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Total Synthesis of the Novel, Biologically Active Epoxyquinone Dimer (±)-Torreyanic Acid: A Biomimetic Approach

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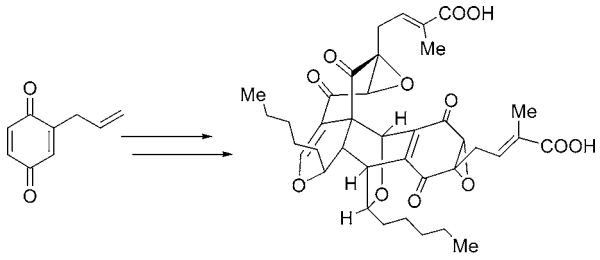
ABSTRACT



Torreyanic acid 1

A total synthesis of the complex, biologically active, dimeric natural product (±)-torreyanic acid, which is composed of seven rings and laced with dense, variegated oxy-functionalization, has been accomplished from readily available allyl-substituted *p*-benzoquinone 8. Our synthetic stratagem involves crafting an epoxyquinone monomer for use in a biomimetic cascade process involving tandem a 6π electrocyclization and a Diels–Alder dimerization.

Among the vast array of polyketide-based natural products, those embodying an epoxyquinone core are being reported regularly from diverse natural sources and have been in the limelight in recent years on account of their structural novelty and their promising and wide-ranging biological profiles.[1,2] In 1996, Lee and co-workers reported the isolation and structure determination of torreyanic acid **1**, a novel dimeric epoxyquinone natural product, from an endophytic fungus *Pestalotiopsis microspora*.[3] Besides its compact multicyclic framework, laced with functionalities and stereochemical intricacies, **1** exhibited impressive biological activity. It was found to be 5 to 10 times more potent at activating human cancer cell lines that are sensitive to the protein kinase C (PKC) agonist, 12-*o*-tetradecanolylnphorbol-13-acetate (TPA). It could also bring about cancer cell death by apoptosis.[3] Torreyanic acid **1** also caused G1 arrest of G0-synchronized cells at the 1−5 μg/mL level depending on the cell lines. The structural and bioactivity attributes of **1** make it a challenging target for total synthesis, and the group of Porco[4] has been the first to reach the post with syntheses of **1** in both racemic[4a] and chiral forms.[4b]

(1) For a recent comprehensive review, see: Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 28572.

(2) Selected examples of epoxyquinone natural products: (a) Oloigosporons: Anderson, M. G.; Jarman, T. B.; Rickards, R. W. *J. Antibiot.* **1995**, *48*, 391. (b) Panepoxydon: Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214. (c) Cycloepoxydon: (i) Gehrt, A.; Erkel, G.; Anke, H. Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 259. (ii) Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 455. (d) Yanuthones: Bugni, T. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Van Wagoner, R. M.; Ireland, C. M. *J. Org. Chem.* **2000**, *65*, 7195. (e) Ambuic acid: Li, J. Y.; Harper, J. K.; Grant, D. M.; Tombe, B. O.; Bashyal, B.; Hess, W. M.; Strobel, G. A. *Phytochemistry* **2001**, *56*, 463. (f) Jesterone: Li, J. Y.; Strobel, G. A. *Phytochemistry* **2001**, *57*, 261.

(3) (a) Lee, J. C.; Yang, X.; Schwartz, M.; Strobel. G. A.; Clardy, J. *J. Chem. Biol.* **1995**, *2*, 721. (b) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.

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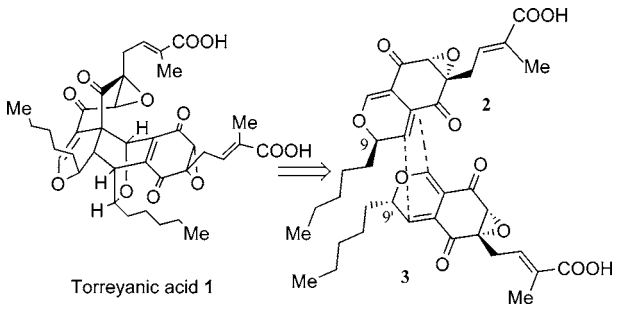
In recent years, our group has been interested in the synthesis of epoxyquinone natural products and we have delineated short, simple approaches to several members of this family from the readily available Diels−Alder adducts of cyclopentadiene and *p*-benzoquinones.[5] As part of these endeavors, we selected torreyanic acid **1** as a synthetic objective. On the face of it, the heptacyclic framework of **1** with 12 oxygen atoms and 8 stereogenic centers appears to be a daunting synthetic challenge. However, during its structural elucidation, Lee et al. proposed[3] a plausible biosynthetic scheme for its origin involving a biomimetic Diels−Alder heterodimerization[6] of 2*H*-pyran monomers **2** and **3** epimeric at C9 (C9′) as shown in (Scheme 1). This

