Natural Product Synthesis

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Total Synthesis and Absolute Configuration of the Bisanthraquinone Antibiotic BE-43472B**

K. C. Nicolaou, Yee Hwee Lim, and Jochen Becker*

The gross structure of a streptomycete-derived bisanthraquinone designated as BE-43472B was first claimed in a Japanese patent in 1996 to be an antitumor agent.[1] Ten years later, Rowley and co-workers reported the isolation of a bisanthraquinone antibiotic to which they assigned the relative configuration of structure (−)-**1** (Figure 1), from streptomyces strain N1-78-1 isolated from cultured cells of an unidentified unicellular green alga (URI strain N36-11-10), which, in turn, was isolated from the ascidian *Ecteinascidia turbinata*, collected from La Parguera, Puerto Rico.[2a] Although the structure (−)-**1** was depicted in that[2a] and a subsequent publication,[2b] these studies left the absolute stereochemistry of this natural product unassigned. It was speculated[2a] on the basis of spectroscopic data comparisons that this antibiotic was most likely the same as the one previously discovered by the Japanese group.[1] In addition to antitumor properties, this bisanthraquinone antibiotic exhibited potent inhibitory activity against clinically derived isolates of methicillin-susceptible, methicillin-resistant, and tetracyclin-resistant *Staphylococcus aureus* (MSSA, MRSA, and TRSA, respectively), and vancomycin-resistant *Enterococcus faecium* (VRE).[2] Most impressively, this compound also demonstrated, in a time–kill study, significant bactericidal activity (> 99.9 % kill) against MSSA, MRSA, and VRE.[2b] Given the urgency for new antibiotics to combat drug-resistant bacteria,[3] the novelty of the molecular structure of (−)-**1**, and the uncertainty about its absolute stereochemistry, this molecule became an attractive target for synthesis in our group.[4] Herein, we report the first total synthesis of both enantiomers of this novel antibiotic and the assignment of its absolute configuration as that depicted by structure (+)-**1** (Figure 1).

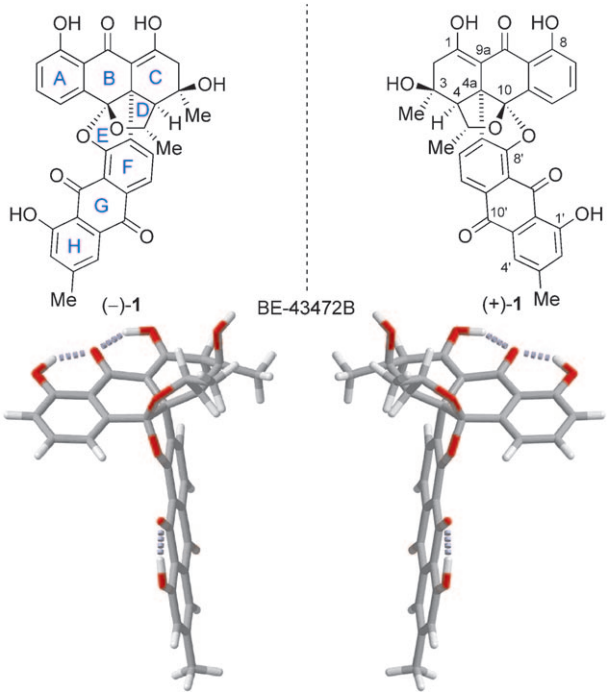

Figure 1. Enantiomers of the bisanthraquinone antibiotic BE-43472B [(−)-**1** and (+)-**1**] and their computer-generated models (fully optimized on B3LYB/6-31G* level) (carbon: gray, hydrogen: white, oxygen: red, hydrogen bonds: dotted blue).

The unprecedented and unique structure of the bisanthraquinone natural product BE-43472B [(+)-**1**] is composed of two different anthraquinone-type molecules joined together by a sterically hindered carbon–carbon bond and an oxygen bridge in an assembly containing no less than eight rings. Its five stereogenic centers are clustered on and around the DE ring system, which contains an oxygen atom in each of its rings forming an internal ketal. Its overall shape is that of a T, with its two sides more or less flat and with its junction where the stereocenters reside slightly distorted (see calculated structures, Figure 1).

