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The first total synthesis and structural determination of benzopyrenomycin

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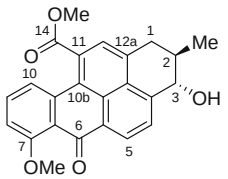
ABSTRACT

The first total synthesis and structural determination of benzopyrenomycin has been achieved. This synthesis contains remarkable transformations including cyclization to afford the benzanthrone skeleton, *syn*-selective vinylogous Mukaiyama aldol reaction, and radical cyclization with the benzanthrone attaching the iodoalkane chain.

Benzopyrenomycin (**1**) was isolated as an antitumor from a culture broth of *Streptomyces lavendulae* (strain Tü 1668).[1] This compound is the first known natural product with a benzo[*a*]pyrene framework (Fig. 1). The structure of benzopyrenomycin (**1**) was determined by NMR spectra. Although the relative structure of **1** was determined, insufficient amount of the isolated **1** made it unsuccessful to determine the absolute configuration. Isolation of rubiginone A_2,[2] having a similar optical rotation with **1**, from the same culture broth gave presumption of the absolute stereochemistry of benzopyrenomycin as shown in Figure 1.[1] Interested in the structure and bioactivities, we embarked the synthesis of **1** to determine the absolute configuration.

Recently, we have developed stereoselective vinylogous Mukaiyama aldol reactions using the chiral silyl ketene *N,O*-acetals to give γ,δ-*anti*-α,β-unsaturated imides.[3] For example, the reaction using vinylketene silyl *N,O*-acetal **2** with 4-bromobenzaldehyde (**3**) gave ***anti*-4** predominantly (Scheme 1).[3g] The feature of the ^{1}H NMR spectrum of ***anti*-4** in $CDCl_3$ was the signal of H5, which existed at δ 4.28 ppm with a large coupling constant ($J_{4,5}$ = 9.0 Hz), while H5 of ***syn*-4** was present at δ 4.85 ppm with a small coupling constant ($J_{4,5}$ = 3.0 Hz). During the further studies of the reaction, we found that 1-formylpyrene (**5**) reacted with vinylketene silyl *N,O*-acetal **2** to give *syn*-adduct (***syn*-6**) predominantly, of which H5 was found at δ 6.07 ppm with the small coupling constant ($J_{4,5}$ = 3.5 Hz).[4] Investigation of the origin of the *syn*-selectivity has been in progress;[5] however, we have decided to apply this phenomenon to the total synthesis of natural products.

Our synthetic plan of benzopyrenomycin (**1**) is shown in Scheme 2. Because of the remarkable conjugation system of benzopyrenomycin (**1**), C1–C12a bond could be constructed with iodide **7** in the final stage of the synthesis. The stereogenic



Benzopyrenomycin (1)

Figure 1. Structure of benzopyrenomycin (**1**).

centers, C2 and C3, would be constructed by our *syn*-selective asymmetric induction method using the chiral dienol ether ***ent*-2**. Tetracyclic aldehyde **8** might be synthesized by the introduction of acetate unit to anthraquinone **9** at C12 position followed by cyclization.

Total synthesis was started by Diels–Alder reaction with quinone **10**[6] and diene **11**[7] (Scheme 3). Treatment of the labile adduct **12** with DBU under air promoted successive reactions including the elimination of AcOH, aromatization of the right ring, and air-oxidation to give anthraquinone **9**. The regioselectivity of the Diels–Alder reaction was confirmed by NOE and HMBC of anthraquinone **9** (Fig. 2). Correlation between H5 and C6 supported the structure of **9**, the desired product. Reduction of **9** with $LiAlH_4$ followed by IBX oxidation provided the unstable aldehyde **13**. The acetate unit for C11–C14 of benzopyrenomycin (**1**) was introduced at once by Wittig reaction to afford the stable α,β-unsaturated ester **14**. Benzannulation[8] to afford benzanthrone **15** was achieved by absorption of γ proton of the α,β-unsaturated ester **14** with sodium methoxide. Condensation at α position of the ester formed C10b–C11 bond smoothly to give benzanthrone **15** in high yield. The structure of **15** was confirmed by HMBC and NOE as shown in Figure 3. Correlation between H12 and C10b made it clear that the product of this reaction possessed the tet-

