsequent oxidation of **8** required some experimentation: TPAP–NMO[16] was ineffective, giving many unidentified products. Activated MnO_2 led to slow reaction even at 80 ºC, giving only low yield of **9**. Dess–Martin periodinane[17] (CH_2Cl_2, 5 °C, 2 h) brought more success, albeit with the unsatisfactory yield of **9** (67%). Finally, IBX[18] proved to be the reagent of choice. While the reaction in EtOAc (reflux, 11 h) gave **9** (28%) accompanied by pyranone **17** (29%), a mixed

solvent (DMSO, CH_2Cl_2) brought about smooth reaction to give 1,3-diketone **9** in 87% yield. Note that the major tautomeric form of **9** is depicted.



Scheme 2. Full carbon skeleton

At this stage, many possibilities were present en route to **5**, differing in the order of performing three missions outlined below (Figure 6). Let us designate the shorthand for our missions as A, B, C; construction of the A-ring (Mission A), aromatization of the B-ring (Mission B), and oxygenation of the C-ring (Mission C).

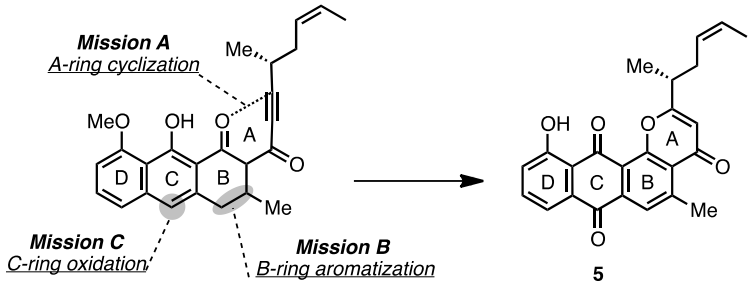
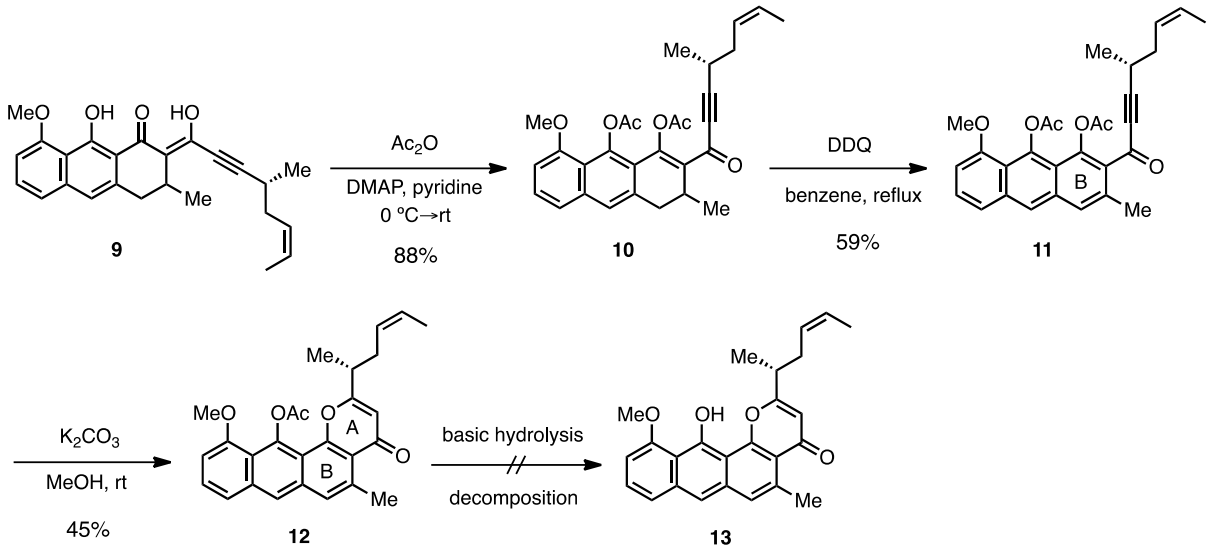


