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A C_2-Symmetric Chiral Pool-Based Flexible Strategy: Synthesis of (+)- and (−)-Shikimic Acids, (+)- and (−)-4-*epi*-Shikimic Acids, and (+)- and (−)-Pinitol

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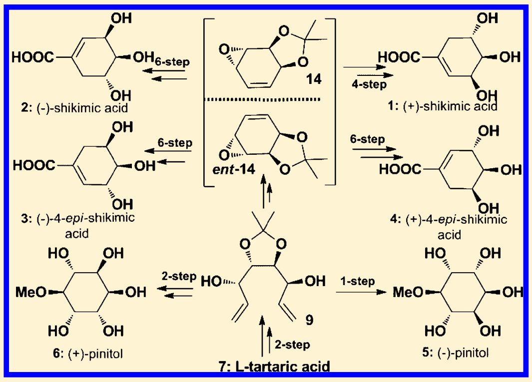
Supporting Information

ABSTRACT: Via combination of a novel acid-promoted rearrangement of acetal functionality with the controlled installation of the epoxide unit to create the pivotal epoxide intermediates in enantiomerically pure form, a simple, concise, flexible, and readily scalable enantiodivergent synthesis of (+)- and (−)-shikimic acids and (+)- and (−)-4-*epi*-shikimic acids has emerged. This simple strategy not only provides an efficient approach to shikimic acids but also can readily be adopted for the synthesis of (+)- and (−)-pinitols. These concise total syntheses exemplify the use of pivotal allylic epoxide **14** and its enantiomer ***ent*-14**. A readily available inexpensive C_2-symmetric L-tartaric acid (**7**) served as key precursor. In general, the strategy here provides a neat example of the use of a four-carbon chiron and offers a good account of the synthesis of functionalized cyclohexane targets.



■ INTRODUCTION

Biologically and chemically important molecules like (+)- and (−)-shikimic acid,[1−5] (+)- and (−)-4-*epi*-shikimic acid,[6] and (+)- and (−)-pinitols[7−9] have provoked long-term interest in their total synthesis because of their potential biological activities. Recently, it has been shown that (−)-shikimic acid (**2**) in combination with a cationic amphiphile enhances tumor protective therapeutic benefits in DC-based DNA vaccination.[5a] The biological importance of 4-*epi*-shikimic acid (**3**) has also been described by Kiessling et al.[6a] Additionally, recent research has revealed that (+)-pinitol **6** is a potent protector against breast cancer.[9] In light of our continual interest in the total synthesis of bioactive natural products and their analogues, focusing on cyclohexane derivatives,[10,11] we have been fascinated by (+)- and (−)-shikimic acid, (+)- and (−)-4-*epi*-shikimic acid, and (+)- and (−)-pinitols, because these molecules also serve as suitable chiral building blocks for the generation of other biologically important molecules.[5,6a,9,12] Shikimic acid, 4-*epi*-shikimic acid, and pinitol have been synthesized in racemic forms and as pure enantiomers by either a chemoenzymatic pathway or a chemical pathway.[2,4,6,7] A significant drawback of many of the reported procedures arises from lengthy protecting group manipulation and utilization of toxic chemicals.

Our goal was to devise an enantiodivergent synthetic strategy called a "common chiral pool strategy", in the hope that it could be amenable to the construction of either a (+)-enantiomer or a (−)-enantiomer as required from the same chiral compound. Herein, we report a common chiral pool-based synthetic strategy that leads from the commercially available and cheap C_2-symmetric L-tartaric acid (**7**) to both enantiomers of shikimic acid, 4-*epi*-shikimic acid, and pinitol.

■ RESULTS AND DISCUSSION

Retrosynthetic Analysis. Scheme 1 outlines, in retrosynthetic format, the overall plan. We envisioned that the cyclohexenediol **11** could be formulated by ring-closing metathesis (RCM) of tartaric acid-derived allylic hydroxyls **9** followed by a novel acid-promoted acetal rearrangement. Subsequently, the controlled installation of an epoxide unit leads to the enantiomerically pure pivotal epoxide **14** and its enantiomer ***ent*-14**. The methoxy and carboxyl functional groups in the cyclohexane ring were contrived at a relatively later stage of the synthesis to achieve a simple, concise, flexible, and readily scalable enantiodivergent synthesis.