Scheme 1 presents, in retrosynthetic format, the blueprint of the devised synthesis of bisanthraquinone antibiotic BE-43472B [(+)-**1**] (and its enantiomer [(−)-**1**]). Thus, disconnection of the ether bridge between the two anthraquinone moieties of the molecule by rupture of the aryl–oxygen bond (opening of ring E) and appropriate modifications of ring C led to the potential precursor **2**. Dismantling the hemiketal ring of **2** then generated cyclohexene derivative **3**, opening the way for the Diels–Alder reaction as the key step of the

[*] Prof. Dr. K. C. Nicolaou, Y. H. Lim,[+] Dr. J. Becker[+]
Department of Chemistry
and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

[+] These authors contributed equally to this work.

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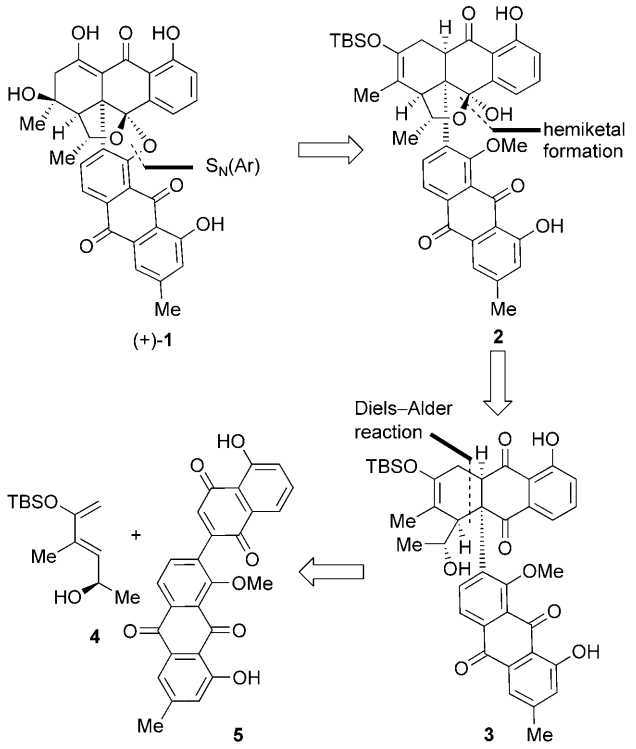


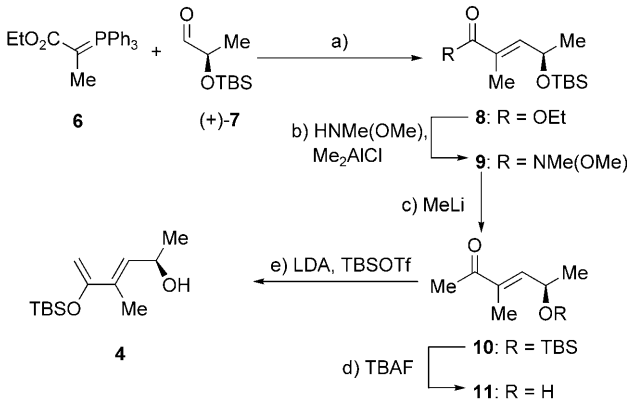
Scheme 1. Retrosynthetic analysis of BE-43472B [(+)-**1**].

strategy.[5] That disconnection defined diene **4** and dienophile **5** as the required building blocks for our projected synthesis. The precise structures of these Diels–Alder partners were crucial for the desired regio- and stereochemical outcome of the [4+2] cycloaddition, as will be discussed below.

Scheme 2 summarizes the synthesis of the required diene **4** containing the first stereocenter of the molecule that would control the remaining four. Our starting material for this construction was an aldehyde derived from lactic acid methyl ester. Since the absolute configuration of our target was not known at the time, we chose the less expensive of the two enantiomers of this aldehyde, (*S*)-(−)-**7**, derived from natural (*S*)-(−)-lactic acid ethyl ester, which also happens to correspond to the structure of the natural product as depicted in the original structural elucidation report.[2] As events transpired, this choice led to (−)-**1**, the enantiomer of BE-43472B.