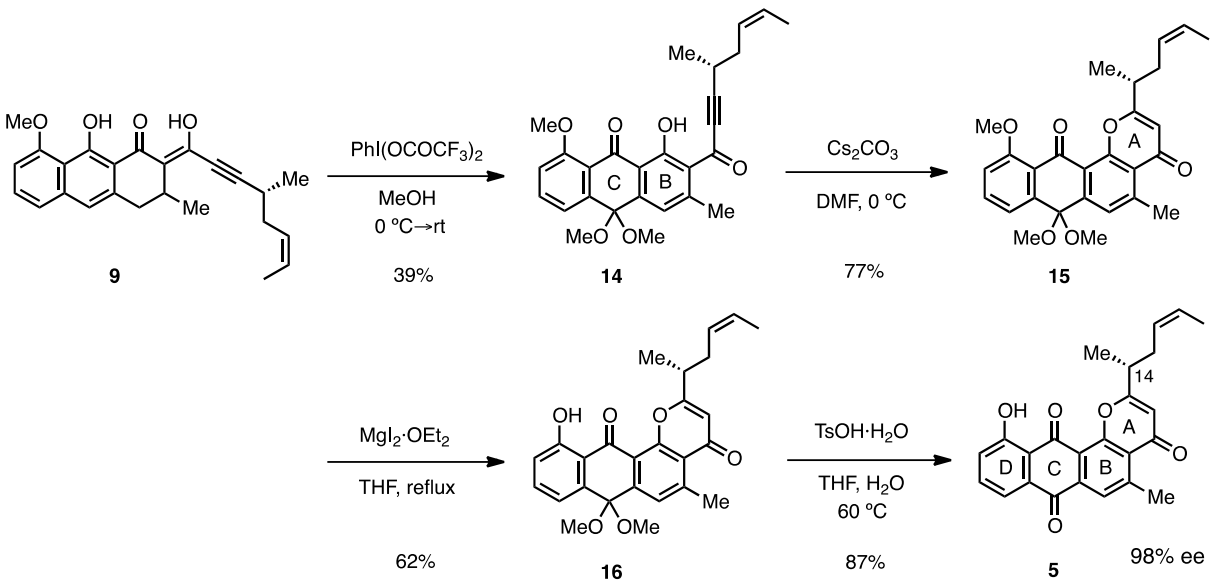
Figure 6. Three missions en route to **5**

Route 1 (Mission B→A→C): *To explore the feasibility of the first B-ring aromatization*, diketone **9** was acetylated to give **10** (Scheme 3). Oxidation of **10** with DDQ (benzene, reflux, 15 h) effected the dehydrogenation at the B-ring, giving anthracene **11** in 59% yield. At this stage, the A-ring cyclization was carried out under basic conditions (K_2CO_3, MeOH), where anthrapyranone **12** was obtained in 45% yield. The next task was removal of the acetyl group in **12**, in preparation for the oxidation of the C-ring. However, basic hydrolysis of **12** caused decomposition exclusively under various conditions, and thus, this route was abandoned.



Scheme 3. Route 1

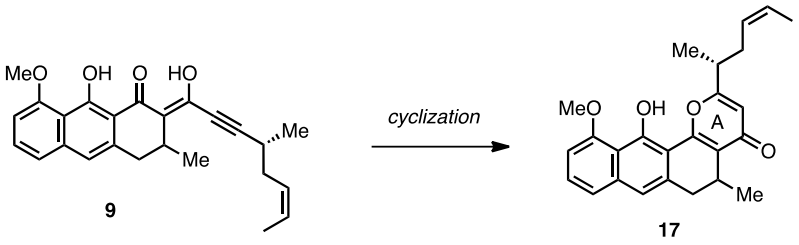
Route 2 (Mission C→B→A): *Initial oxidation of the C-ring in* ***9*** was attempted with $PhI(OCOCF_3)_2$ in aq. acetonitrile, which gave numerous products (TLC assay). In anhydrous methanol, however, the reaction gave the quinone acetal **14** in 39% yield. It should be noted that the B-ring underwent aromatization under these conditions. Subsequent A-ring cyclization of **14** was effected by Cs_2CO_3 (DMF, 0 °C, 40 min) to give **15** in 77% yield. For removal of the methyl-protecting group in **15**, several Lewis acids were screened. While BBr_3 only led to decomposition, $MgI_2 \cdot OEt_2$[19] nicely worked for the purpose to afford **16** in 62% yield. Finally, hydrolysis of the dimethyl acetal by TsOH (aq. THF, 60 °C, 4.5 h) gave the target **5** in 87% yield. The *ee* of **5** was assessed by chiral HPLC to be 98%, confirming that the overall conversion proceeded without loss of the stereochemical integrity of the C14 chiral center.



Scheme 4. Route 2

Route 3 (Mission A→B→C): Finally addressed was *the prior cyclization of the A ring* (Table 1). Organic bases, such as Et_2NH and DMAP, gave γ-pyrone **17** in moderate yield (runs 1, 2). *t*-BuOK gave no desired product (run 3). In the case of Cs_2CO_3 in DMF, **17** was obtained in 23% yield (run 4). Screening of several polar solvents showed MeOH to be most effective, giving **17** in 85% yield (runs 5–7). In MeOH, K_2CO_3 was also effective, giving γ-pyrone **17** in 89% yield (run 8). In all runs, only the 6-*endo* cyclization was observed, and no furanone derived from the 5-*exo*-cyclization was detected.