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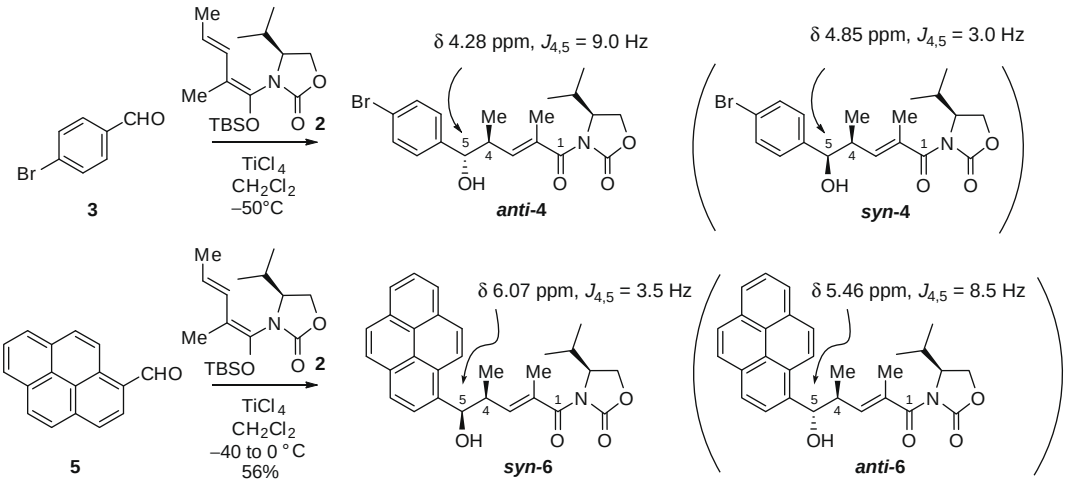
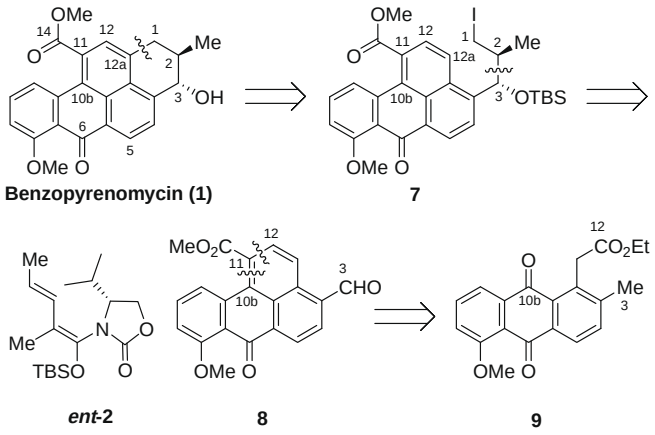


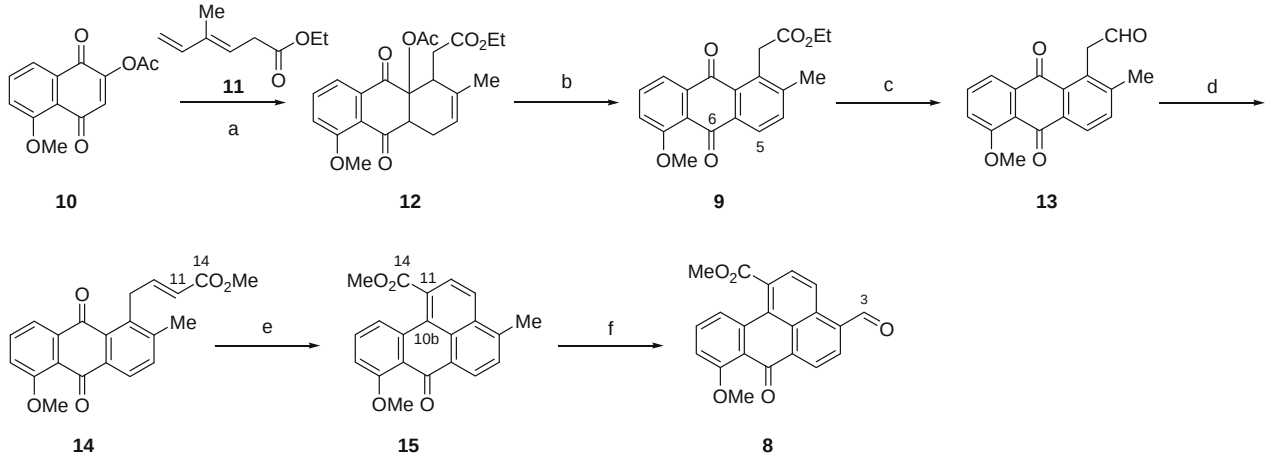
Scheme 1. Vinylogous Mukaiyama aldol reactions using 4-bromobenzaldehyde **3** and 1-formylpyrene **5**.