Starting with (*R*)-(+)-**7** (derived from unnatural (*R*)-(+)-lactic acid methyl ester)[6] we then synthesized (+)-**1**, the naturally occurring enantiomeric form of antibiotic BE-43472B; it is this synthesis we describe herein. Wittig reaction[7] of aldehyde (+)-**7** with phosphorane **6** gave α,β-unsaturated ester **8** (95% yield, $E/Z > 95:5$), which was converted to ketone **10** (57% yield over two steps) by addition of MeLi to the intermediate Weinreb amide **9**.[8] Desilylation of **10** (TBAF, quantitative yield) led to allyl alcohol **11**, which was converted to diene **4** by treatment with 2.3 equiv of LDA followed by trapping of the resulting dianion with 1 equiv of TBSOTf (33% yield, 93% *ee* as determined by HPLC).

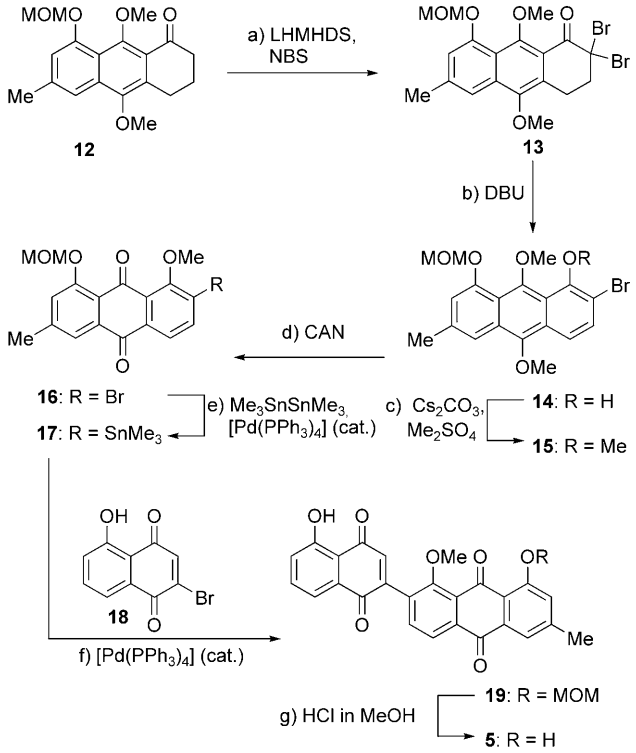
The synthesis of the dienophile **5** commenced with the known tricyclic system **12** and proceeded as shown in



