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Natural Product Synthesis

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Total Synthesis of the Antibiotic BE-43472B**

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Dedicated to Professor Shigeo Katsumura

The antitumor antibiotic BE-43472B (**1**) was first isolated in 1996 by researchers at Banyu from *Streptomyces* sp. A43472 (Figure 1),[1] and recently rediscovered by Rowley and co-workers from a Caribbean ascidian (*Ecteinascidia turbinata*).[2] In addition to antitumor activity, the latter study uncovered a significant bactericidal activity of **1** against drug-resistant pathogens, such as MSSA, MRSA, and VRE. The basic structure of **1** is composed of two nonidentical anthraquinone moieties connected by a highly hindered carbon–carbon bond. Also notable is the stereochemical complexity associated with the five contiguous stereogenic centers. Important biological activities as well as the uniquely complex molecular architecture of **1** have stimulated considerable synthetic interests, and Nicolaou and co-workers reported the first total synthesis of **1**, which was accomplished in 21 steps in 1.0% yield by exploiting a cascade sequence including a Diels–Alder reaction.[3]

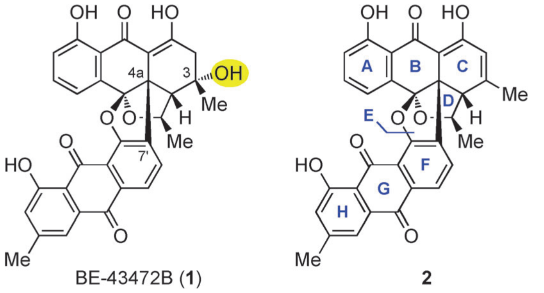
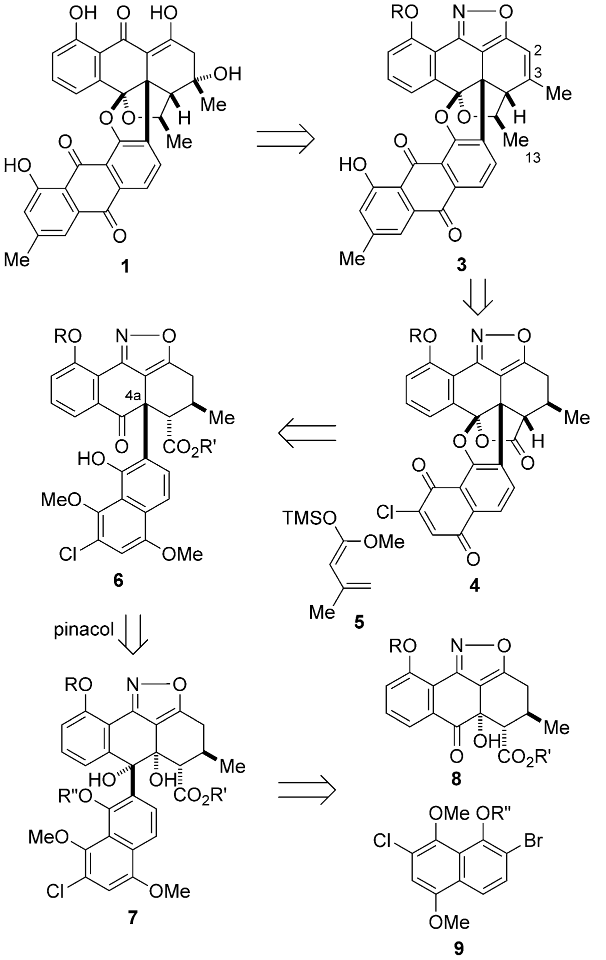


Figure 1. Structures of BE-43472B (**1**) and its dehydration artifact **2**.

Herein, we describe the second total synthesis of (±)-**1** through an isoxazole-based polyketide assembly strategy[4] and a 1,2-rearrangement to install the angular substituent.[5] The three major challenges in planning a synthetic route were: 1) C–C bond (C4a–C7′) formation at the highly hindered angular position, 2) construction of the octacyclic framework, and 3) stereocontrolled installation of the C3 hydroxy group.