Table 1. Cyclization of diketone **9**

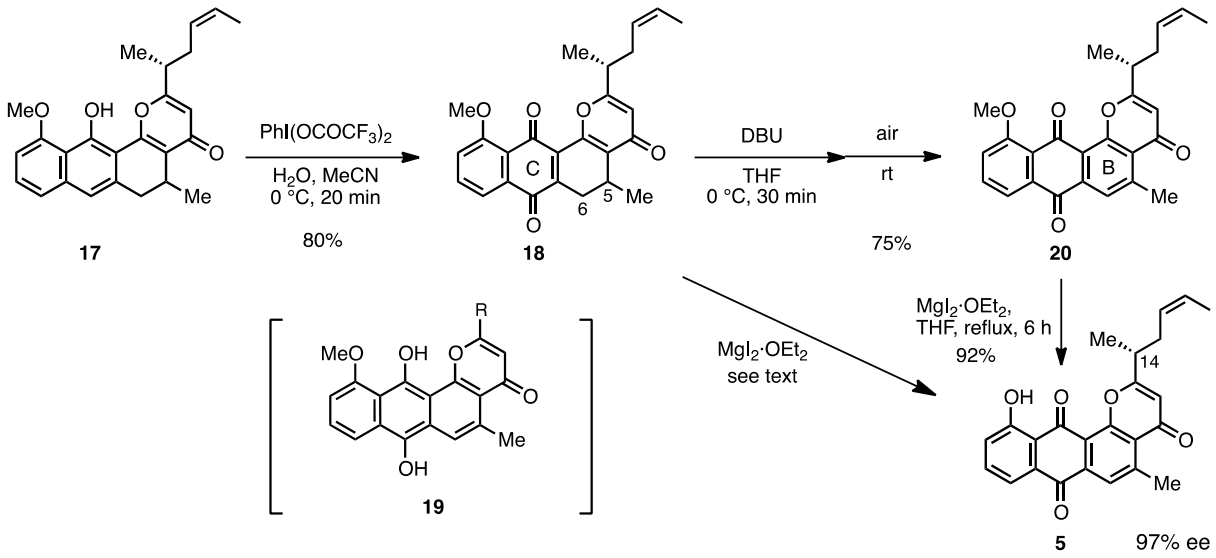


run	reagent	solvent	temp. [ºC]	time [h]	yield [%]
1	$HNEt_2$	EtOH	60	10.5	61
2	DMAP	DMF	50	10.5	42
3	*t*-BuOK	THF	rt	19	dec.
4	Cs_2CO_3	DMF	50	68	23
5	Cs_2CO_3	MeCN	50	43	56
6	Cs_2CO_3	acetone	40	7	63
7	Cs_2CO_3	MeOH	rt	29	85
8	K_2CO_3	MeOH	rt	6.5	89

Tetracycle **17** was oxidized by $PhI(OCOCF_3)_2$ in aq. acetonitrile[20] (0 ºC, 20 min) to give naphthoquinone **18** in 80% yield (Scheme 5). Treatment of **18** with DBU (0 ºC, 30 min)[21] followed by exposure to air gave anthraquinone **20** in 75% yield from **18**. This conversion is rationalized by the following processes. DBU (pK_a of the corresponding conjugate acid = 12) brought about the crisscross bis-enolization by abstracting the protons at C6 and then at C5, generating dihydroquinone **19**, and its mono- and/or dianionic forms. Upon quenching and exposure to air, spontaneous oxidation gave pyranoanthraquinone **20**. The final step was removal of the methyl protection, for which the combination of $AlCl_3$ and *n*-Bu_4NI (MeCN, reflux) was effective, giving the desired compound **5** in 63% yield. $MgI_2 \cdot OEt_2$ was even more effective, affording **5** in 92% yield (THF, reflux, 6 h). The enantiomeric excess of **5** was 97%, as assessed by chiral HPLC analysis. However, prolonged reaction caused partial epimerization of the C14 stereogenic center.

It is interesting to note an observation in this relevance. Upon treatment of naphthoquinone **18** with $MgI_2 \cdot OEt_2$ (toluene, 0 °C), anthraquinone **20** was observed on TLC. This suggested that a similar

crisscross bis-enolization stated above occurred with of $MgI_2 \cdot OEt_2$, and the TLC spot of **20** was produced by aerial oxidation upon the spotting operation. Upon further stirring at higher temperature (80 ºC, 2.5 h), the demethylation proceeded in one-pot, giving aglycon **5** in 72% yield, which may provide a convenient protocol in total synthesis. At this moment, however, it has not been optimized and mechanistically unclear. The entity that undergoes the demethylation is unknown whether the magnesio derivative of hydroquinone **19** or quinone **20** derived from the unintentional contamination of oxygen.