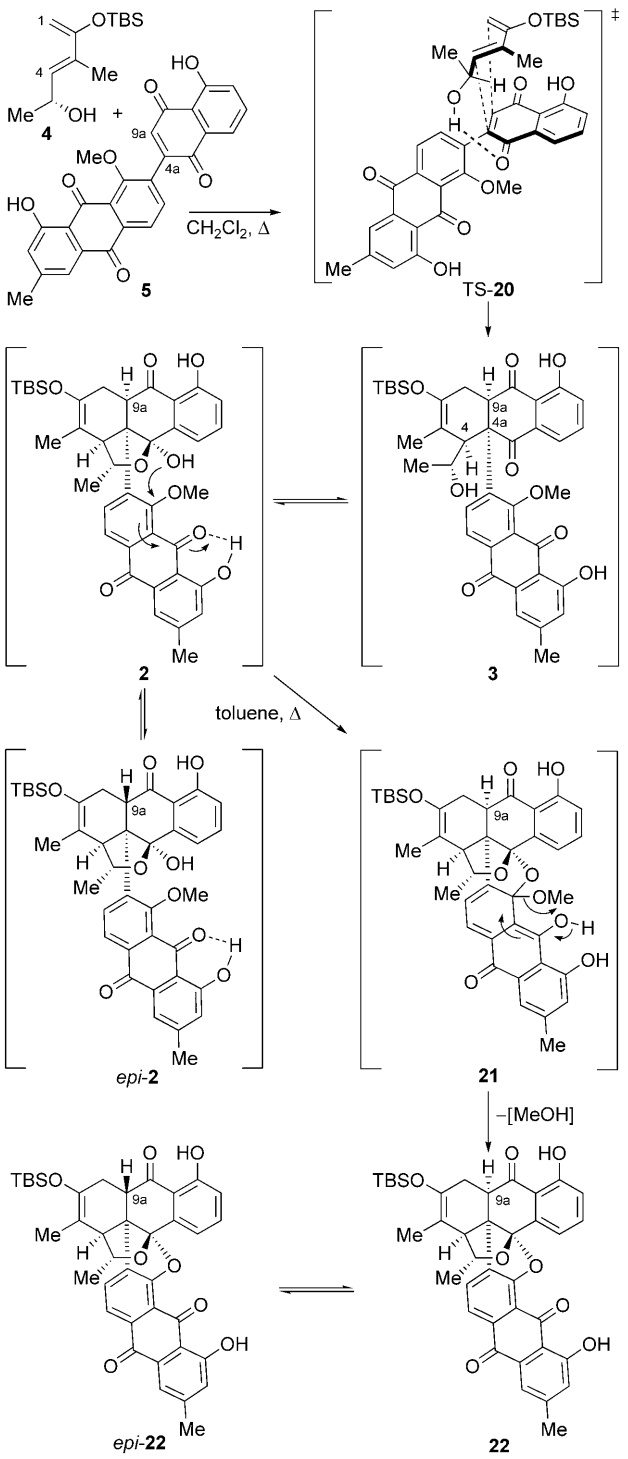
Scheme 2. Synthesis of diene **4**. Reagents and conditions: a) **7** (1.0 equiv), **6** (1.1 equiv), CH_2Cl_2, 25 °C, 6 h, 95%; b) HNMe(OMe)·HCl (5.0 equiv), Me_2AlCl (5.0 equiv), CH_2Cl_2, 0→25 °C, 16 h; c) MeLi, (2.0 equiv), Et_2O, −78 °C, 1 h, 57% over the two steps; d) TBAF (1.1 equiv), THF, 25 °C, 2.5 h, 100%; e) LDA (2.3 equiv), THF, −78 °C, then TBSOTf (1.0 equiv), −78 °C, 1.5 h, −78→25 °C, 30 min, 33% (93% *ee*, 70% yield brsm). brsm = based on recovered starting material, LDA = lithium diisopropylamide, TBAF = tetra-*n*-butylammonium fluoride, TBSOTf = *tert*-butyldimethylsilyl triflate.

Scheme 3.[9] Dibromination of **12** (LHMDS, NBS) yielded dibromoketone **13** (98% yield), which upon sequential exposure to DBU and $CsCO_3$–Me_2SO_4 resulted in the formation of anthracene derivative **15**, through phenol **14**, in 74% overall yield for the two steps. Subsequent CAN oxidation furnished anthraquinone **16** in 77% yield. Stannylation of **16** with $Me_3SnSnMe_3$ in the presence of catalytic $[Pd(PPh_3)_4]$ led to stannane **17** (95% yield), whose $[Pd(PPh_3)_4]$-catalyzed Stille coupling with bromoquinone **18** furnished pentacycle **19** in 65% yield. Finally, removal of the MOM protecting group from **19** under acidic conditions (1% HCl in MeOH) led to the desired dienophile bisquinone **5** in 85% yield.

With the two components **4** and **5** in hand, the stage was now set for their much anticipated union through a Diels–Alder reaction.[5] As seen in Scheme 4, heating **4** and **5** in CH_2Cl_2 at 85 °C in a sealed tube for 48 h followed by addition of toluene and refluxing with a Dean–Stark apparatus for another 24 h led to a remarkable series of transformations to afford octacyclic product **22** and its C-9a epimer *epi*-**22** (*epi*-**22**/**22** ≈ 2:1) in 98% overall yield. The only structural element not controlled in this fascinating cascade sequence was the easily epimerizable stereogenic center at C-9a, an element of little consequence, if any, since this stereocenter had to be subsequently erased. The success of this cascade depended crucially on special features encoded in the two reacting partners, diene **4** and dienophile **5**. To explain the high diastereoselectivity in forming the challenging quaternary stereocenter at C-4a, it is assumed that in the *endo* transition state TS-**20** (Scheme 4) the free hydroxy group within **4** forms a hydrogen bond with the more Lewis basic carbonyl oxygen of the quinone moiety of dienophile **5** (the other carbonyl group is already engaged in hydrogen bonding), orienting the reactive species in the indicated facial arrangement as a result of 1,3-allylic strain[10] and steric reasons.[11,12] The exquisite regiocontrol leading to the exclusive formation of Diels–