The last issue seemed particularly challenging given the pronounced lability of **1**, which underwent elimination to give the dehydrated product **2** even when kept standing in [D$_6$]DMSO.[2a] Thus, we envisioned that the C3 hydroxy group should be introduced at a late synthetic stage.

Scheme 1 outlines the retrosynthetic analysis of **1**: The immediate precursor **3** was envisaged, having the C2–C3 alkene for the late-stage installation of the C3 hydroxy group, and an isoxazole as a 1,3-diketone surrogate.[6] The next precursor **4** was planned by assuming the construction of the anthraquinone moiety by the regioselective Diels–Alder reaction of the chloroquinone moiety in **4** with siloxydiene **5**, and installation of the 13-methyl group on the tetrahydro-



Scheme 1. Retrosynthetic analysis of BE-43472B (**1**).

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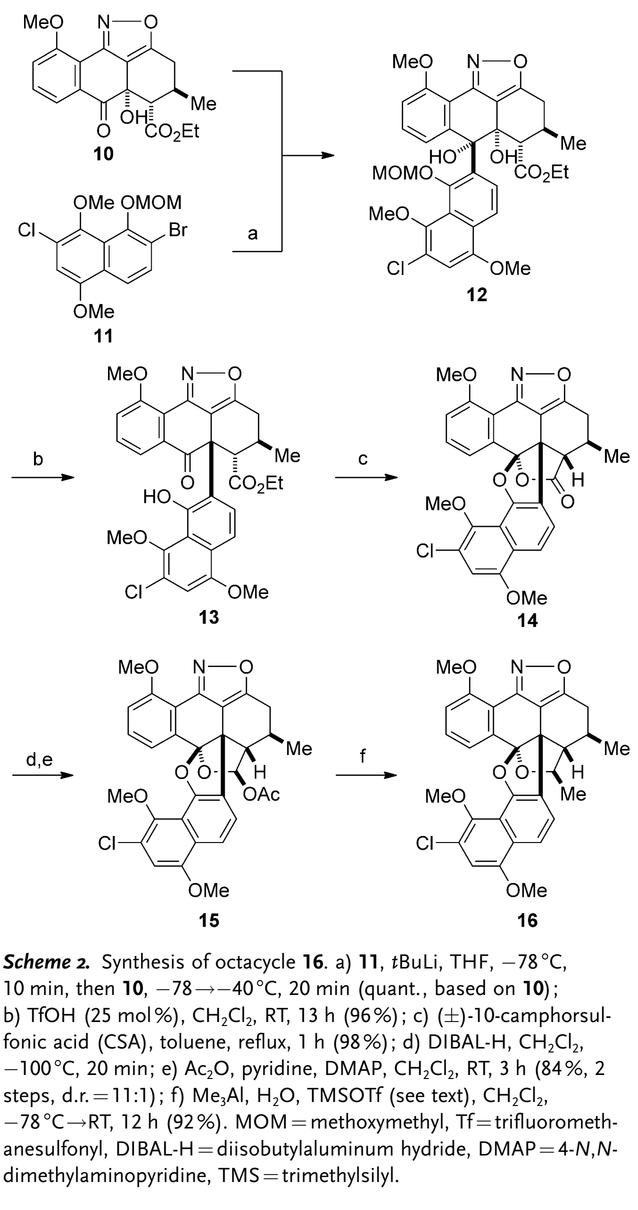
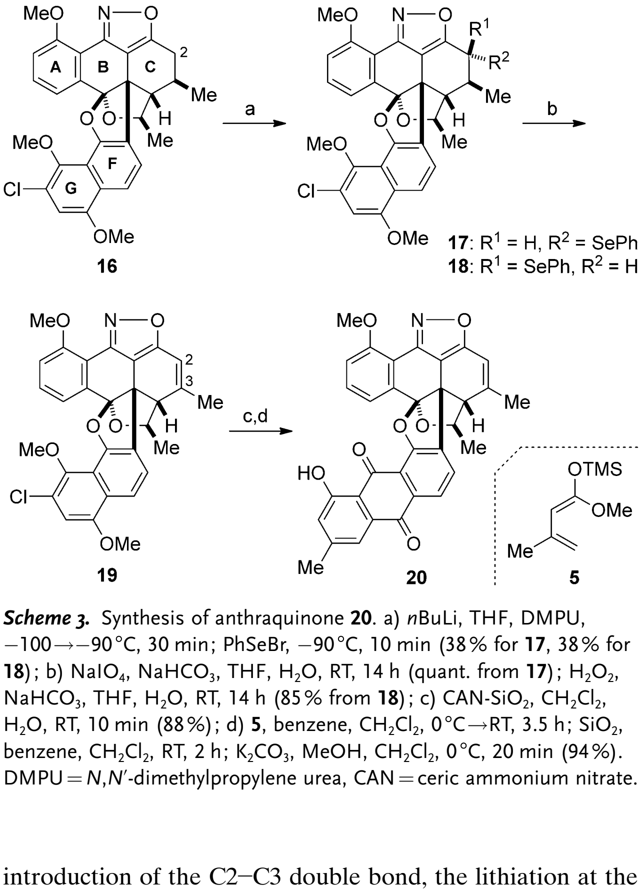
furan ring by exploiting the γ-lactone moiety in **4**. Further disconnection at the central spiroacetal suggested keto ester **6** as the key intermediate, which would allow installation of the angular naphthyl group through a isoxazole-directed regioselective pinacol-type 1,2-shift[5a] of diol **7**. Final disconnection of **7** suggested α-ketol **8** and naphthyl bromide **9** as the starting materials.

