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Synthesis of (±)-Epoxysorbicillinol Using a Novel Cyclohexa-2,5-dienone with Synthetic Applications to Other Sorbicillin Derivatives

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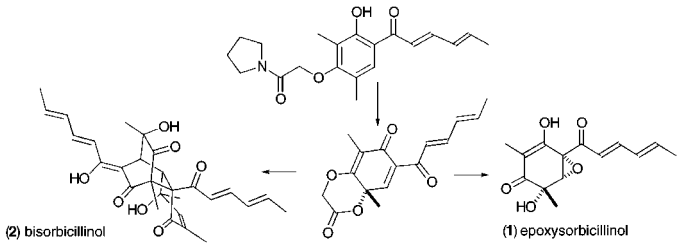
ABSTRACT



A novel route to epoxysorbicillinol as well as dimers of sorbicillin is reported. The synthesis is—in principle—amenable to enantioselectivity. The key step is an oxidative dearomatization to produce a stable and highly malleable *p*-quinol intermediate, which undergoes a highly diastereoselective epoxidation.

Cyclohexanones **1**−**3** (Figure 1) belong to a family of structurally diverse natural products isolated from both marine and terrestrial sources that encompass a wide range of biological activities.[1] A highly functionalized tautomeric cyclohexadienone, **4**,[2] has been proposed as the common intermediate in the biosynthetic pathway.[3b] Indeed, several dimeric members of this natural product family, **2**−**3** along with trichodimerol, have yielded to synthesis by resolution of the racemic precursor **5**, followed by its saponification and dimerization. These investigations[3] testify to the difficulties that surround manipulating a ring system that contains both a dienic and dienophilic segment, predisposed toward dimerization.[4]

We were interested in developing a synthetic method that avoided resolution of **5** and furnished a sturdier ring system that was less prone toward dimerization. Such a process might lead to both monomeric and dimeric members of the

(1) For isolation and medicinal value of sorbicillinoids, see: (a) Andrade, R.; Ayer, W. A.; Mebe, P. P. *Can. J. Chem.* **1992**, *70*, 2526−2535. (b) Andrade, R.; Ayer, W. A.; Trifonov, L. S. *Can. J. Chem.* **1996**, *74*, 371−379. (c) Andrade, R.; Ayer, W. A.; Trifonov, L. S. *Aust. J. Chem.* **1997**, *50*, 255−257. (d) Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011−10014. (e) Abe, N.; Yamamoto, K.; Murata, T.; Hirota, A. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1999**, *41*, 553−558. (f) Abe, N.; Murata, T.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 661−666. (g) Shirota, O.; Pathak, V.; Hossain, C. F.; Sekita, S.; Takatori, K.; Satake, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 2961−2964. (h) Mazzucco, C. E.; Warr, G. *J. Leukocyte Biol.* **1996**, *60*, 271−277. (i) Warr, G. A.; Veitch, J. A.; Walsh, A. W.; Hesler, G. A.; Pirnik, D. M.; Leet, J. E.; Lin, P.-F. M.; Medina, I. A.; McBrien, K. D.; *J. Antibiot.* **1996**, *49*, 234−240. (j) Gao, Q.; Leet, J. E.; Thomas, S. T.; Matson, J. A.; Bancroft, D. P. *J. Nat. Prod.* **1995**, *58*, 1817−1821.

(2) Abe, N.; Sugimoto, O.; Tanji, K.-I.; Hirota, A. *J. Am. Chem.* Soc. **2000**, *122*, 12606−12607.

(3) (a) Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503−1504. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071−3079. (c) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555−3559. (d) Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem. Eur. J.* **1999**, *5*, 3651−3665. (e) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−30, 2000; American Chemical Society: Washington, DC, 2000; ORGN 848.

(4) A [4 + 2] cycloaddition of **4** produces bisorbicillinol **2**, while a net [4 + 4] cycloaddition of **4** results in trichodimerol, see refs 3a,b.