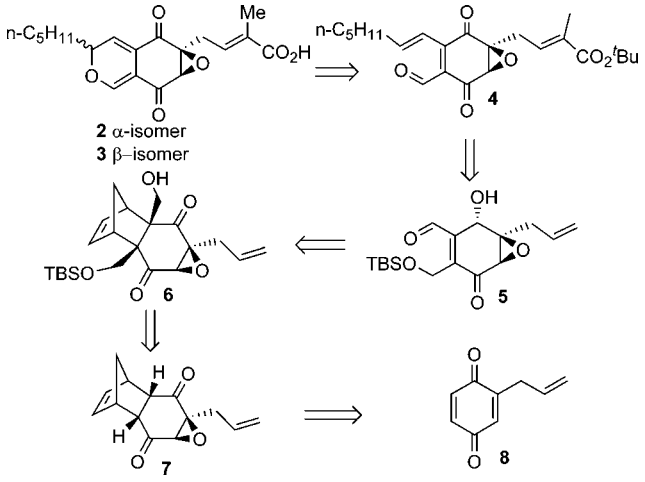
Scheme 1. Proposed Biosynthesis of Torreyanic Acid **1**



biosynthetic proposal makes torreyanic acid appear less awesome as a synthetic target and provides an important strategic clue toward its construction that has been elegantly exploited by Porco et al.[4] Herein, we describe a total synthesis of racemic torreyanic acid **1**, following the biosynthetic lead, from simple, readily available starting materials. In this endeavor, two consecutive, back-to-back electrocyclic processes, involving 2*H*-pyran formation via a 6π-electron ring closure of the corresponding dienal and a [4 + 2]-heterodimerization, were pivotal steps.

A retrosynthetic analysis (Scheme 2) of the target molecule **1**, involving the intermediacy of monomers **2/3**, led to the identification of 2-allyl-*p*-benzoquinone **8**[7] as the starting point for our synthesis in which the allyl group was to serve as a surrogate for the tiglic acid side chain present in torreyanic acid **1**. Additionally, the norbornyl scaffold **7**

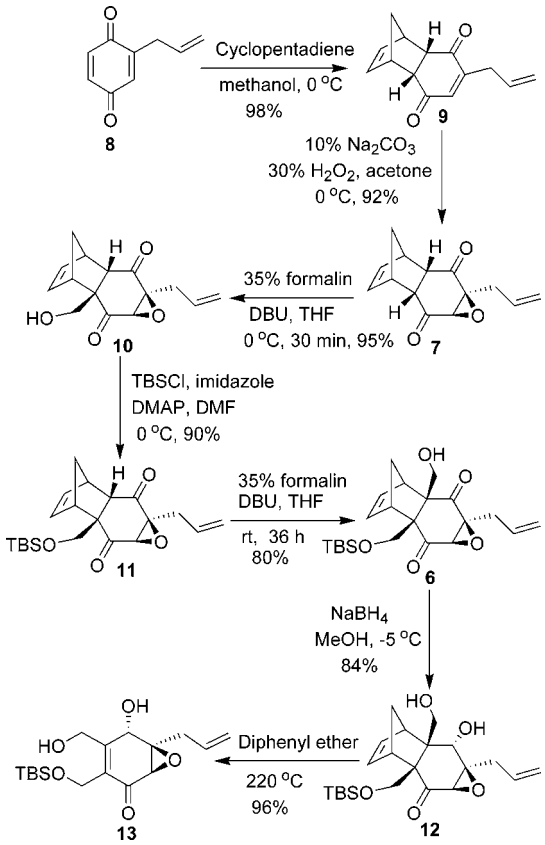
Scheme 2. Retrosynthetic Analysis of **1**



generated through the Diels−Alder reaction was to serve as a matrix for effecting stereo-, regio-, and chemoselective operations.

Diels−Alder reaction between **8** and cyclopentadiene led exclusively to the tricyclic *endo*-adduct **9** in near quantitative yield (Scheme 3). Epoxidation of **9** with hydrogen peroxide in the presence of base was stereo- and chemoselective, furnishing a single epoxide **7** in high yield. Hydroxymethylation of **7** with formaldehyde in the presence of DBU was