Our synthesis started with the generation of a naphthyllithium species from bromide **11** (*t*BuLi, THF, −78 °C), which was treated with ketone **10**[4e] to give the single *cis*-diol **12** in quantitative yield (Scheme 2).[7] The key pinacol 1,2-shift of diol **12** was nicely promoted by TfOH (25 mol %), along with concomitant removal of the MOM group to give the desired ketone **13** in 96 % yield. This transformation proceeded in a regio- and stereospecific manner owing to the excellent cation-stabilizing ability of the isoxazole moiety in **12**.[5] Upon heating ketone **13** in toluene in the presence of CSA (110 °C, 1 h), lactone **14** was obtained in 98 % yield via the hemiacetal intermediate followed by ester exchange. For the installation of the 13-methyl group, lactone **14** was reduced (DIBAL-H, CH_2Cl_2, −100 °C) and acetylated to give acetate **15** in 84 % combined yield ($\beta/\alpha = 11{:}1$). The completely stereoselective methylation[8] of **15** was achieved under carefully optimized conditions with three key requirements: 1) presence of water,[9] 2) use of TMSOTf as a Lewis acid, and 3) the precise ratio of the reagents. Thus, treatment of acetate **15** with Me_3Al (7.5 equiv), H_2O (4.5 equiv), and TMSOTf (10 equiv) afforded **16** with complete diastereoselectivity in 92 % yield.[10] The stereostructure of **16** was unambiguously determined by X-ray crystallography.[11]



Scheme 2. Synthesis of octacycle **16**. a) **11**, *t*BuLi, THF, −78 °C, 10 min, then **10**, −78→−40 °C, 20 min (quant., based on **10**); b) TfOH (25 mol %), CH_2Cl_2, RT, 13 h (96 %); c) (±)-10-camphorsulfonic acid (CSA), toluene, reflux, 1 h (98 %); d) DIBAL-H, CH_2Cl_2, −100 °C, 20 min; e) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, 3 h (84 %, 2 steps, d.r. = 11:1); f) Me_3Al, H_2O, TMSOTf (see text), CH_2Cl_2, −78 °C→RT, 12 h (92 %). MOM = methoxymethyl, Tf = trifluoromethanesulfonyl, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-*N*,*N*-dimethylaminopyridine, TMS = trimethylsilyl.