Scheme 2. Retrosynthetic analysis of benzopyrenomycin (**1**).

racyclic structure. Tetracyclic **15** was converted to aldehyde **8** by one-pot transformation including bromination of the C3 position and subsequent DMSO oxidation.

Achievement of the total synthesis of benzopyrenomycin (**1**) is shown in Scheme 4. Treatment of aldehyde **8** with the chiral dienol ether ***ent*-2** in the presence of $BF_3{\cdot}OEt_2$ at −60 °C gave alcohol **16** having the desired stereogenic centers. The coupling constant between H2 and H3 (J = 3.4 Hz) revealed *syn*-relation as expected. The absolute configuration of **16** was determined by Mosher's method.[9] The hydroxy group of **16** was protected as TBS ether **17**. The double bond cleavage of the α,β-unsaturated imide **17** by ozonolysis was followed by reduction to afford alcohol **18**. The primary alcohol **18** was converted to iodide **7**, which was submitted to the radical cyclization to produce C1–C12a bond. Treatment of **7** with tributyltin hydride (4 equiv) in the presence of dibenzoyl peroxide (3 equiv) in toluene at 80 °C promoted cyclization[10] and sequential oxidation to provide benzo[*a*]pyrene **19**. The structure of **19** was confirmed by correlation between H1 and C12 as well as NOE between H2 and the methyl group of TBS (Fig. 4). De-O-protection with HF·pyridine proceeded smoothly to give benzopyrenomycin (**1**) as yellow needles. The spectral data of synthetic **1** including ^1H and ^{13}C NMR, IR, and HR-MS were identical with those of natural product as well as the dextro-rotation of the yellow solution [synthetic **1**: $[\alpha]_D^{24}$ +25 (*c* 0.3, $CHCl_3$); lit.[1] (natural **1** [a yellow solid]) $[\alpha]_D^{20}$ +38 (*c* 0.3, $CHCl_3$)].[11] Therefore, the absolute



Scheme 3. Reagents and conditions: (a) PhMe, 110 °C, 74%; (b) DBU, PhMe, rt, 76%; (c) $LiAlH_4$, THF–CH_2Cl_2, 0 °C, 5 min; IBX, PhMe–DMSO, 50 °C, 1 h, 54%; (d) $Ph_3P{=}CHCO_2Me$, PhMe, 80 °C, 5 h, 83%; (e) NaOMe, MeOH, rt, 12 h, 95%; (f) NBS, AIBN, CCl_4, 80 °C, 1 h, then DMSO, 80 °C, 1 day, 91%.

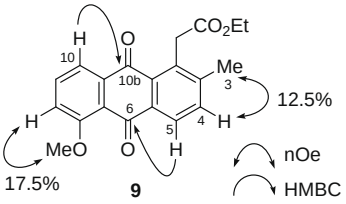


Figure 2. Structure of anthraquinone **9**.

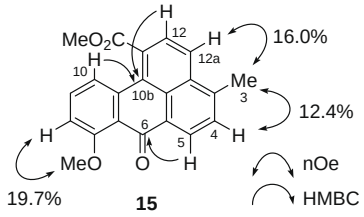


Figure 3. Structure of benzanthrone **15**.

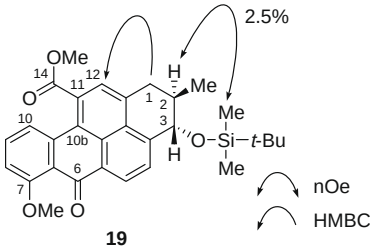


Figure 4. Structure of benzo[*a*]pyrene **19**.

structure of benzopyrenomycin (**1**) was determined to be (2*R*,3*S*)-configuration.

