# Total Synthesis of (±)-Torreyanic Acid

Chaomin Li,[†] Emil Lobkovsky,[‡] and John A. Porco, Jr.*,[†]

*Department of Chemistry and Center for Streamlined Synthesis, Boston University, 590 Commonwealth Avenue Boston Massachusetts 02215*
*Department of Chemistry, Baker Laboratory Cornell University, Ithaca, New York 14853-1301*

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In 1996, Lee and co-workers reported the isolation and structural characterization of the quinone epoxide dimer torreyanic acid (**1**), a natural product produced by the fungus *Pestalotiopsis microspora.*[1] Torreyanic acid was found to be cytotoxic to tumor cells and 5−10 times more potent in cell lines that are sensitive to protein kinase C agonists. In their report, a biosynthetic scheme for the synthesis of the natural product was proposed involving Diels−Alder dimerization of 2*H*-pyran monomers epimeric at C9 (C9′) (Figure 1). Recently, a related monomeric epoxyquinol, ambuic acid (**2**), was isolated from *P. microspora*, which supports the proposed biosynthesis of torreyanic acid via oxidative dimerization of a monomeric intermediate.[2] Although 2*H*-pyrans have been employed in intermolecular Diels−Alder reactions with reactive dienophiles,[3] their Diels−Alder dimerization has not been previously reported, which prompted our interest in torreyanic acid as a synthetic target. In this Communication, we report the first total synthesis of (±)-torreyanic acid, which confirms its postulated Diels−Alder biogenesis.

A retrosynthetic analysis for the synthesis of torreyanic acid is shown in Figure 2. Bis-*tert*-butyl ester **3** was chosen as the immediate precursor to **1** due to the reported stability of quinone epoxides to acidic conditions[4] and the general instability to basic conditions and nucleophiles.[5] Compound **3** may be derived from Diels−Alder heterodimerization of diastereomeric 2*H*-pyran monomers **4**/**4**′. Although dimerization of 2*H*-pyran-4,5 diones has not been previously described, room-temperature dimerizations of 6-spiroepoxycyclohexadienones[6] and cyclohexa-2,4-dienones[7] have been reported. It was envisioned that the diastereomers **4**/**4**′ could be derived from epoxy vinyl quinone **5** by oxidation, and 2*H*-pyran formation via 6$\pi$-electrocyclic ring-closure of the corresponding dienal (inset).[8] Quinone epoxide **5** may be derived from α-bromoenone **6** by consecutive transition metal coupling of an *E*-vinyl stannane followed by removal of protecting groups. In principle, **6** could be obtained by regio- and stereoselective epoxidation of quinone monoketal **7**, followed by elaboration of the allyl group to a protected tiglic acid side chain.

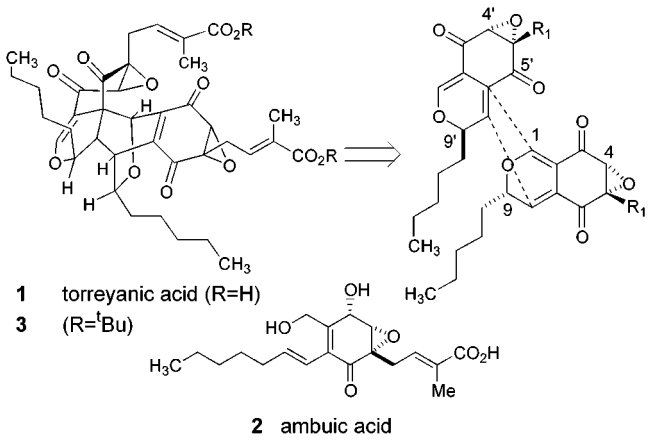


**Figure 1.**

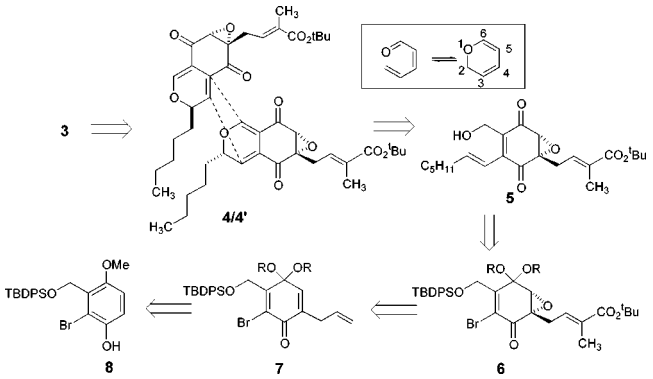


**Figure 2.**

Compound **7** could likewise be accessed by allylation and oxidation of monoprotected hydroquinone **8**.