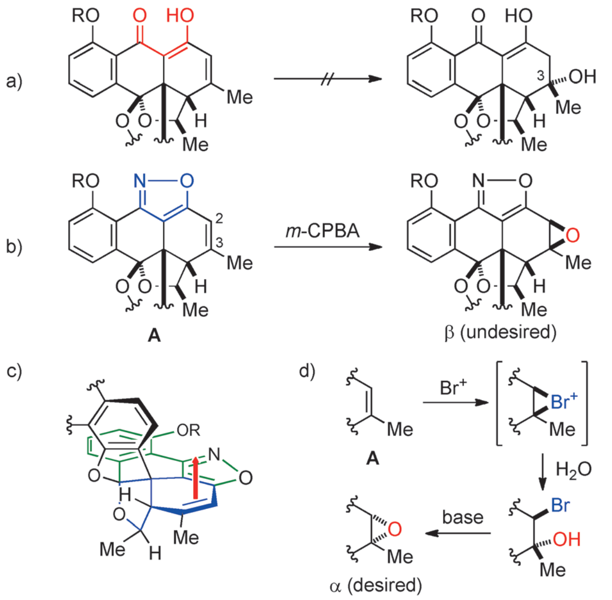
After having constructed the A–G rings in a fully stereocontrolled manner, further conversion into anthraquinone **20** was undertaken (Scheme 3). In preparation for the introduction of the C2–C3 double bond, the lithiation at the C2 position of isoxazole **16** was examined, and a suitable set of conditions was found: *n*BuLi in a solvent mixture (THF, DMPU, $v/v = 5{:}1$) at −90 °C for 30 min. Among methods tested for introducing the C2–C3 double bond in **16**, the selenoxide-based protocol[12] proved effective; lithiation of isoxazole **16** (see above) and subsequent treatment with PhSeBr gave a 1:1 separable mixture of diastereomeric selenides **17** and **18** in 76 % combined yield. Upon oxidative treatment, selenides **17** and **18** nicely converged into olefin **19** in high yield.[13] Oxidation of naphthalene **19** with CAN-SiO_2[14] afforded the corresponding naphthoquinone in 88 % yield, which was subjected to a Diels–Alder reaction with siloxydiene **5**[15] to give, after successive treatment with SiO_2 and K_2CO_3, anthraquinone **20** in 94 % yield.



Scheme 3. Synthesis of anthraquinone **20**. a) *n*BuLi, THF, DMPU, −100→−90 °C, 30 min; PhSeBr, −90 °C, 10 min (38 % for **17**, 38 % for **18**); b) $NaIO_4$, $NaHCO_3$, THF, H_2O, RT, 14 h (quant. from **17**); H_2O_2, $NaHCO_3$, THF, H_2O, RT, 14 h (85 % from **18**); c) CAN-SiO_2, CH_2Cl_2, H_2O, RT, 10 min (88 %); d) **5**, benzene, CH_2Cl_2, 0 °C→RT, 3.5 h; SiO_2, benzene, CH_2Cl_2, RT, 2 h; K_2CO_3, MeOH, CH_2Cl_2, 0 °C, 20 min (94 %). DMPU = *N*,*N′*-dimethylpropylene urea, CAN = ceric ammonium nitrate.

Having constructed the full carbon framework, the remaining tasks toward the total synthesis were: 1) unmasking of the isoxazole to give the 1,3-diketone, 2) deprotection, and 3) introduction of the labile C3 hydroxy group. Extensive model studies, however, suggested that only a narrow window was open to the target owing to many limiting factors.