Scheme 5. Route 3

CONCLUSION AND FUTURE OUTLOOK

We have described the development of two viable routes to convert anthrone **6** into saptomycinone B (**5**), differing in the order of elaboration of A, B, C-rings. One of these routes has secured as basis for our recent total synthesis of saptomycin B (**4**).[15] Finally, it is worth noting further challenges in these tough synthesis. The first is the high lability of the natural products toward light and oxygen: we really had a hard time in the final stages of the synthesis of **4**. Although basic protocols were established for purification and isolation, still great precaution must be paid.[1a,12] The last challenging issue is the α-selective construction of vancosamine *C*-glycoside, which is the less favorable anomer, easily undergoing isomerization into the favorable β-anomer.[1a,3c] Further work is ongoing, seeking for the general synthesis of the pluramycins, including members bearing α-*C*-glycoside linkage.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Specially Promoted Research (No. 23000006) from Japan Society for the Promotion of Science (JSPS). We are grateful to Ms. Mhairi Matheson for careful proofreading.

EXPERIMENTAL

General. Melting points were measured on a Yanako MP-500 instrument. Optical rotations were determined on a Jasco DIP-1000 polarimeter. Infrared spectra were recorded on a Jasco IR-Report-100, or a Perkin Elmer Spectrum 100 spectrometer. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectra were recorded on a Perkin Elmer 100 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III 600 (600 MHz) spectrometer, and chemical shifts (δ) are expressed in ppm using tetramethysilane as an internal standard (TMS = 0.0 ppm). Elemental analyses were recorded on an Elementar vario MICRO cube analyzer. High performance liquid chromatography analyses were performed using a Jasco CO-2060 apparatus. Low-resolution mass spectra (MS) were obtained with Shimadzu GCMS-QP 5050A spectrometer, and high-resolution MS from micrOTOF-Q II (Bruker Daltonics). Column chromatography was performed using silica gel 60N (Spherical, neutral, 63–210 μm; Kanto Chemical). Ethereal solvents (anhydrous; Kanto Chem. Co., Inc.) were used as received. Dichloromethane, acetonitrile, methanol, and DMSO were distilled prior to use by standard protocols. Other reagents were used without further purification as received.

9-Hydroxy-2-[(*R*,*Z*)-1-hydroxy-4-methyloct-6-en-2-yn-1-yliden]-8-methoxy-3-methyl-3,4-dihydroanthracen-1(2*H*)-one (9): To a THF solution of LDA (0.156 M, 34.0 mL, 5.30 mmol) was added anthrone **6**[14] (546 mg, 2.13 mmol) in THF (15 mL) at –78 ºC. After stirring at 0 ºC for 1 h, the mixture was re-chilled to –78 ºC, to which was slowly added aldehyde **7** (867 mg, 6.37 mmol) in THF (20 mL), and the stirring was continued for 30 min. After quenching by adding sat. NH_4Cl soln, the products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (silica gel, hexane/acetone = 8/2) gave aldol **8** (812 mg, 97%, diastereomers) as yellow solids. Aldol **8** was dissolved in DMSO (18 mL) and CH_2Cl_2 (36 mL) and chilled to 0 ºC, to which was added IBX (1.19 g, 4.25 mmol). After stirring (2.5 h, room temp.), the reaction was stopped by adding sat. aq. $NaHCO_3$. After extraction with EtOAc (×3), the combined organic extracts were washed with brine, 10% aq. $Na_2S_2O_3$ and brine, and dried (Na_2SO_4). Concentration in vacuo and purification (SiO_2 column chromatography, hexane/acetone = 9/1) gave ketone **9** (700 mg, 87%) as an orange oil: IR (neat) 2959, 2931, 2222, 1627, 1583, 1554, 1448, 1395, 1321, 1263, 1245, 1167, 1098, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.05 (d, 3H, J = 7.0 Hz), 1.29 (d, 1.5H, J = 7.0 Hz), 1.30 (d, 1.5H, J = 7.0 Hz), 1.65 (d, 3H, J = 6.8 Hz), 2.28–2.39 (m, 2H), 2.68 (brd, 1H, J = 15.0 Hz), 2.76–2.82 (m, 1H), 3.14 (dd, 1H, J = 15.0, 5.3 Hz), 3.21–3.27 (m, 1H), 4.01 (s, 3H), 5.46–5.52 (m, 1H), 5.59–5.65 (m, 1H), 6.80 (d, 1H, J = 7.9 Hz), 6.95 (s, 1H), 7.20 (d, 1H, J = 8.1 Hz), 7.45 (dd, 1H, J = 8.1, 7.9 Hz), 14.28 (s, 1H, OH), 14.46 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.0, 19.7, 19.8, 20.15, 20.17, 27.09, 27.13, 30.0, 33.3, 35.7, 56.2, 75.2, 105.7, 106.2, 110.8, 115.4, 117.4, 117.9, 119.8, 126.5, 126.6, 126.7, 126.8, 130.8, 135.9, 140.3, 156.5, 159.7, 164.8, 192.4; HRMS