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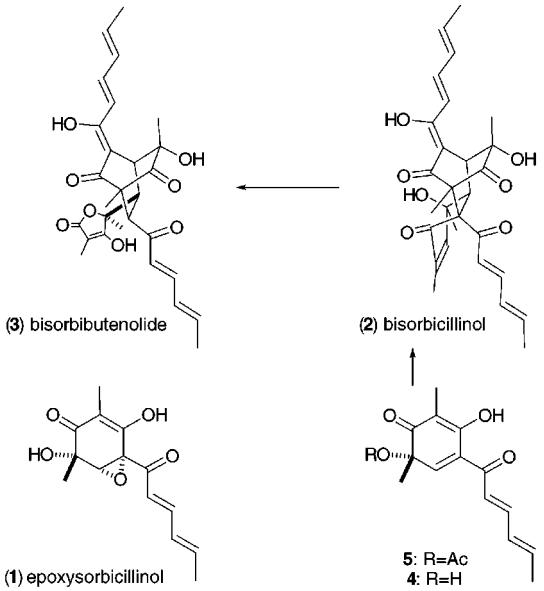


Figure 1.

sorbicillin family of natural products and prove useful in the synthesis of other complex molecules. Our plan entailed developing an asymmetric oxidative dearomatization procedure starting with the resorcinol derivative, **6**,[5] and affording the chiral quinoid **7**, which we anticipated would be more manageable and therefore more synthetically useful than its counterpart, the cyclohexa-2,4-dienone **5**. The ultimate synthetic value of **7**, however, remained in doubt. The adequacy of the 3°-alcoholic stereocenter in **7** to control the formation of subsequent stereocenters was questionable and potentially obviated efficient application of **7** to **1**. Another issue was the stability of **7**. If the 3°-alcohol residue is protected, the addition of certain nucleophilic reagents is known to cause single electron transfer and elimination, reforming **6**, rather than adding to the enone or ketone (Figure 2).[6] In addition, in acidic media **7** is predisposed toward a sigmatropic shift resulting in **8**.[7] Perhaps, a structural feature

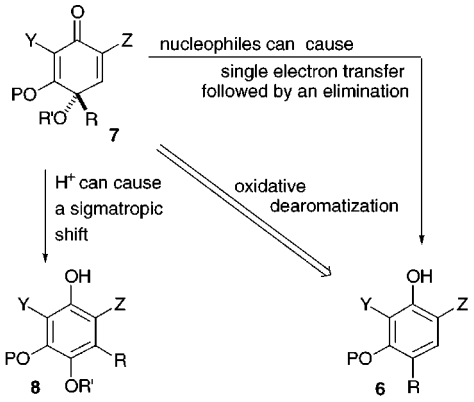


Figure 2.

could be incorporated in **7** that would promote stability, govern the formation of a particular diastereomer in subsequent reactions, and expedite the eventual development of an enantioselective method.

For these reasons the [P] and [R′] residues of **7** were to be combined in a δ-lactone, **9**, a structure we speculated could be formed by electrophilic cyclization of an amide, which was tethered *ortho* to a cationic site generated by exposure of **6** [P = $-CH_2C(O)NR_2$] or a similar resorcinol, such as **12**, to an oxidant [cf. Figure 3]. Scrutiny of the