In conclusion, the first total synthesis and structural determination of benzopyrenomycin has been achieved. This synthesis contains remarkable transformations including cyclization to afford benzanthrone skeleton (**14**→**15**), *syn*-selective vinylogous Mukaiyama aldol reaction (**8**→**16**), and radical cyclization with the benzanthrone attaching the iodoalkane chain (**7**→**19**). The absolute structure of benzopyrenomycin (**1**) was determined as (2*R*,3*S*)-configuration.

Acknowledgments

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Supplementary data

The spectral data of compounds **7**, **8**, **9**, **15**, **16**, **19**, and synthetic benzopyrenomycin (**1**), ^{1}H NMR spectrum (600 MHz in $CDCl_3$ and 600 MHz in DMSO-d_6), and ^{13}C NMR (150 MHz in $CDCl_3$ and 150 MHz in DMSO-d_6) spectrum of synthetic benzopyrenomycin (**1**) are available. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2009.09.089.

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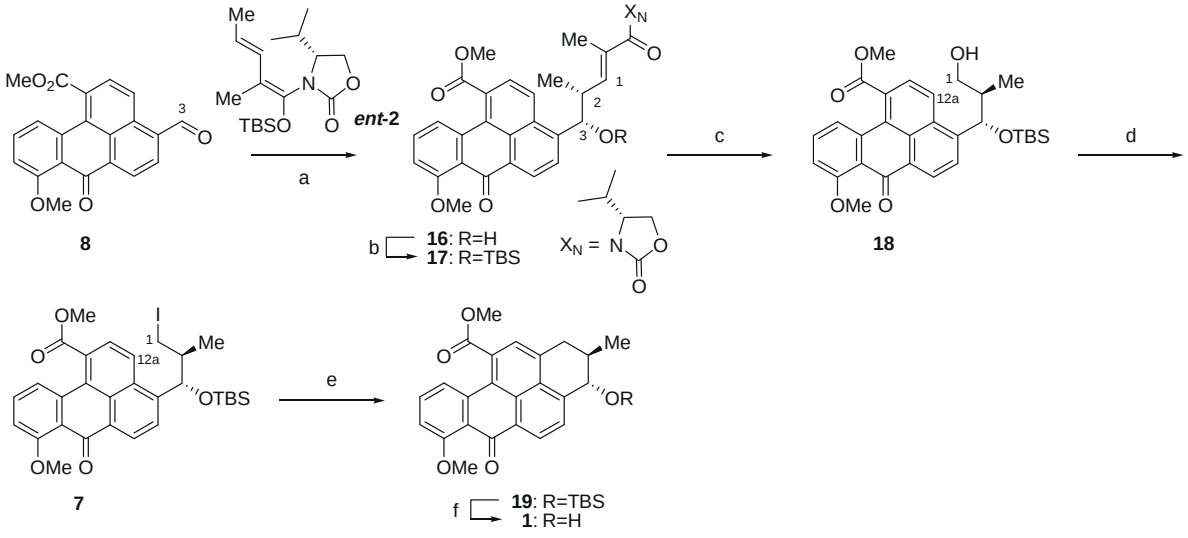
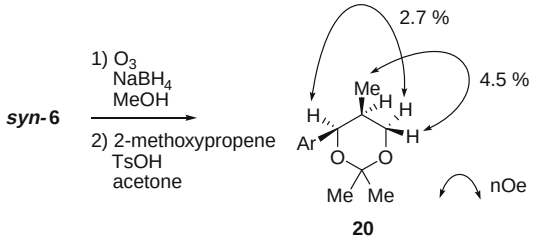


Scheme 4. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −60 °C, 86%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min, 91%; (c) O_3, CH_2Cl_2–MeOH, −78 °C, then Me_2S; LiAlH(O*t*-Bu)$_3$, THF, 0 °C, 87%; (d) I_2, PPh_3, imidazole, PhMe, 50 °C, 88%; (e) *n*-Bu_3SnH, benzoyl peroxide, PhMe, 80 °C, 5 h, 85%; (f) HF–pyridine, MeCN, rt, 5 min, 76%.

4. The absolute configuration of ***syn*-6** was determined by Mosher's method[9] and derivation to the cyclic compound **20** as shown below.



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