Scheme 3. Synthesis of dienophile **5**. Reagents and conditions: a) LHMDS (2.2 equiv), NBS (2.2 equiv), THF, 0→25 °C, 1 h, 98%; b) DBU (1.0 equiv), CH_2Cl_2, 25 °C, 12 h; c) Me_2SO_4 (1.2 equiv), Cs_2CO_3 (1.2 equiv), acetone, reflux, 5 h, 74% over the two steps; d) CAN (2.0 equiv), CH_2Cl_2, MeCN, H_2O, 0 °C, 30 min, 77%; e) $[Pd(PPh_3)_4]$ (0.1 equiv), $Me_3SnSnMe_3$ (1.5 equiv), toluene, 110 °C, 2 h, 95%; f) **17** (1.0 equiv), **18** (1.5 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), CuI (0.2 equiv), THF, 70 °C, 22 h, 65%; g) 1% HCl in MeOH, CH_2Cl_2, 25 °C, 16 h, 85%. CAN = cerium(IV) ammonium nitrate, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, LHMDS = lithium hexamethyldisilazide, MOM = methoxymethyl, NBS = *N*-bromosuccinimide.



Scheme 4. Cascade sequence consisting of Diels–Alder reaction, hemiketal formation, and nucleophilic aromatic substitution to form octacyclic structure **22**. Reagents and conditions: **5** (1.0 equiv), **4** (2.0 equiv), CH_2Cl_2, 85 °C, sealed tube, 2 days; then toluene, 135 °C, distillation with a Dean–Stark trap, 1 day, *epi*-**22**:**22** (ca. 2:1 mixture of epimers) 98% overall yield based on **5**.

Alder adduct **3** can be explained by intuitive analysis of the molecular orbital interactions of the reactants, if the bis-anthraquinone substituent on the quinone dienophile is construed to be an electron-withdrawing group and thereby enhancing the MO coefficient at C-9a (for the diene a larger coefficient is expected at C-1). The regioselective hydrogen bonding may amplify the required orbital interactions.[13] Adduct **3** was observed by NMR spectroscopic analysis to exist in equilibrium with its hemiketal form **2** (**2**/**3** ≈ 4:1, [D_6]benzene). Manual molecular modeling indicated that **2** finds itself in a favorable conformation to undergo an intramolecular nucleophilic *ipso* substitution (**2**→**22**),[14] expelling a molecule of MeOH to afford the desired octacycle **22**. This novel cyclization is apparently facilitated by the presence of the adjacent phenolic quinone moiety, which, being self-activated through hydrogen bonding, invites the attack by the initiating hemiketal hydroxy group as shown in structures **2** and **21**.[15] The product **22** of this cascade reaction apparently epimerizes partially at C-9a under the reaction conditions (toluene at reflux), which also ensures the removal of the departing MeOH, as well as on silica gel to furnish *epi*-**22**. In refluxing benzene we also observed partial epimerization of hemiketal **2**, yielding an equilibrating mixture of **2** and *epi*-**2**. With compounds *epi*-**22** and **22** in hand, the stage was now set for the final drive to the target molecule (+)-**1**.

Scheme 5 depicts the final sequence that led to the completion of the total synthesis of antibiotic BE-43472B [(+)-**1**]. Thus, *m*CPBA epoxidation of *epi*-**22**/**22** (2:1)[16] furnished epoxides **23** (major epimers, ca. 4:1 mixture with its α epimers, not shown), which were desilylated (HF·py) and then oxidized with SeO_2 in AcOH to afford enone **25** (49% yield over the three steps) through hydroxy ketone intermediates **24**, together with its chromatographically separable 3-*epi*-stereoisomer (*epi*-**25**, not shown, 39% yield).