The order of these transformations was crucial, and the third task proved extremely difficult; 1) no feasible conditions were found for hydrating the olefin once the 1,3-diketo functionality was unmasked, because the double bond was too unreactive (Scheme 4a). 2) In the case of olefin **20** with the isoxazole, even if the hydration was successful, the labile C3 hydroxy group would not survive the conditions for converting the isoxazole into the corresponding 1,3-diketone.

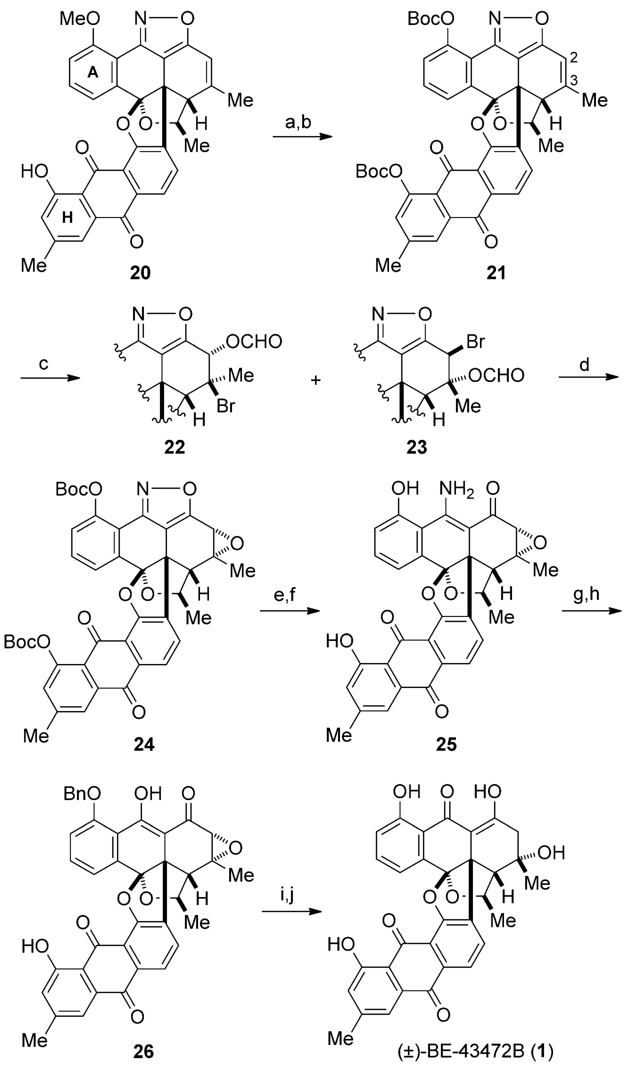


Scheme 4. Problems and solution for installing the C3-hydroxy group.

The latter notion led us to focus on the C2–C3 epoxide as a masked form of the C3 hydroxy group until the final synthetic stage. However, the model epoxidation experiment gave only the wrong stereoisomer, the β-epoxide (Scheme 4b); this outcome gave insight into the molecular geometry in the vicinity of the C2–C3 double bond. The β-face is available for the approaching reagents (Scheme 4c). We focused on the epoxide formation via a halohydrin intermediate, expecting that the halonium ion formation from the β-side followed by capture by an oxygen nucleophile would give a halohydrin derivative that would be convertible to the α-epoxide (Scheme 4d).

Two additional issues arose: 1) The double bond next to the isoxazole was also unreactive, and 2) the strong halogenating reagents, thus needed, also halogenated other sites of the aromatic rings. Therefore, Boc groups were employed for the protection of two phenols to avoid halogenation on the A and H rings (see **20**→**21**, Scheme 5).

For enhancing the reactivity of the halogenating agent, we focused on the acid activation,[16] and formic acid gave an excellent result. Upon treatment of olefin **21** with N-bromosaccharin[17] in formic acid at 0°C, two products formed. Careful structure assignment identified these products to be isomeric bromoformates **22** and **23** in a ratio of 1.8:1. Preferential formation of the anti-Markovnikov product **22** was unexpected, but rationalized by the extreme steric hindrance of the α-side at the C3 position (inside of the concave pocket), thereby forcing the oxygen nucleophile to attack the C2 position, albeit electronically unfavorable. This unexpected result, however, caused no problem for our purpose, as both regioisomers converged to the desired α-epoxide **24** as a sole product in 83% yield (two steps) by treatment with Na_2CO_3 (MeOH, RT).