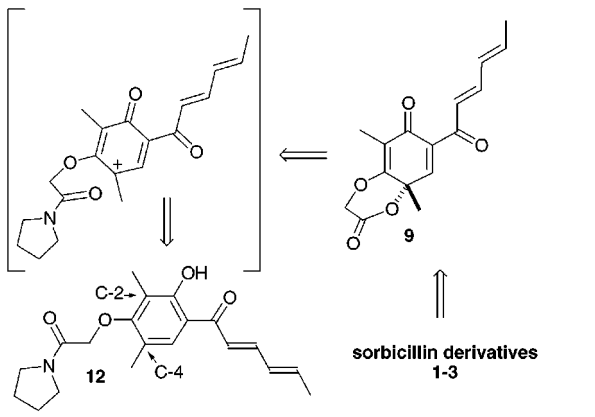


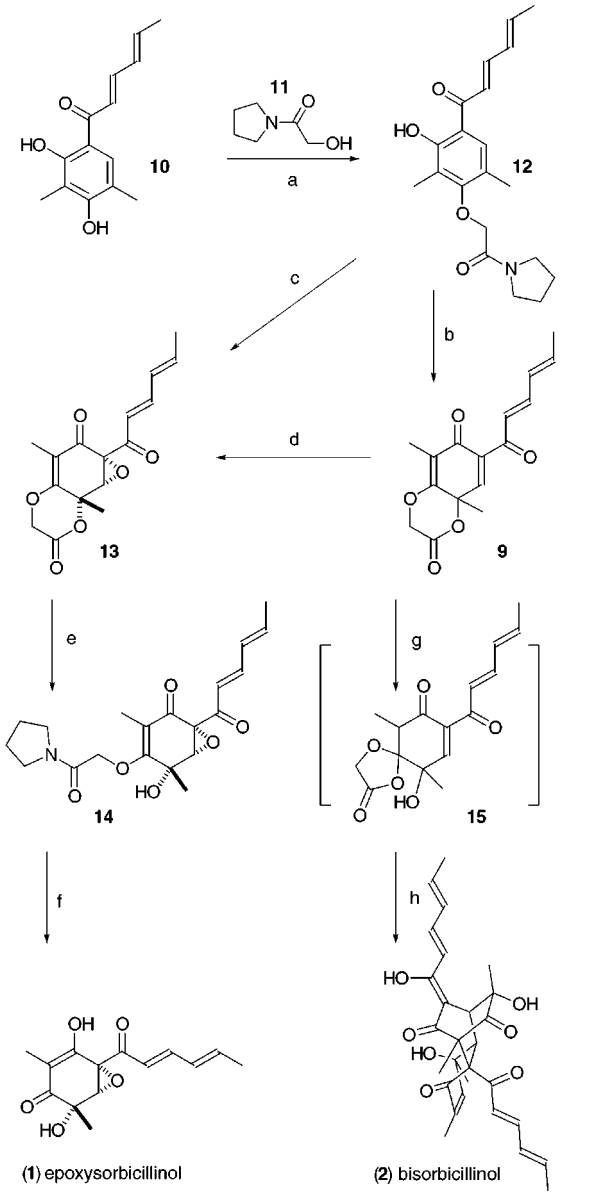
Figure 3.

chemical literature for effective conditions for this intramolecular oxidative cyclization revealed, however, that electrophilic amide cyclizations generally yielded γ-lactones,[8] while oxidative dearomatization usually involved an *ipso* closure.[9] Thus, precedent argued against the success of our strategy for **1**−**3**. Nevertheless, the oxidation was investigated to test these notions in a racemic sense.

Coupling of sorbicillin **10**[2b] with the α-hydroxy amide **11**[10] using Mitsunobu's conditions produces **12** (90%, Scheme 1). Oxidation of this resorcinol nucleus with 1 equiv of PhI-$(OCOCF_3)_2$ followed by aqueous workup cleanly affords **9** (45%) along with epoxide **13** (5%). No other regioisomer or derivative is apparent in ^{1}H NMR spectra obtained for the crude mixture. However, the mass transfer is inexplicably low. The stability of **9** was remarkable, but not entirely unexpected. The 3° [OR′] substituent disposed equatorially in **9** is improperly aligned to eliminate, and being an electron-deficient component of a lactone, a poor facilitator of a

(5) Van De Water, R. W.; Magdziak, D.; Chau, J.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502−6503.
(6) Morrow, G. W.; Schwind, B. *Synth. Commun.* **1995**, *25*, 269−276.
(7) Schultz, A. G.; Antoulinakis, E. G. *J. Org. Chem.* **1996**, *61*, 4555−4559.
(8) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681−13736.
(9) There is but one example of an oxidative cyclization occurring with an oxygen nucleophile tethered *ortho* to the site of cyclization, see: Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273−282. For an *ipso* example, see: Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195−7203.
(10) Antonsson, T.; Gustafsson, D.; Hoffmann, K.-J.; Nystrom, J.-E.; Sorensen, H.; Sellen, M. PCT Int. Appl. WO 9723499 A1 19970703, 1997, 94 pp.