Synthesis of Allylic Epoxides 14 and *ent*-14. The synthesis commenced with the preparation of allylic hydroxyls **9** from cheap L-tartaric acid (**7**), according to a two-step procedure (Scheme 2).[10,11,13] RCM of allylic hydroxyls **9** was performed with a second-generation Grubbs catalyst under diluted reaction conditions to generate the desired cyclohexenol derivative **10** in 92% yield.[10,11,14,15] The solvent used in this step was recycled and reused without yield losses. We next focused on the conversion of the *trans* acetonide to more stable *cis* acetonide. Toward this end, we examined the reaction with several acid catalysts, including CSA, TfOH, PTSA, $FeCl_3$, acetic acid, PPTS, and TFA. Gratifyingly, exposure of the *in situ*-generated C_2-symmetric *trans* acetonide **10** to 0.2 mol %

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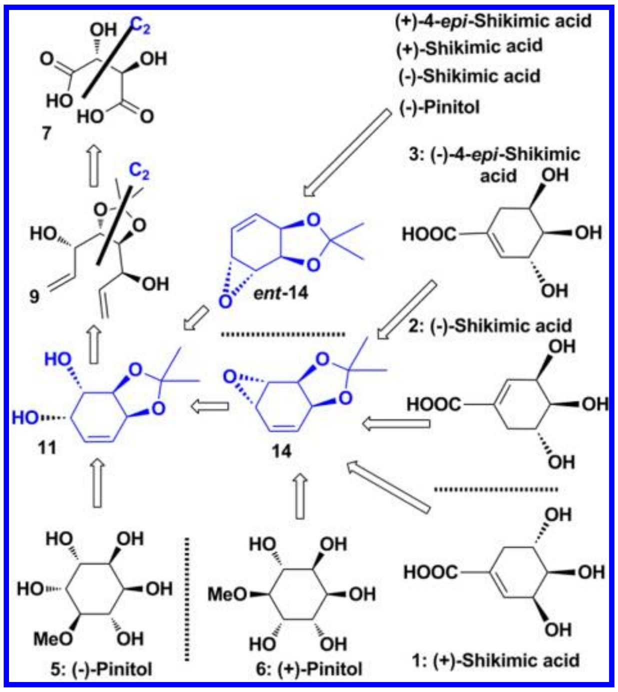
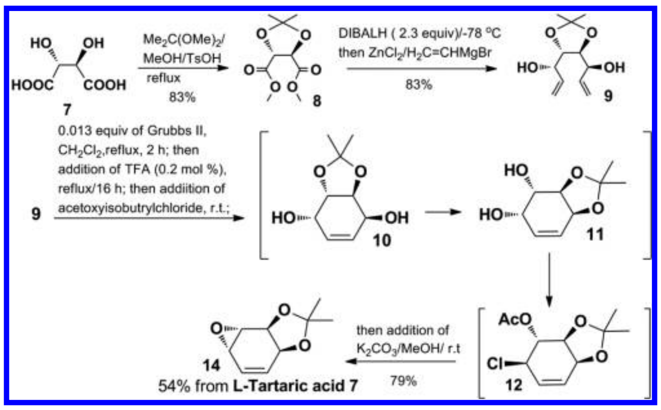
Scheme 1. Retrosynthetic Analysis



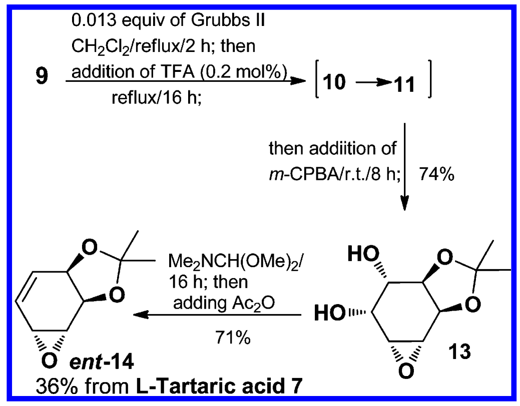
Scheme 2. Enantiospecific Synthesis of Allylic Epoxide 14



TFA resulted in the efficient formation of the thermally stable *cis*-fused acetonide **11**. Other catalysts failed to produce good yields at various concentrations and temperatures. With enantiopure cyclohexenediol **11** in hand (92% from compound **9**), the key step is the transformation of enediol **11** into allylic epoxide **14** with retention of configuration. Fortunately, subsequent treatment of the *in situ*-generated enediol **11** with α-acetoxyisobutryl chloride[16] led smoothly to the corresponding *trans*-chlorocyclohexyl acetate **12**, which underwent saponification and intramolecular S_N2 nucleophilic attack to yield allylic epoxide **14**. Remarkably, a one-pot conversion of allylic hydroxyls **9** into allylic epoxide **14** was developed, delivering the final product in 79% yield.