(ESI-TOF) calcd for $C_{25}H_{27}O_4$ ($[M+H]^+$) *m/z* 391.1904, found *m/z* 391.1902; Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.91; H, 6.78.

2-[(*R*,*Z*)-Hex-4-en-2-yl]-12-hydroxy-11-methoxy-5-methyl-5,6-dihydroanthra[1,2-*b*]pyran-4-one (17): To a soln of ketone **9** (288 mg, 0.738 mmol) in MeOH (26 mL) was added K_2CO_3 (413 mg, 2.99 mmol) at 0 ºC, and the mixture was stirred for 6.5 h at room temp. After quenching with 1 M aq. HCl, the products were extracted with EtOAc (×3). Combined organic extracts were washed with brine, and dried (Na_2SO_4). Concentration in vacuo and purification (SiO_2 column chromatography, hexane/acetone = 7/3) gave pyranone **17** (257 mg, 89%) as a pale yellow oil: IR (neat) 3327, 2967, 1645, 1585, 1495, 1455, 1421, 1364, 1266, 1235, 1178, 1091, 980, 925, 854, 802, 752, 723, 634 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.99 (d, 3H, *J* = 7.0 Hz), 1.34 (d, 1.5H, *J* = 7.0 Hz), 1.36 (d, 1.5H, *J* = 7.0 Hz), 1.58 (d, 1.5H, *J* = 6.7 Hz), 1.61 (d, 1.5H, *J* = 6.7 Hz), 2.35–2.44 (m, 1H), 2.57–2.66 (m, 1H), 2.71–2.77 (m, 2H), 3.07–3.13 (m, 1H), 3.44–3.50 (m, 1H), 4.12 (s, 3H), 5.38–5.45 (m, 1H), 5.52–5.59 (m, 1H), 6.216 (s, 0.5H), 6.222 (s, 0.5H), 6.81 (d, 1H, *J* = 7.6 Hz), 7.13 (s, 1H), 7.33 (d, 1H, *J* = 8.1 Hz), 7.37 (dd, 1H, *J* = 8.1, 7.6 Hz), 10.35 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.78, 12.80, 16.87, 16.93, 17.4, 17.7, 24.1, 24.2, 31.60, 31.62, 36.10, 36.11, 38.75, 38.82, 56.5, 104.7, 109.6, 111.68, 111.73, 114.7, 118.6, 118.7, 121.3, 125.9, 126.2, 126.3, 127.1, 127.7, 137.1, 137.4, 153.97, 154.00, 157.1, 159.1, 170.9, 178.6; HRMS (ESI-TOF) calcd for $C_{25}H_{27}O_4$ ($[M+H]^+$) *m/z* 391.1904, found *m/z* 391.1905; Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.79; H, 6.41.