An X-ray crystallographic analysis (see ORTEP drawing, Figure 2)[17,18] of single crystals of **25** (m.p. > 250 °C, CH_2Cl_2) proved its relative configuration and confirmed the outcome of both the Diels–Alder and the epoxidation reactions. With

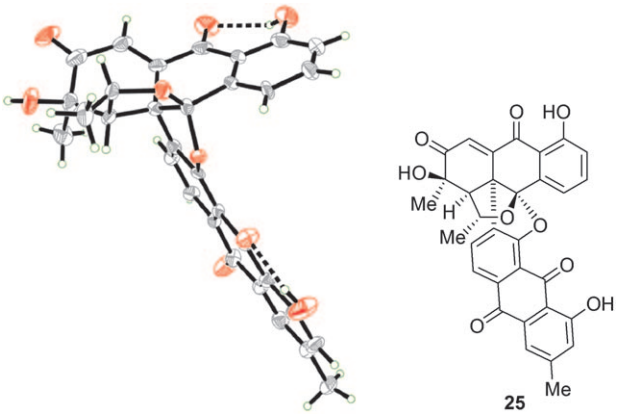
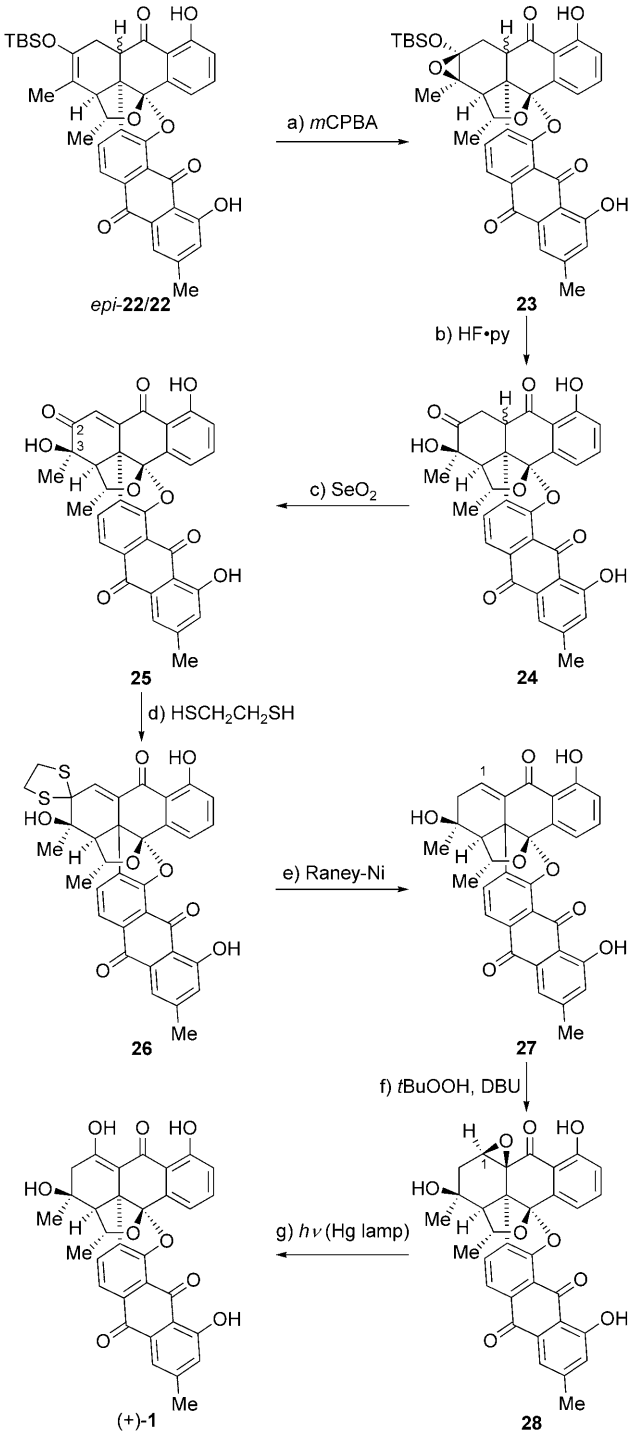


Figure 2. X-ray crystal structure of **25** (ORTEP; thermal ellipsoids are shown at 30% probability).[17]