Scheme 1[a]



[a] DEAD, PPh_3, CH_2Cl_2 **11**, 90%; (b) 1.00 equiv of $PhI(OCOCF_3)$ in CH_2Cl_2/CH_3NO_2 (3:1), 45%; (c) 2.2 equiv of $PhI(OCOCF_3)_2$ in CH_2Cl_2/CH_3NO_2 (3:1), 40%; (d) 1.1 equiv of $PhI(OCOCF_3)_2$ in CH_2Cl_2, 98%; (e) dimethylaluminum amide, CH_2Cl_2, 90%; (f) $SnCl_4$, CH_2Cl_2, 80%; (g) 8 equiv of concd HCl in THF, **15** not isolated; (h) 15 equiv of KOH in H_2O, 83%.

sigmatopic shift. Although the regiospecificity of the cyclization was predictable,[11] the formation of epoxide **13** in small quantities was quite surprising. We had anticipated that formation of **13** would require a Julia epoxidation or some similar type of procedure. However, treatment of **12** with 2.2 equiv of $PhI(OCOCF_3)_2$ exclusively affords the epoxide **13** as the sole diastereomer. Alternatively, treatment of **9** with 1.1 equiv of either $PhI(OCOCF_3)_2$ or treatment with a similar amount of PhIO affords **13** in almost quantitative yield. Thus, we assume that **9** precedes **13** along the synthetic pathway and further speculate that $PhI(OCOCF_3)_2$ in CH_2Cl_2 exists in equilibrium with PhIO. Epoxidation of **9** most likely occurs by conjugate addition of PhIO to the activated enone and cleavage of the [PhI−Osubstrate] bond by the resulting enolate.[12] The initial addition of PhIO occurs *anti* to the angular methyl residue, which shields one side of the enone and vinylogous ester from reaction. The relative stereochemistry in **13** was assigned using NOE and comparison with **16**, a structure that was rigorously established using X-ray cystallography (Figure 4).[13]

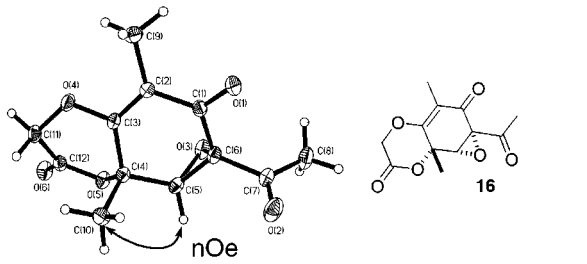


Figure 4.

Vinyl ether **13** proved quite resistant to hydrolysis conditions, which are usually employed with vinylogous esters of this type.[14] Therefore, the lactone was submitted to a Weinreib procedure, which results in amide **14** (90%).[15] This material succumbs to $SnCl_4$-mediated dealkylation of the vinylogous ester and affords epoxysorbicillinol (**1**) (80%) after acid cleavage of the tin enolate with 2 N HCl.

Access to the dimeric sorbicillinoids is achieved by cleaving the tether to reveal the underlying cyclohexa-2,4-dienone core. This is accomplished by treatment of **9** with concentrated HCl, which contracts the lactone and produces what we suppose is the mixed ketal **15**.[16] Subsequent addition of aqueous KOH to the reaction mixture followed by acidic workup produces bisorbicillinol (**2**) in 83% by the [4 + 2] cycloaddition expected for these conditions.[3b] Synthesis of **2** also constitutes a formal synthesis of bisorbibutenolide (**3**).

The intramolecular cyclization leading to **9** should simplify the development of an asymmetric oxidative dearomatization procedure. During the conversion of **12** to **9**, the oxygen atom of the amide tether is restricted to two possible topologies of closure, a compact transition state and a noncompact

(11) The coefficient of both the C-2 and C-4 sites in the cation are sizable and within striking distance of the tether. However, the coefficient at C-2 is significantly reduced by its proximity to the adjacent carbonyl.