On the other hand, the preparation of its isomer, ***ent*-14** (Scheme 3), started with the direct conversion of compound **9** to *cis*-epoxydiol **13**. Thus, via the subsequent treatment of **11** with *m*-CPBA that led to *cis*-epoxydiol **13**, as anticipated, hydrogen bonding directs the formation of this required epoxide. Notably, the conversion of **9** to **13** was also performed in one pot. Treatment of compound **13** with *N*,*N*-dimethylformamide dimethylacetal[17] for 16 h, followed by

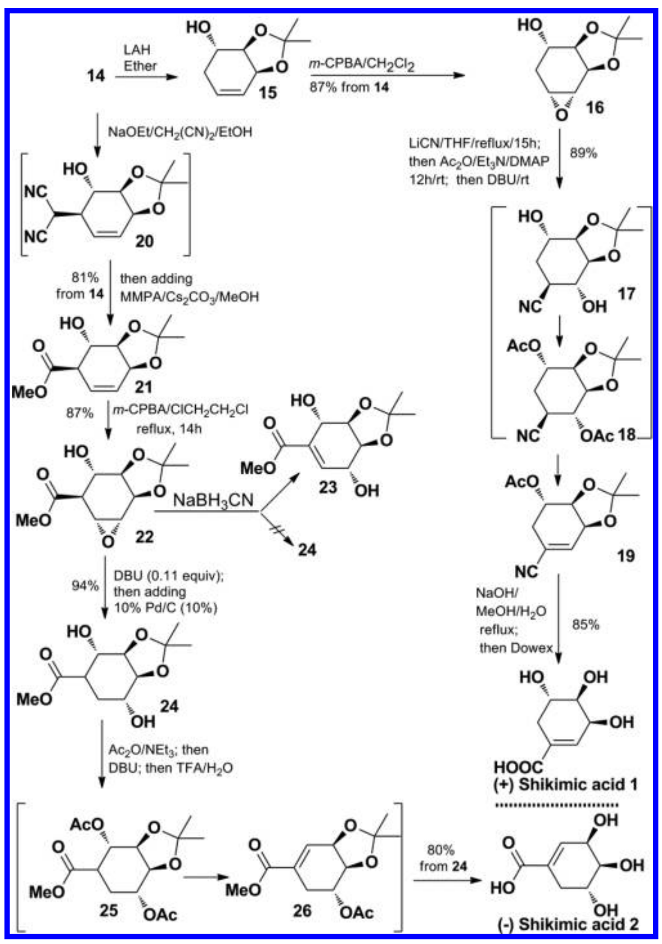
Scheme 3. Enantiospecific Synthesis of Allylic Epoxide *ent*-14



addition of acetic anhydride, afforded cyclohexane derivative ***ent*-14** in good yield. This enantiodivergent sequence offers a flexible approach to epoxide **14** and its enantiomer ***ent*-14** in 54 and 36% overall yields, respectively, from cheap L-tartaric acid (**7**).

Synthesis of (+)-Shikimic Acid. With a facile route to **14** in hand, we turned our attention to construction of (+)-shikimic acid **1** (Scheme 4). Attempts to perform the reduction of **12** with superhydride gave an unsatisfactory yield of **15**. On the other hand, addition of LAH to epoxide **14** gave