Scheme 5. Endgame. a) BBr_3, CH_2Cl_2, $-78\rightarrow-10\,^{\circ}C$, 3 h; b) Boc_2O, DMAP, CH_2Cl_2, $-20\,^{\circ}C$, 20 min (82%, 2 steps); c) *N*-bromosaccharin, HCOOH, CH_2Cl_2, 0°C, 20 min; d) Na_2CO_3, MeOH, RT, 1.5 h (83%, 2 steps); e) CF_3CO_2H, CH_2Cl_2, RT, 2 h; f) $[Mo(CO)_6]$, MeCN, H_2O, 85°C, 40 min (97%, 2 steps); g) benzyl bromide, Ag_2O, DMF, RT, 1 h (93%); h) *t*BuONO, TfOH, DMSO, RT, 40 min (61%); i) PhSeSePh, $NaBH_4$, AcOH, EtOH, THF, 0°C, 20 min (82%); j) BBr_3, CH_2Cl_2, $-78\rightarrow-55\,^{\circ}C$, 1 h (76%). Boc = *tert*-butoxycarbonyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, Tf = trifluoromethanesulfonyl, DMSO = dimethyl sulfoxide.

After the two Boc protecting groups in **24** were removed, the isoxazole was cleaved with $[Mo(CO)_6]$[18] to give enaminone **25**. Our previous experience suggested that an enaminone moiety in such a polycyclic construct would be resistant to usual acid hydrolysis, for which a protocol through diazotization was developed.[19,20] After the selective protection of phenol **25** with a benzyl group, the enaminone was hydrolyzed by using *t*BuONO and TfOH to give the desired diketone **26** in 61 % yield. Epoxide **26** was subjected to the reductive ring opening under Miyashita conditions[21] (PhSeSePh, $NaBH_4$, EtOH) to give the corresponding *tert*-alcohol, which was treated with BBr_3 (CH_2Cl_2, −78→−55 °C). Fortunately, in contrast to the pronounced lability of the *tert*-alcohol, the Lewis acidic conditions lead to removal of the benzyl protecting group at low temperature to afford the long-sought target **1**. The synthetic material was identical in all respects (^{1}H-, ^{13}C NMR, IR, HRMS) to the natural sample. Recrystallization from $CDCl_3$ gave nice crystals (yellow plates, m.p. 211–213 °C), and X-ray analysis gave further structural proof (Figure 2).[11]

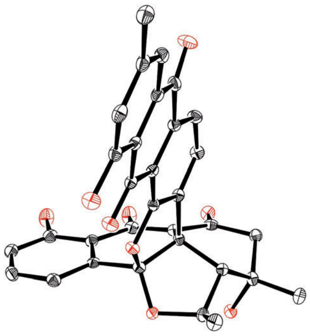


Figure 2. X-ray crystal structure of BE-43472B (**1**). Hydrogen atoms are omitted for clarity. O red, C black. Thermal ellipsoids are shown at the 50% probability level.

In summary, total synthesis of (±)-BE-43472B (**1**) has been accomplished in 27 steps and 3.0 % yield from a commercially available material. The synthesis features: 1) use of isoxazole as a 1,3-diketone surrogate, 2) the isoxazole-directed pinacol 1,2-shift for connecting two anthraquinone precursors at the angular position, and 3) perfect control of five contiguous stereogenic centers. The synthetic route described herein is efficient enough to allow the synthesis of the chiral, nonracemic ones as well as the various congeners with potential biological activities. Further work along these lines is in progress.

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[11] CCDC 923753 (**10**), 923754 (**16**), and 925606 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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