(12) Moriarity, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686−688.

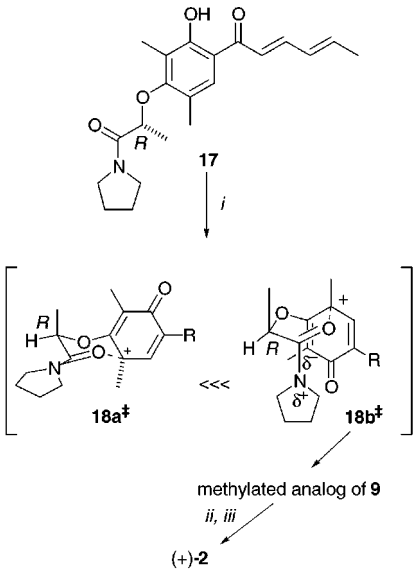
(13) Compound **16** was synthesized in a fashion analogous to that of **13**. The X-ray data for **16** has been submitted to the Cambridge Crystallographic database.

(14) (a) Obara, H.; Machida, Y.; Namazi, S.; Onodera, J. *Chem. Lett.* **1985**, 1393−1394; (b) Johns, S. R.; Lamberton, J. A.; Morton, T. C.; Suars, H.; Wiling, R. *Aust. J. Chem.* **1987**, *40*, 79−96.

(15) Basha, A.; Lipton, M.; Weinreb, S. *Tetrahedron Lett.* **1977**, 4171−4173.

(16) We were unable to purify **15**; however, replacing the sorbyl side chain with an acetyl residue furnished a mixed ketal presumed to be an analogue of **15**.

Scheme 2[a]



[a] (i) 1.00 equiv of $PhI(OCOCF_3)$ in CH_2Cl_2/CH_3NO_2 (3:1); (ii) 8 equiv of concd HCl in THF, **15** not isolated; (iii) 15 equiv of KOH in H_2O, 30% overall with (+)-**2** having 51% optical purity.

transition state (cf. **18a**‡ and **18b**‡ for examples). In principle, asymmetry can be induced during the cyclization by controlling both the reactive face of the amide carbonyl and the topology of the cyclization. To this end, a stereocenter installed in **12** at either one of two sites, between the carbonyl and oxygen atoms in the tether moiety or adjacent to the nitrogen atom in the pyrrolidine ring, may lead to optically enriched products.

Although we have not yet completed satisfactory asymmetric syntheses of **1**, **2**, and **3**, similar treatment of **17**, a compound derived by Mitsunobu inversion of *S*-lactic acid (Scheme 2), affords (+)-**2** in 51% ee when the diastereomeric mixture of analogues that corresponds to methylated derivatives of **9** is carried forward without separation.[17] We suspect that A-1,3 strain between the chiral methyl residue and the pyrrolidine ring restricts the cyclization to transition states **18a**‡ and **18b**‡, where the methyl group is disposed in a *pseudo*-axial orientation. These two transition states lead to opposite enantiomers of **2**. Because (+)-**2** is obtained as the major product, the pathway proceeding through the dipole-stabilized intermediary **18b**‡ appears to be the energetically favored reaction coordinate for this transformation.[18]

Studies directed at optimizing the yield[19] and enhancing the enantioselectivity of the oxidative dearomatization are underway. Applications to other natural products exhibiting a highly oxidized core ring system such as manumycin, scyphostatin, rishirilide B, and diazaphilonic acid are envisioned.

Acknowledgment. Support from the University of California Cancer Research Coordinating Committee is greatly appreciated.

Supporting Information Available: Spectral characterization for **9**, **12**, **13**, **14**, **16**, **17**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The optical purity was determined by comparison of the $[\alpha]_D$ of synthetic and natural **2** at similar concentrations.

(18) Sevin, A. *J. Org. Chem.* **1986**, *51*, 2671−2675.

(19) Ley, S. V.; Finch, H.; Thomas, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *10*, 669−671.