Scheme 4. Synthesis of (+)-Shikimic Acid and (−)-Shikimic Acid



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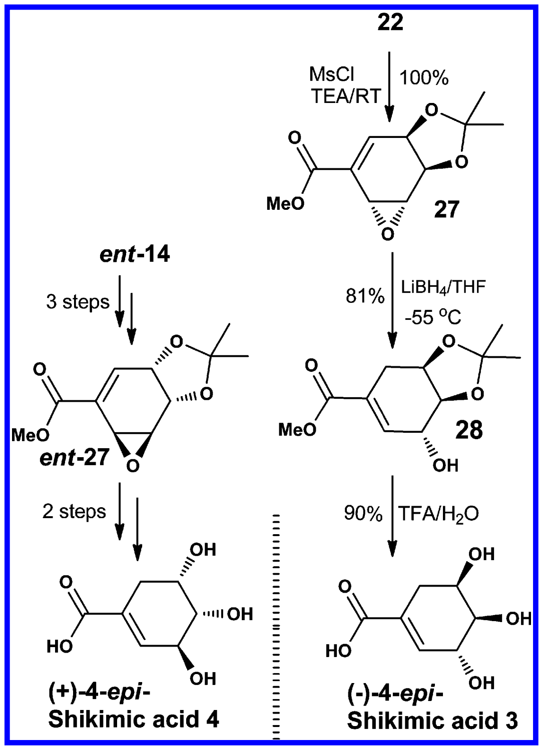
exclusively compound **15** in excellent yield. In a similar way, ***ent*-15** was prepared from ***ent*-14**. Epoxidation of cyclohexenol **15** with *m*-CPBA afforded the desired epoxide **16** in 87% yield. Regiospecific ring opening of oxirane **16** with a cyanide nucleophile turned out to be challenging. All attempts to perform the Lewis acid-promoted epoxide ring opening led to either extensive decomposition of oxirane **16** or a trace of the desired epoxide ring opening. Finally, reaction of epoxide **16** with lithium cyanide[18] in refluxing THF led to the desired attack from the less hindered face to give cyanohydrin **17**, which was converted into diacetate **18**. The latter was the precursor of the unsaturated nitrile **19**. The direct conversion of epoxide **16** into nitrile **19** was achieved in 89% yield. Finally, compound **19** underwent acetate saponification followed by acid hydrolysis of acetal, yielding (+)-shikimic acid **1**, whose physical properties are identical to those of the reported compound.[2b] This efficient asymmetric synthesis requires seven steps from L-(+)-tartaric acid (**7**) to give (+)-shikimic acid (**1**) in 36% overall yield (Scheme 4).

Synthesis of (−)-Shikimic Acid. Having achieved an efficient synthesis of **1**, we turned our focus to the concise synthesis of (−)-shikimic acid **2** (Scheme 4). We aimed to devise a simple approach to shikimic acid without cyanide. As a nucleophilic carboxyl group equivalent, we chose to use malononitrile as the better alternate for cyanide. Gratifyingly, the addition of allylic epoxide **14** to a mixture of malononitrile and sodium ethoxide led to regio- and stereocontrolled introduction of the malononitrile group by S_N2 chemistry to afford **20**. With **20** in hand, the stage was set for the transformation of malononitrile into carboxylate ester. All attempts to perform this transformation using various peroxides such as UHP, *m*-CPBA, and *t*-BuOOH led to disappointing results. On the other hand, addition of **20** to a mixture of Cs_2CO_3 and magnesium bis(monoperoxy phthalate) (MMPA),[19] an eco-friendly and highly safe peroxide, gave reproducibly the desired **21** in 81% yield from **14**. Treatment of **21** with *m*-CPBA yielded epoxide **22** in only ~60% yield; nevertheless, the same reaction furnished an 87% yield in the presence of 10 mol % 2,6-di-*tert*-butyl-4-methylphenol. Attention was then focused on the regiospecific reductive cleavage of epoxide. We anticipated that the neighboring carboxylate group would facilitate nucleophilic hydride attack at its adjacent position. Surprisingly, treating **22** with many reducing agents such as $LiBH_4$, DIBAL, Zn-TMSCl, $Zn(BH_4)_2$, $NaBH(t\text{-}OBu)_3$, and $NaBH_4$ led to trace amounts of elimination product **23** along with starting material **22**. Interestingly, treatment of **22** with $NaBH_3(CN)$ yielded **23** as the sole product. To simplify the synthesis of diol **24**, we found another protocol; thus, treating **22** with DBU (0.11 equiv) and H_2/Pd/C provided the desired product in 94% yield. Acetylation of compound **24** using Ac_2O followed by DBU-promoted elimination of HOAc and aqueous TFA-mediated acetonide deprotection[2c] and ester hydrolysis yielded (−)-shikimic acid[2d] **2** in 80% yield. This chiral pool-based synthesis requires nine steps from L-(+)-tartaric acid **7** to give (−)-shikimic acid **2** in 29% overall yield (Scheme 4).