Synthesis of monomeric derivatives required for Diels−Alder dimerization was initiated by lithiation[9] of 1,3-dioxane derivative **9** (hexanes−PhH, −25 °C) followed by bromination and acidic hydrolysis to afford benzaldehyde **10** (Scheme 1). Regioselective demethylation of methyl ether **10** to phenol **11** was accomplished in 52% yield using a modification of the literature procedure for selective demethylation of 2,5-dimethoxybenzaldehyde.[10] **11** was converted by sequential allylation, borohydride reduction, and silyl protection to **12**. The requisite allyl side chain was installed by thermal Claisen rearrangement of **12** (neat, 180 °C, 2 h) to afford an unstable allyl phenol which was directly subjected to hypervalent iodine oxidation[11] to afford quinone monoketal **13**. Dimethoxyacetal **13** was found to be essentially unreactive to nucleophilic epoxidation conditions known to effect monoepoxidation of quinone monoketals or quinones (e.g., $^t$BuOOH/DBU,[12] TBD,[5b] or BuLi,[13] $H_2O_2/K_2CO_3$, and cumene hydroperoxide/NaH[14]). After considerable experimentation, it was found that epoxidation of **13** with $Ph_3COOH$[15] (KHMDS, −78 to −35 °C, 72 h) led to approximately 20% conversion to a monoepoxide product. However, acetal exchange of **13** with 1,3-propanediol

[†] Boston University.
[‡] Cornell University.

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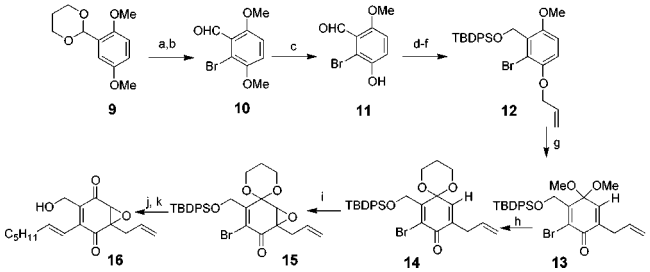
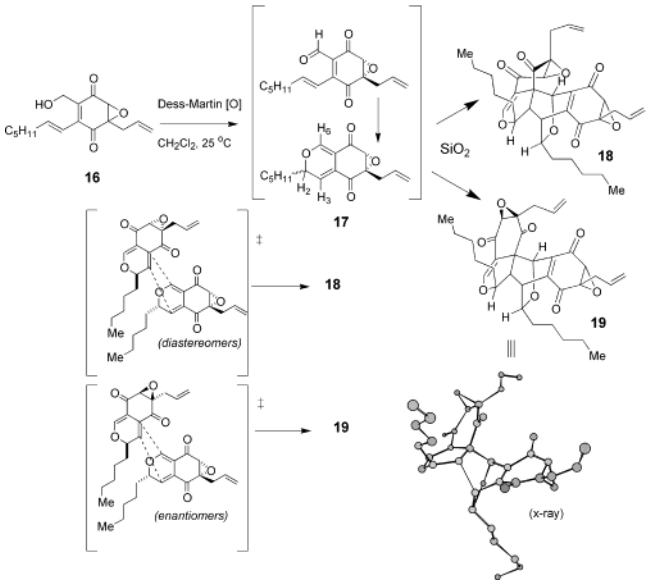
**Scheme 1**[a]



[a] Reagents: (a) (i) BuLi, 3:1 hexane/benzene, −25 °C, 10 h, (ii) $BrCF_2CF_2Br$, THF, 0.5 h, 70%; (b) 13 M HCl, THF, 10 min, 100%; (c) $H_2SO_4$, 70 °C, 14 h, 52%; (d) allyl bromide, $K_2CO_3$, DMF, 3 h; (e) $NaBH_4$, EtOH, 0.5 h; (f) TBDPSCl, imidazole, DMF, 2.5 h (90% for three steps); (g) (i) neat, 180 °C, 2 h, (ii) $PhI(OAc)_2$, MeOH, 20 min; 70%; (h) $HO(CH_2)_3OH$, PPTS, $C_6H_6$, 80 °C, 20 min, 90%; (i) $Ph_3COOH$, KHMDS, THF, −78 → −20 °C, 6 h, 81%; (j) (*E*)-tributyl-1-heptenyl stannane, $Pd(PPh_3)_4$, $PhCH_3$, 110 °C, 4 h, 98%; (k) 48% HF, $CH_3CN$, 7 h, 76%.