Scheme 3. Synthesis of the Key Intermediate **13**



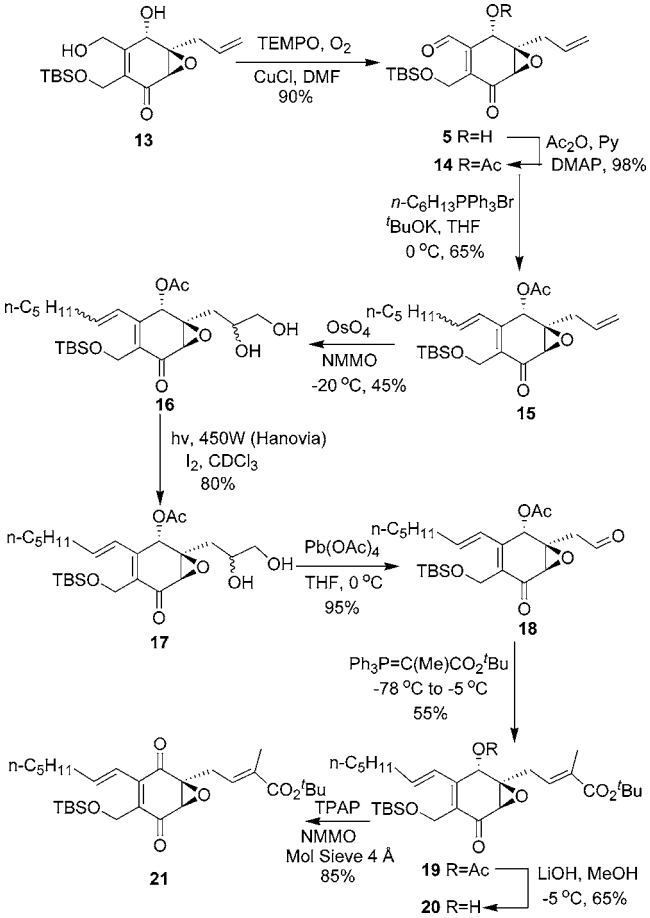
(4) (a) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484. (b) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(5) (a) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 3569. (b) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985. (c) Mehta, G.; Islam, K. *Org. Lett.* **2004**, *6*, 807. (c) Mehta, G.; Pan, S. C. *Org. Lett.* **2004**, *6*, 811. (d) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 3611. (e) Mehta, G.; Roy, S. *Org. Lett.* **2004**, *6*, 2389.

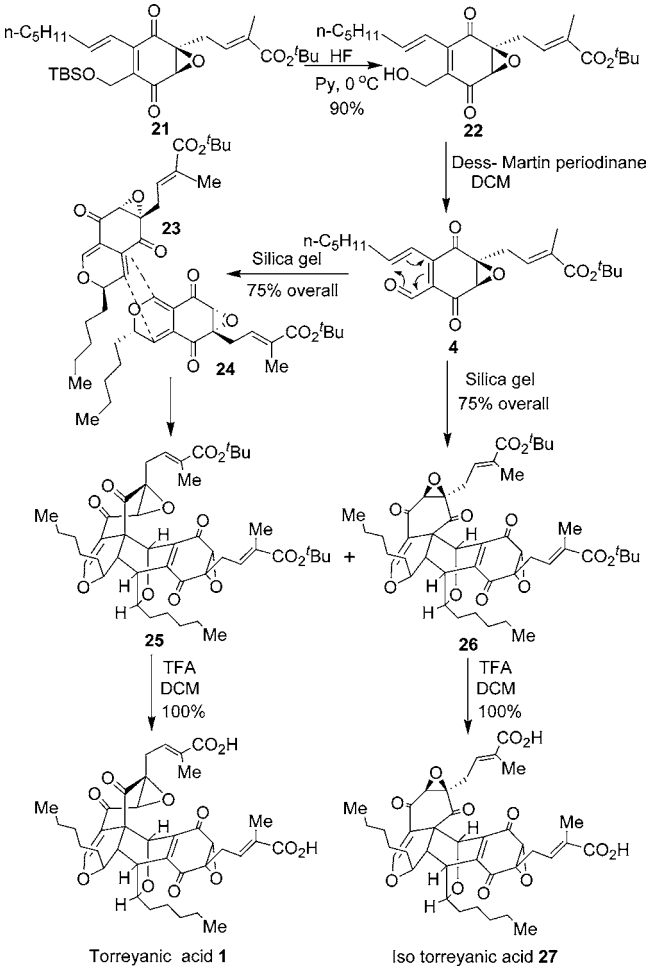
(6) For recent reviews on biomimetic Diels−Alder reactions, see: (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (b) de la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160.

(7) Allylated benzoquinone **8** was prepared from *p*-methoxyphenol according to a new route devised by us involving Claisen rearrangement and CAN oxidation. For earlier preparation, see: (a) Shuki, A.; Nobuhito, K.; Yasuo, B. *J. Organomet. Chem.* **1991**, *415*, 7. (b) Fausta, C.; Francesca, F.; Edoardo, L.; Francesco, M. *Chem. Lett.* **1992**, *7*, 1299 and references therein.