Synthesis of (+)-4-*epi*-Shikimic Acid and (−)-4-*epi*-Shikimic Acid. To ensure the effectiveness of our devised flexible strategy, we intended to generate 4-*epi*-shikimic acid **3** (Scheme 5). Treatment of **22** with methanesulfonyl chloride and TEA affords corresponding unsaturated carboxylate **27** in 100% yield. While substrate **27** was treated with reducing agents, a competition reaction between S_N2 and S_N2' arose.

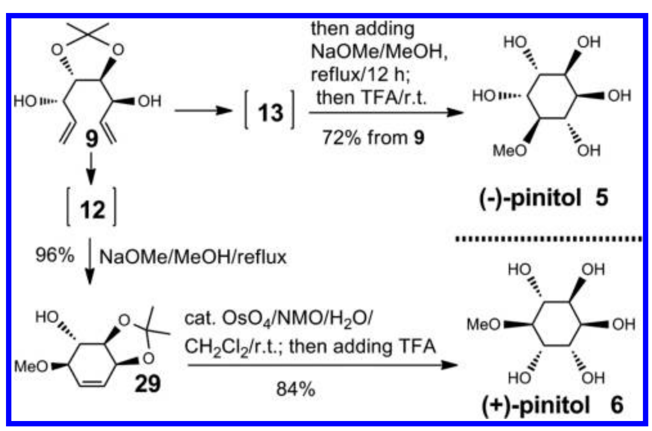
Scheme 5. Synthesis of (−)-4-*epi*-Shikimic Acid and (+)-4-*epi*-Shikimic Acid



Exposure of unsaturated carboxylate **27** to reducing reagents like $NaBH_4$/MeOH, BH_3/THF, DIBAL, and $Zn(BH_4)_2$ gave an unsatisfactory yield of **28**. Finally, we found that treating compound **27** with $LiBH_4$ at −55 °C furnished **28** in 81% yield. Treatment of **28** with aqueous TFA resulted in efficient ester hydrolysis and acetonide deprotection to give 4-*epi*-shikimic acid **3** in 90% yield. Comparison of the spectral properties to those recorded confirms its identity.[6a] As before, transformation of intermediate ***ent*-27** furnished (+)-4-*epi*-shikimic acid **4** in two steps. Thus, (−)-4-*epi*- and (+)-*epi*-shikimic acids were available by this flexible strategy from L-tartaric acid **7**.

Synthesis of (+)-Pinitol and (−)-Pinitol. The novel effectiveness of this C_2-symmetric chiral pool-based flexible strategy was next turned to the asymmetric synthesis of (+)- and (−)-pinitols (Scheme 6). Methanolysis of epoxide **13** with NaOMe/MeOH followed by the deprotection of acetonide with TFA resulted in the efficient formation of the desired

Scheme 6. Synthesis of (−)-Pinitol and (+)-Pinitol



(−)-pinitol **5**, whose physical properties are identical to those of the reported compound.[7e] The entire operations from **9** to **5** were performed in a single vessel to deliver (−)-pinitol in 72% yield. In the same way, transestrification of acetate **12** with sodium methoxide at reflux simultaneously effected epoxide formation and regiospecific opening of an allylic epoxide to give methoxy alcohol **29** in 96% yield. Dihydroxylation of **29** with OsO_4 followed by addition of TFA provided the desired (+)-pinitol **6** in 84% yield. By this flexible strategy, inexpensive L-(+)-tartaric acid **7** can be converted into (+)-pinitol **6** and (−)-pinitol **5** in 56% (four steps) and 50% (three steps) overall yields, respectively.