this pleasing advance, the removal of the superfluous oxygen atom at C-2 and the introduction of the hydroxy group at C-1 became the next tasks. In a notably regioselective manner, tetracarbonyl compound **25** was reacted with ethane-1,2-dithiol (as solvent) in the presence of excess $BF_3{\cdot}OEt_2$ to afford the desired dithioketal **26** (63% yield), a substrate that underwent reductive desulfurization with Raney-Ni to generate enone **27** (45% yield). All that now remained to reach the target molecule was the insertion of the missing oxygen atom in the C–H bond of the enone moiety of the latter compound. This was achieved through a remarkably smooth procedure involving, first, epoxidation of **27** to give epoxide **28** (*t*BuOOH, 84% yield, plus the β epimer of **28**, 7% yield, separable by preparative TLC, silica), and, then, reorganization of the epoxide structural motif to the required enol moiety through photolysis[19] of **28** to afford bisanthraquinone antibiotic BE-43472B [(+)-**1**] in 77% yield (83% yield brsm, 92% conversion).[20] Synthetic (+)-**1** exhibited essentially identical physical properties to those reported for the natural product,[1,2a] and so did (−)-**1**, except for its optical rotation which was of the opposite sign.[21]

In addition to assigning the absolute configuration of bisanthraquinone antibiotic BE-43472B [(+)-**1**], the described total synthesis demonstrates the increasing power of cascade reactions in chemical synthesis[22] and opens the way



Scheme 5. Completion of the total synthesis of BE-43472B [(+)-**1**]. Reagents and conditions: a) *m*CPBA (1.2 equiv), CH_2Cl_2, −20 °C, 2 h; b) HF·py (10.0 equiv), THF, 25 °C, 20 min, then TMSOMe; c) SeO_2 (5.0 equiv), AcOH, 120 °C, 15 h, **25**, 49% and *epi*-**25**, 39% over the three steps; d) $HSCH_2CH_2SH$ as solvent, $BF_3{\cdot}OEt_2$ (10.0 equiv), 25 °C, 30 min, 63%; e) Raney-Nickel 2400, MeOH, air, 25 °C, 1.5 h, then aq. HCl, **27**, 45% (56% brsm); f) *t*BuOOH (5.0 equiv), DBU (3.0 equiv), CH_2Cl_2, −25 °C, **28**, 84% and β-**28**, 7%; g) *hν* (mercury lamp), benzene, 25 °C, 7 h, 77% (83% yield brsm). *m*CPBA = *meta*-chloroperbenzoic acid, py = pyridine.

for the construction of designed analogues of this intriguing antitumor antibiotic for biological investigations.