2-[(*R*,*Z*)-Hex-4-en-2-yl]-11-methoxy-5-methyl-5,6-dihydro-4*H*-anthra[1,2-*b*]pyran-4,7,12 trione (18): To pyranone **17** (25.1 mg, 64.2 μmol) in MeCN (2 mL) and H_2O (23 μL, 1.3 mmol) was added $PhI(OCOCF_3)_2$ (56.1 mg, 130 μmol) at 0 ºC. After stirring (20 min, 0 ºC), the reaction was quenched by adding sat. aq. $NaHCO_3$. The products were extracted with CH_2Cl_2 (×3), and the combined organic extracts were washed with brine, and dried (Na_2SO_4). Removal of the solvents in vacuo and purification (SiO_2 column chromatography, hexane/acetone = 8/2) gave quinone **18** (20.9 mg, 80%) as a yellow oil: IR (ATR) 2971, 2933, 1644, 1586, 1471, 1419, 1368, 1307, 1273, 1214, 1066, 954, 925, 861, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.06 (d, 3H, *J* = 7.1 Hz), 1.32 (d, 1.5H, *J* = 7.0 Hz), 1.35 (d, 1.5H, *J* = 7.0 Hz), 1.60 (d, 1.5H, *J* = 7.1 Hz), 1.62 (d, 1.5H, *J* = 7.1 Hz), 2.33–2.43 (m, 1H), 2.52–2.64 (m, 2H), 2.74–2.82 (m, 1H), 3.13 (brd, 1H, *J* = 18.6 Hz), 3.43–3.49 (m, 1H), 4.02 (s, 3H), 5.36–5.42 (m, 1H), 5.53–5.60 (m, 1H), 6.22 (s, 1H), 7.33 (d, 1H, *J* = 8.3 Hz), 7.68 (dd, 1H, *J* = 8.3, 7.6 Hz), 7.75 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.8, 12.9, 17.45, 17.47, 17.7, 22.8, 26.5, 31.59, 31.60, 38.5, 38.6, 56.7, 112.5, 112.6, 118.29, 118.30, 119.0, 121.0, 126.5, 126.6, 126.7, 126.8, 129.45, 129.46, 134.0, 134.4, 134.6, 143.5, 154.8, 159.5, 172.3, 172.4, 177.9, 179.7, 184.3; HRMS (ESI-TOF) calcd for $C_{25}H_{25}O_5$ ($[M+H]^+$) *m/z* 405.1697, found *m/z* 405.1698; Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.00; H, 6.19.

2-[(*R*,*Z*)-Hex-4-en-2-yl]-11-methoxy-5-methyl-4*H*-anthra[1,2-*b*]pyran-4,7,12 trione (20): To quinone **18** (155 mg, 0.383 mmol) in THF (8 mL) was added DBU (287 μL, 1.92 mmol) at 0 ºC. After stirring (0.5 h, 0 ºC), the reaction was quenched by 1 M aq. HCl. The products were extracted with CH_2Cl_2 (×3), and the combined organic extracts were washed brine, and dried (Na_2SO_4). Concentration in vacuo and purification (SiO_2 column chromatography, hexane/acetone = 8/2) gave anthraquinone **20** (116 mg, 75%) as orange powders: Mp 177.5–178.2 ºC; $[\alpha]_D^{30}$ –6.2 (*c* 0.17, $CHCl_3$); IR (ATR) 2973, 2928, 1670, 1646, 1587, 1464, 1443, 1381, 1329, 1302, 1278, 1225, 1188, 1074, 1038, 968, 949, 849, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.43 (d, 3H, *J* = 6.9 Hz), 1.61 (d, 3H, *J* = 6.7 Hz), 2.50 (ddd, 1H, *J* = 14.3, 7.2, 7.0 Hz), 2.72 (ddd, 1H, *J* = 14.3, 7.1, 7.0 Hz), 2.90 (ddq, 1H, *J* = 7.0, 7.0, 6.9 Hz), 2.97 (s, 3H), 4.04 (s, 3H), 5.42 (ddd, 1H, *J* = 10.8, 7.2, 7.1 Hz), 5.55 (dq, 1H, *J* = 10.8, 6.7 Hz), 6.21 (s, 1H), 7.36 (d, 1H, *J* = 8.3 Hz), 7.69 (dd, 1H, *J* = 8.3, 7.6 Hz), 7.87 (d, 1H, *J* = 7.6 Hz), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.8, 17.7, 23.9, 31.5, 38.7, 56.7, 110.8, 118.5, 119.3, 122.6, 123.6, 124.4, 126.4, 126.5, 126.8, 134.4, 134.5, 135.0, 147.2, 155.9, 159.6, 172.6, 179.6, 180.6, 183.2; LRMS (EI-MS) *m/z* calcd for $C_{25}H_{22}O_5$ [M^+] 402; found: 402, 348, 295 (base peak); HRMS (ESI-TOF) Calcd for $C_{25}H_{23}O_5$ ([M+H]$^+$) *m/z* 403.1540, found *m/z* 403.1549; Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.56; H, 5.52.