CONCLUSION

In conclusion, less abundant and unnatural pinitols, shikimic acids, and their analogues were synthesized from highly abundant L-tartaric acid. In other words, we successfully synthesized enantiomerically diverse molecules from a single enantiomer. The flexible technology described above should be applicable to the preparation of various functionalized cyclohexane natural products, which are required for biological evaluations and applications. That work is currently ongoing and will be reported in due course.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all nonaqueous reactions were conducted under an atmosphere of N_2 in oven-dried apparatus. Commercial grade solvents were dried by known methods. Flash chromatography was performed over silica gel (230−400 mesh). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using the indicated solvent at ambient temperature. Chemical shifts are reported in parts per million and coupling constants (J) (H,H) in hertz; spectral splitting patterns have been assigned as singlet (s), doublet (d), triplet (t), quadruplet (q), broad (br), broad band (br b), multiplet or more overlapping signals (m), etc. Optical rotations were measured at 25 °C in the stated solvents. Mass spectra were obtained using orbitrap apparatus from a high-resolution ESI mass spectrometer. Mass spectra were obtained using double-focusing apparatus from a high-resolution EI and FAB mass spectrometer. IR spectra were recorded as a thin film and expressed in inverse centimeters. Substrates **8** and **9** were prepared in accordance with our previous report.[10] Reaction mass and room temperature are abbreviated as RM and rt, respectively.

Experimental Procedure and Characterization Data. *(1S,4S,5S,6S)-5,6-(Isopropylidenedioxy)-2-cyclohexene-1,4-diol* ***(10)***.[14] To a solution of allylic hydroxyls **9** (3.0 g, 14 mmol) in CH_2Cl_2 (1800 mL) at rt was added a solution of the second-generation Grubbs catalyst (156 mg, 0.18 mmol, 0.013 equiv) in CH_2Cl_2 (10 mL). The RM was stirred at reflux for 2 h, and then the solvent was carefully distilled (oil bath temperature of 50 °C, and −10 °C as condenser cooling). The residue was flash chromatographed (1.5:1 hexane:acetone) to give cyclic diol **10** (2.4 g, 12.88 mmol, 92%): R_f = 0.48 (EtOAc); $[\alpha]_D^{25}$ = +338.6 (c = 0.7, $CHCl_3$); IR (film) ν_{max} 3349, 3037, 2987 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, J = 3.2, 1.6, 2H), 4.53−4.52 (m, 2H), 3.96 (dd, J = 2.0, 1.2, 2H), 2.30 (br b, 2H), 1.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.4 (CH), 110.4 (C), 73.4 (CH), 64.6 (CH), 26.8 (CH_3); HRMS (FAB) calcd for $C_9H_{15}O_4$ [M + H]$^+$ 187.0970, found 187.0965.

(1S,2S,3S,4S)-3,4-(Isopropylidenedioxy)cyclohex-5-ene-1,2-diol ***(11)***.[26] To a solution of allylic hydroxyls **9** (3.0 g, 14 mmol) in CH_2Cl_2 (1800 mL) at rt was added a solution of the second-generation Grubbs catalyst (156 mg, 0.18 mmol, 0.013 equiv) in CH_2Cl_2 (10 mL). The RM was stirred at reflux for 2 h, and then a solution of CF_3COOH (320 mg, 2.8 mmol) in 4 mL of CH_2Cl_2 was added dropwise. The RM was stirred at reflux for an additional 16 h and then cooled to 0 °C. The RM was quenched with saturated aqueous sodium bicarbonate (100 mL). The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was flash chromatographed with a 1:1 hexane/ethyl acetate mixture to give *cis*-cyclic diol **11** (2.4 g, 12.9 mmol, 92%): R_f = 0.58 (EtOAc); $[\alpha]_D^{25}$ = +148.9 (c = 2.8, $CHCl_3$); IR (film) ν_{max} 3419, 3036, 1219, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91−5.90 (m, 2H), 4.64 (d, J = 6, 1H), 4.34 (t, J = 6.4, 1H), 4,29 − 4.28 (m, 1H), 3.95 (dd, J = 6.4, 3.2, 1H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.0 (CH), 127.3 (CH), 109.4 (C), 75.7 (CH), 71.8 (CH), 71.0 (CH), 65.9 (CH), 27.8 (CH_3), 25.8 (CH_3); HRMS (FAB) calcd for $C_9H_{15}O_4$ [M + H]$^+$ 187.0970, found 187.0965.