Scheme 4. Synthesis of the Monomer **21**



Scheme 5. Biomimetic Heterodimerization to **1**



efficient and stereo- and regioselective, giving **10** as the predominant product (Scheme 3).[8]

TBS protection of the hydroxyl group in **10** to obtain **11** and repetition of the hydroxymethylation protocol furnished **6** as a single product; the topology of the *endo*-tricyclic scaffold once again dictated the *exo*-stereoselectivity. The topological bias and the presence of the free hydroxymethyl arm in **6** were used to effect regio- and stereoselective $NaBH_4$ reduction to deliver the *endo*-alcohol **12** exclusively (Scheme 3). The retro Diels−Alder reaction of **12** smoothly disengaged the cyclopentadiene moiety and led to highly embellished epoxyquinone derivative **13**,[8] harboring all the necessary functional elements for further evolution into the target natural product torreyanic acid **1**.

The primary hydroxyl group of **13** was chemoselectively oxidized with the TEMPO-O_2 milieu[9] to furnish the aldehyde **5**, and its secondary hydroxyl group was protected as the acetate **14** (Scheme 4). Wittig olefination of **14** with the ylide derived from *n*-hexyltriphenylphosphonium bromide furnished **15** as a mixture of *E*:*Z* isomers (1:3) in which the (*Z*)-isomer was the major product. At this stage, from a practical point of view, it was more appropriate to install the crucial tiglic acid side chain by elaborating the allyl group. Controlled OsO_4-mediated catalytic dihydroxylation on **15** gave **16** as a mixture of diastereomers. The *E*:*Z* mixture of diols **16** was now subjected to photochemical *E*:*Z* equilibration.

Thus, irradiation of **16** from a 450W Hannovia lamp isomerized it completely into the desired (*E*)-isomer **17** (Scheme 4). The glycol moiety in **17** was cleaved with lead tetraacetate, and the resulting aldehyde **18** was subjected to Horner−Wittig olefination with (1-*t*-butoxycarbonylethylidene)triphenylphosphorane to install the tiglic acid side chain and furnish **19**[8] as a single product. Acetate hydrolysis in **19** thereafter provided **20**, and TPAP oxidation delivered the epoxyquinone **21** with the properly positioned and functionalized sidearms (Scheme 4).

TBS group deprotection from **21** gave the primary alcohol **22**, and further oxidation with Dess−Martin periodinane[10] generated the requisite dienal functionality as of **4** to trigger the cascade of events that eventuate in the synthesis of the natural product torreyanic acid **1**. Upon standing for a few

(8) All new compounds were fully characterized on the basis of spectral data (IR, ^1H and ^{13}C NMR, and HRMS). See Supporting Information for experimental details and spectral data.

(9) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc*. **1984**, *106*, 3374.

(10) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

hours at room temperature or on SiO_2-gel chromatography, the two 2*H*-pyrans **23** and **24** rapidly undergo *endo*-selective Diels−Alder heterodimerization to furnish the *tert*-butylesters **25** and **26** of torreyanic acid and "iso"torreyanic acid[11] in a ratio of 45:55, respectively (Scheme 5).[4,12]

Under ambient conditions, dienal **22** undergoes 6π-electron cyclization in two disrotatory modes to furnish two fleeting diastereomeric 2*H*-pyrans **23** and **24**, corresponding to the putative biosynthetic precursors **2** and **3** (Scheme 1), respectively.[3b,4] The spectral data for both **25** and **26** were found to be identical with those reported in the literature.[4,8] On brief exposure to trifluoroacetic acid, the *tert*-butyl ester group in **25** was removed to furnish racemic torreyanic acid **1**, which was found to be spectroscopically identical with the natural product.[3b] In a similar manner, **26** was elaborated to "iso"torreyanic acid **27**, which was fully characterized.[4a]

In summary, we have achieved a total synthesis of the dimeric natural product torreyanic acid **1** from readily available allylated *p*-benzoquinone **8** through a series of simple maneuvers that lead to a biomimetic precursor **4** in which sequential 6π electrocyclization and Diels−Alder dimerization are orchestrated in a one-pot operation under ambient conditions to deliver the natural product.

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Supporting Information Available: Experimental procedures and spectral data (^{1}H and ^{13}C NMR and HRMS) of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) While torreyanic acid ester **25** originates from the *endo*-selective heterodimerization of racemic **23** and **24** with the two *n*-pentyl chains positioned on opposite faces to minimize the steric interaction, the "iso"torreyanic acid framework is derived through heterochiral dimerization of either **23** or **24**, and here again the two alkyl chains are located far apart.

(12) Stereoselectivity in the [4 + 2]-addition in the 2*H*-pyrans **23** and **24** leading to the formation of just two heterodimerization products **25** and **26** is quite exceptional and has been incisively probed by Porco through transition-state calculations and elaborated upon.[4b] Quite remarkably, when chiral precursors of **23** and **24** were deployed, only a single diastereomer **25** was formed.[4b]