Saptomycinone B (5): To a soln of anthraquione **20** (12.7 mg, 31.5 μmol) in THF (0.8 mL) was added $MgI_2 \cdot OEt_2$ (0.2 M in Et_2O, 0.80 mL, 0.16 mmol) at 0 ºC. After stirring (6 h, 80 ºC), the reaction was quenched by adding sat. aq. $NaHCO_3$. The products were extracted with EtOAc (×3), and the combined organic extracts were washed by brine, 10% aq. $Na_2S_2O_3$, brine, and dried (Na_2SO_4). Removal of the solvents in vacuo and purification (SiO_2 column chromatography, hexane/acetone = 85/15) gave **5** (11.3 mg, 92%) as orange powders: Mp 141–147 ºC ($CHCl_3$/hexane); $[\alpha]_D^{20}$ –24 (*c* 0.10, $CHCl_3$); IR (ATR) 2975, 2926, 1674, 1648, 1578, 1458, 1448, 1374, 1315, 1259, 1207, 1159, 1083, 1011, 914, 839, 790, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.44 (d, 3H, *J* = 6.8 Hz), 1.60 (dd, 3H, *J* = 6.8, 1.5 Hz), 2.51 (ddd, 1H, *J* = 14.3, 7.1, 7.0 Hz), 2.73 (ddd, 1H, *J* = 14.3, 7.2, 7.0 Hz), 2.86 (ddq, 1H, *J* = 7.0, 7.0, 6.8 Hz), 3.02 (s, 3H), 5.38–5.44 (m, 1H), 5.53–5.59 (m, 1H), 6.24 (s, 1H), 7.36 (dd, 1H, *J* = 8.3, 1.0 Hz), 7.67 (dd, 1H, *J* = 8.3, 7.5 Hz), 7.82 (dd, 1H, *J* = 7.5, 1.1 Hz), 8.05 (s, 1H), 12.94 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.9, 17.6, 24.2, 31.6, 39.0, 111.2, 116.8, 119.3, 119.7, 125.3, 125.5, 126.5, 126.6, 126.7, 132.3, 135.9, 136.3, 149.7, 156.7, 162.6, 172.4, 179.2, 182.0, 187.2; UV (MeOH) λ_{max} nm (ε) 240 (47000), 268 (24000), 417 (8000); LRMS (EI-MS) *m/z* calcd for $C_{24}H_{20}O_5$ [M^+] 388; found: 388, 334, 281 (base peak); HRMS (ESI-TOF) calcd for $C_{24}H_{21}O_5$ ([M+H]$^+$) *m/z* 389.1383, found *m/z* 389.1395; Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.04; H, 5.47; HPLC [CHIRALPAK® AD-H (Daicel) φ 0.46×25 cm, hexane:isopropyl alcohol = 9:1, 1.0 mL/min, 30 ºC, 254 nm] t_R: 9.0 min for **5** (10.8 min for *ent*-**5**).

REFERENCES AND NOTES

1. (a) U. Séquin, *Fortschr. Chem. Org. Naturst.,* 1986, **50**, 57; (b) T. Bililign, B. R. Griffith, and J. S. Thorson, *Nat. Prod. Rep.*, 2005, **22**, 742.
2. (a) K. Maeda, T. Takeuchi, K. Nitta, K. Yagishita, R. Utahara, T. Osato, M. Ueda, S. Kondo, Y. Okami, and H. Umezawa, *J. Antibiot. Ser. A*, 1956, **9**, 75; (b) S. Kondo, M. Miyamoto, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1977, **30**, 1143; (c) M. Ceroni and U. Séquin, *Helv. Chim. Acta,* 1982, **65**, 302.
3. (a) N. Kanda, *J. Antibiot.,* 1971, **24**, 599; (b) M. Furukawa, A. Itai, and Y. Iitaka, *Tetrahedron Lett.,* 1973, **14**, 1065; (c) M. Furukawa and Y. Iitaka, *Tetrahedron Lett.,* 1974, **15**, 3287.
4. (a) U. Séquin, C. T. Bedford, S. K. Chung, and A. I. Scott, *Helv. Chim. Acta,* 1977, **60**, 896; (b) U. Séquin, *Tetrahedron,* 1978, **34**, 761; (c) M. Zehnder, U. Séquin, and H. Nadig, *Helv. Chim. Acta,* 1979, **62**, 2525.
5. (a) N. Abe, Y. Nakakita, T. Nakamura, N. Enoki, H. Uchida, and M. Munekata, *J. Antibiot.,* 1993, **46**, 1530; (b) N. Abe, N. Enoki, Y. Nakakita, H. Uchida, T. Nakamura, and M. Munekata, *J. Antibiot.,* 1993, **46**, 1536.
6. (a) M. R. Hansen and L. H. Hurley, *Acc. Chem. Res.*, 1996, **29**, 249; (b) B. Willis and D. P. Arya, *Curr. Org. Chem.*, 2006, **10**, 663.
7. kidamycinone: (a) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.,* 1979, **101**, 1628; (b) Z.-B. Fei and F. E. McDonald, *Org. Lett.,* 2005, **7**, 3617; espicufolin: (c) H. Uno, K. Sakamoto, E. Honda, and N. Ono, *Chem. Commun.,* 1999, 1005; (d) L. F. Tietze, K. M. Gericke, R. R. Singidi, and I. Schuberth, *Org. Biomol. Chem.,* 2007, **5**, 1191; indomycinone: (e) D.-S. Hsu, T. Matsumoto, and K. Suzuki, *Chem. Lett.,* 2006, **35**, 1016; (f) L. F. Tietze, R. R. Singidi, and K. M. Gericke, *Org. Lett.,* 2006, **8**, 5873; (g) K. Krohn, H. T. Tran-Thien, and I. Ahmed, *Eur. J. Org. Chem.,* 2011, 2223; other related aglycons: (h) K. Krohn and J. Vitz, *Eur. J. Org. Chem.,* 2004, 209; (i) K. Krohn, H. T. Tran-Thien, J. Vitz, and A. Vidal, *Eur. J. Org. Chem.,* 2007, 1905; (j) L. F. Tietze, R. R. Singidi, K. M. Gericke, H. Böckemeier, and H. Laatsch, *Eur. J. Org. Chem.,* 2007, 5875; (k) L. F. Tietze, R. R. Singidi, and K. M. Gericke, *Chem. Eur. J.,* 2007, **13**, 9939; (l) B. J. D. Wright, J. Hartung, F. Peng, R. V. de Water, H. Liu, Q.-H. Tan, T.-C, Chou, and S. J. Danishefsky, *J. Am. Chem. Soc.,* 2008, **130**, 16786.
8. (a) K. A. Parker and Y.-H. Koh, *J. Am. Chem. Soc.,* 1994, **116**, 11149; (b) D. E. Kaelin, Jr., S. M. Sparks, H. R. Plake, and S. F. Martin, *J. Am. Chem. Soc.*, 2003, **125**, 12994; (c) Z.-B. Fei and F. E. McDonald, *Org. Lett.,* 2007, **9**, 3547; (d) M. Shigeta, T. Hakamata, Y. Watanabe, K. Kitamura, Y. Ando, K. Suzuki, and T. Matsumoto, *Synlett,* 2010, 2654.
9. (a) B. M. O'Keefe, D. M. Mans, D. E. Kaelin, Jr., and S. F. Martin, *J. Am. Chem. Soc.,* 2010, **132**,