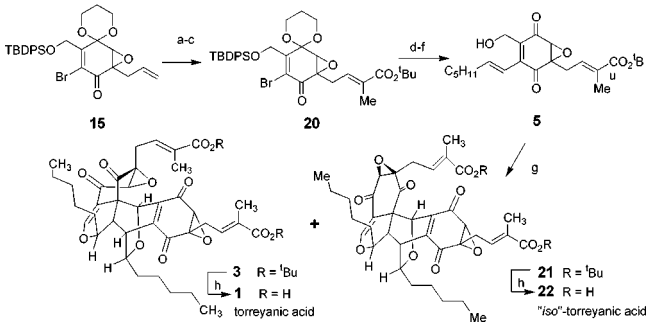
**Scheme 2**



afforded 1,3-dioxane **14**, which was smoothly epoxidized to afford monoepoxide **15** (81%).[16] Attachment of the alkenyl side chain was accomplished by a Stille coupling reaction[17] with (*E*)-tributyl-1-heptenyl stannane. Exposure of the diene intermediate to HF/$CH_3CN$ effected sequential hydrolysis of cyclic acetal and silyl ether protecting groups to afford the target quinone epoxide **16**.

Gratifyingly, Dess−Martin oxidation of **16** ($CH_2Cl_2$, 1 h) initiated the tandem oxidation−6$\pi$-electrocyclization−dimerization process to afford a crude mixture of 2*H*-pyran **17** (approximately 1:1 mixture of diastereomers) and two dimeric products (monomer:dimers approximately 2.6:1) (Scheme 2).[18] After silica gel chromatography,[19] only dimeric products **18** (26%) and **19** (46%) were isolated, indicating acid catalysis of the dimerization. The major dimeric product **19** was produced by *exo*-Diels−Alder dimerization of *2H-pyran epoxide enantiomers*, as determined by single X-ray crystal structure analysis. The structure of the minor dimer **18** was assigned as the torreyanic core structure by comparison to the $^1$H NMR of the natural product and subsequent preparation of (±)-**1**. It should be noted that both **18** and **19** are produced from Diels−Alder dimerization reactions in which the pentyl side chains are anti to one another[1a] and the dienophile approaches the diene anti to the epoxide moiety.

**Scheme 3**[a]



[a] Reagents: (a) catalytic $OsO_4$, NMO, acetone/$H_2O$, 25 °C, 15 h; (b) $Pb(OAc)_4$, THF, 15 min, 96%; (c) $PPh_3{=}C(CH_3)COO^tBu$, $CH_2Cl_2$, −35 → −10 °C, 4 h, 64%; (d) (*E*)-tributyl-1-heptenyl stannane, $Pd(PPh_3)_4$, $PhCH_3$, 110 °C, 1.5 h, 97%; (e) TBAF/AcOH (1:1), THF, 18 h, 72%; (f) 48% HF, $CH_3CN$, 15 min, 93%; (g) Dess−Martin periodinane, $CH_2Cl_2$, 1 h, $SiO_2$, 80%; (h) TFA/$CH_2Cl_2$ (25:75), 2 h, 100%.

Completion of the synthesis of (±)-**1** required installation of the 2-methyl-2-butenoic acid side chain, which we elected to perform at the monomer stage (Scheme 3). This was accomplished by terminal olefin oxidation to an intermediate aldehyde, which was converted by two-carbon homologation[20] to enoate **20**. Stille vinylation of **20**, silyl deprotection (TBAF/AcOH), and acetal hydrolysis proceeded smoothly to afford quinone epoxide **5**. Treatment of **5** with Dess−Martin periodinane afforded a crude product mixture, which was purified[19] to afford dimeric products **3** and **21** in 39 and 41% yields, respectively. Treatment of **3** and **21** with TFA/$CH_2Cl_2$ effected *tert*-butyl ester removal to afford torreyanic acid **1** and stereoisomer **22** (*iso*-torreyanic acid). The structure of **1** was confirmed to be identical to natural torreyanic acid by $^1$H and $^{13}$C NMR, IR, and TLC $R_f$ values in three solvent systems.

In summary, the first total synthesis of racemic torreyanic acid has been achieved by the proposed biomimetic route employing a [4 + 2] dimerization of diastereomeric 2*H*-pyran monomers. An additional stereoisomer has been identified in these tandem reactions resulting from dimerization of 2*H*-pyran enantiomers to produce a compound which may not be available from Nature. Continued studies on torreyanic acid and related epoxyquinoids and further chemistry of 2*H*-pyrans are in progress and will be reported in due course.

**Acknowledgment.** We thank Professor Gary Strobel (Montana State University) for supplying a sample of natural torreyanic acid and Professor Jon Clardy (Cornell University) for helpful discussions.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds, including X-ray structural analyses of compound **19** (PDF). X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Structural analyses designed to further understand this change in reactivity are in progress and will be reported separately.

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(18) Partial $^1$H NMR for 2*H*-pyran **17** ($CDCl_3$): $\delta$ 7.52 (s, 1H, H6), 6.19 (m, 1H, H2), 6.25 (overlapping d, 1H, $J$ = 4 Hz, H3) ppm.

(19) The reaction mixture was allowed to stand on a silica gel column for 1 h to effect complete Diels−Alder dimerization prior to elution of products. See the Supporting Information for further details.

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