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[1] "Antitumoric BE-43472 manufacture with streptomyces": H. Kushida, S. Nakajima, T. Koyama, H. Suzuki, K. Ojiri, H. Suda, JP 08143569, **1996**.
[2] a) A. M. Socha, D. Garcia, R. Sheffer, D. C. Rowley, *J. Nat. Prod.* **2006**, *69*, 1070; b) A. M. Socha, K. L. LaPlante, D. C. Rowley, *Bioorg. Med. Chem.* **2006**, *14*, 8446.
[3] For recent reviews on this topic, see: a) G. Taubes, *Science* **2008**, *321*, 356; b) K. C. Nicolaou, J. S. Chen, D. J. Edmonds, A. A. Estrada, *Angew. Chem.* **2009**, *121*, 670; *Angew. Chem. Int. Ed.* **2009**, *48*, 660.
[4] For previous synthetic studies inspired by BE-43472B, see: a) K. Suzuki, H. Takikawa, Y. Hachisu, J. W. Bode, *Angew. Chem.* **2007**, *119*, 3316; *Angew. Chem. Int. Ed.* **2007**, *46*, 3252; b) H. Takikawa, K. Hikita, K. Suzuki, *Angew. Chem.* **2008**, *120*, 10035; *Angew. Chem. Int. Ed.* **2008**, *47*, 9887.
[5] a) O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1926**, *450*, 237; Reviews: b) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650; c) K. C. Nicolaou, *Angew. Chem.* **2002**, *114*, 1742; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
[6] J. A. Marshall, M. M. Yanik, N. D. Adams, K. C. Ellis, H. R. Chobanian, *Org. Synth.* **2005**, *81*, 157.
[7] G. Wittig, U. Schöllkopf, *Chem. Ber.* **1954**, *87*, 1318.
[8] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
[9] a) K. C. Nicolaou, Y. H. Lim, C. D. Papageorgiou, J. L. Piper, *Angew. Chem.* **2005**, *117*, 8131; *Angew. Chem. Int. Ed.* **2005**, *44*, 7917; b) K. C. Nicolaou, Y. H. Lim, J. L. Piper, C. D. Papageorgiou, *J. Am. Chem. Soc.* **2007**, *129*, 4001.
[10] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
[11] For Diels–Alder reactions with substituted naphthoquinones, see: a) B. M. Trost, J. Ippen, W. C. Vladuchick, *J. Am. Chem. Soc.* **1977**, *99*, 8116; b) R. K. Boeckman, Jr., T. M. Dolak, K. O. Culos, *J. Am. Chem. Soc.* **1978**, *100*, 7098; c) T. R. Kelly, M. Montury, *Tetrahedron Lett.* **1978**, *19*, 4311; d) M. D. Rozeboom, I.-M. Tegmo-Larsson, K. N. Houk, *J. Org. Chem.* **1981**, *46*, 2338; e) L. F. Tietze, K. M. Gericke, R. R. Singidi, I. Schuberth, *Org. Biomol. Chem.* **2007**, *5*, 1191.
[12] For a discussion of transition states of Diels–Alder reactions with chiral 1,3-dienes, see: a) P. G. McDougal, J. M. Jump, C. Rojas, J. G. Rico, *Tetrahedron Lett.* **1989**, *30*, 3897; b) M. C. Carreño, S. Garciá-Cerrada, A. Urbano, C. Di Vitta, *J. Org. Chem.* **2000**, *65*, 4355; c) L. Barriault, J. D. O. Thomas, R. Clément, *J. Org. Chem.* **2003**, *68*, 2317.
[13] The rather puzzling exquisite regiochemical outcome of this Diels–Alder reaction cannot be fully explained at this time, and studies directed toward its further understanding are continuing. It should be noted, however, that that a diene corresponding to **4** with a MEM-O group at its C-1 terminus (rather than a TBS-O group at its C-2 position) reacted with dienophile **5** to give exclusively the opposite regioisomeric Diels–Alder product. Further details will be reported in the full account of this work.
[14] An alternative, but less likely, mechanism for the conversion of **2** to **22**/*epi*-**22** may involve initial oxonium ion formation followed by intramolecular attack from the nearby MeO group and extrusion of MeOH.
[15] For examples of intermolecular $S_N(Ar)$ *ipso* substitution of a MeO group by carbon nucleophiles, see: a) R. C. Fuson, S. B. Speck, *J. Am. Chem. Soc.* **1942**, *64*, 2446; b) A. I. Meyers, E. D. Mihelich, *J. Am. Chem. Soc.* **1975**, *97*, 7383; c) S. Aki, Y. Haraguchi, H. Sakikawa, M. Ishigami, T. Fujioka, T. Furuta, J.-I. Minikawa, *Org. Process Res. Dev.* **2001**, *5*, 535; Reviews: d) R. Gaertner, *Chem. Rev.* **1949**, *45*, 493; e) J. F. Burnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273. To the best of our knowledge, the present case is the first example of an intramolecular $S_N(Ar)$ *ipso* substitution of a MeO group by an oxygen nucleophile. For the introduction of the term *ipso* substitution, see: f) C. L. Perrin, G. A. Skinner, *J. Am. Chem. Soc.* **1971**, *93*, 3389.
[16] Since epimers **22** and *epi*-**22** are hardly separable and because the subsequent intermediates **23** and **24** were also shown to epimerize under the reaction conditions employed for their generation, it was more expedient and efficient to carry the mixture of *epi*-**22** and **22** through the three-step sequence and separate the obtained enone **25** and its C-3 epimer *epi*-**25** by chromatography.
[17] CCDC 714178 (**25**) contains 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.
[18] In the initial synthesis of (−)-**1**, we also obtained the X-ray crystal structure of *ent*-**25**. CCDC 711967 (*ent*-**25**) contains 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.
[19] a) S. Bodforss, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 214; b) O. Jeger, K. Schaffner, *Pure Appl. Chem.* **1970**, *21*, 247.
[20] Interestingly, the minor epimeric oxirane *epi*-**28** remained unchanged under the same photolytic conditions.
[21] Since the spectroscopic data and optical rotation of our synthetic BE-43472B [(+)-**1**] are essentially the same as those reported in the Japanese patent[2] and Ref. [2a] for naturally occurring BE-43472B [(+)-**1**], we assume that the two latter compounds are one and the same.
[22] Reviews: a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; b) L. F. Tietze, G. Brasche , K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p. 672; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