15528; (b) B. M. O'Keefe, D. M. Mans, D. E. Kaelin, Jr., and S. F. Martin, *Tetrahedron,* 2011, **67**, 6524.

10. K. Kitamura, Y. Ando, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.,* 2014, **53**, 1258.
11. A. Das and C. Khosla, *Acc. Chem. Res.,* 2009, **42**, 631.
12. (a) A. Fredenhagen and U. Séquin, *Helv. Chim. Acta,* 1985, **68**, 391; (b) A. Fredenhagen and U. Séquin, *J. Antibiot.,* 1985, **38**, 236.
13. (a) S. Kobayashi, *Eur. J. Org. Chem.,* 1999, 15; (b) A. Ben, T. Yamauchi, T. Matsumoto, and K. Suzuki, *Synlett,* 2004, 225.
14. (a) F. J. Leeper and J. Stauton, *J. Chem. Soc., Perkin Trans. 1,* 1984, 1053; (b) J. H. Dodd, J. E. Starrett, and S. M. Weinreb, *J. Am. Chem. Soc.,* 1984, **106**, 1811.
15. K. Kitamura, Y. Maezawa, Y. Ando, T. Kusumi, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.,* 2014, **53**, 1262.
16. S. V. Ley, J. Norman, W. P. Griffith, and S. P. Marsden, *Synthesis,* 1994, 639.
17. D. B. Dess and J. C. Martin, *J. Org. Chem.,* 1983, **48**, 4155.
18. (a) M. Frigerio, M. Santagostino, and S. Sputore, *J. Org. Chem.,* 1999, **64**, 4537; (b) A. Duschek and S. F. Kirsch, *Angew. Chem. Int. Ed.,* 2011, **50**, 1524.
19. (a) S. Yamaguchi, K. Sugiura, R. Fukuoka, K. Okazaki, M. Takeuchi, and Y. Kawase, *Bull. Chem. Soc. Jpn.,* 1984, **57**, 3607; (b) S. A. Snyder, Z.-Y. Tang, and R. Guptav, *J. Am. Chem. Soc.,* 2009, **131**, 5744.
20. (a) R. Barret and M. Daudon, *Tetrahedron Lett.,* 1990, **31**, 4871; (b) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299.
21. (a) D. M. Gorden and S. J. Danishefsky, *J. Org. Chem.,* 1992, **57**, 7052; (b) T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata, and K. Suzuki, *Tetrahedron,* 1995, **51**, 7347.