(1R,2R,3S,4S)-1-Chloro-2-acetoxy-3,4-(isopropylidenedioxy)-cyclohex-5-ene ***(12)***. To a solution of allylic hydroxyls **9** (3.0 g, 14 mmol) in CH_2Cl_2 (1800 mL) at rt was added a solution of the second-generation Grubbs catalyst (156 mg, 0.18 mmol, 0.013 equiv) in CH_2Cl_2 (10 mL). The RM was stirred at reflux for 2 h, and then a solution of CF_3COOH (320 mg, 2.8 mmol) in 4 mL of CH_2Cl_2 was added dropwise. The RM was stirred at reflux for an additional 16 h and then cooled to 0 °C. The RM was treated with 2-acetoxyisobutyryl chloride (2.76 g, 16.8 mmol). The RM was stirred at rt for 1 h, washed with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was flash chromatographed with a 15:1 hexane/ethyl acetate mixture to give chloro ester **12** (2.9 g, 11.8 mmol, 84%): R_f = 0.6 (3:1 hexane:EtOAc); $[\alpha]_D^{25}$ = −15.0 (c = 2.2, $CHCl_3$); IR (film) ν_{max} 3018, 1754, 1224, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (br, 2H), 5.25 (dd, J = 9.2, 8.8, 1H), 4.62−4.60 (m, 1H), 4.38 (dt, J = 8.8, 1.2, 1H), 4.12 (dd, J = 9.2, 6.0, 1H), 2.14 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C), 132.2 (CH), 124.7 (CH), 111.2 (C), 75.7 (CH), 74.1 (CH), 72.1 (CH), 56.5 (CH), 27.7 (CH_3), 26.2 (CH_3), 20.9 (CH_3); HRMS (FAB) calcd for $C_{11}H_{16}ClO_4$ [M + H]$^+$ 247.0737, found 247.0746.

(1R,2S,3R,4S,5R,6R)-3,4-(Isopropylidenedioxy)-5,6-epoxycyclo-hexane-1,2-diol ***(13)***. To a solution of allylic hydroxyls **9** (3.0 g, 14 mmol) in CH_2Cl_2 (1800 mL) at rt was added a solution of the second-generation Grubbs catalyst (156 mg, 0.18 mmol, 0.013 equiv) in CH_2Cl_2 (10 mL). The RM was stirred at reflux for 2 h, and then a solution of CF_3COOH (320 mg, 2.8 mmol) in 4 mL of CH_2Cl_2 was added dropwise. The RM was stirred at reflux for an additional 16 h, allowed to reach rt, and then treated with *m*-CPBA (4.8 g, 28 mmol). The RM was stirred at rt for 8 h, cooled to 0 °C, treated with iodine until a red-yellow color persisted, and then washed with saturated aqueous sodium bisulfite and aqueous sodium carbonate. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was flash chromatographed with a 1:1 hexane/ethyl acetate mixture to give *cis*-epoxydiol **13** (2.1 g, 10.4 mmol, 74%): R_f = 0.7 (EtOAc); $[\alpha]_D^{25}$ = +1.6 (c = 1.9, $CHCl_3$); IR (film) ν_{max} 3247, 2906, 1227, 1087, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (d, J = 6.4, 1H), 4.52−4.49 (m, 1H), 4.21 (d, J = 3.6, 1H), 4.03 (m, 1H), 3.52−3.51 (m, 1H), 3.38−3.37 (m, 1H), 2.84 (br b, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.9 (C), 76.9 (CH), 69.7 (CH), 68.4 (CH), 64.2 (CH), 57.7 (CH), 55.9 (CH), 27.3 (CH_3), 25.0 (CH_3); HRMS (EI) calcd for $C_9H_{14}O_5$ 202.0841, found 202.0835.

(3aS,5aS,6aS,6bS)-2,2-Dimethyl-3a,5a,6a,6b-tetrahydrooxireno-[2′,3′:3,4]benzo[1,2-d][1,3]dioxole ***(14)***. To a solution of allylic hydroxyls **9** (3.0 g, 14 mmol) in CH_2Cl_2 (1800 mL) at rt was added a solution of the second-generation Grubbs catalyst (156 mg, 0.18 mmol, 0.013 equiv) in CH_2Cl_2 (10 mL). The RM was stirred at reflux for 2 h, and then a solution of CF_3COOH (320 mg, 2.8 mmol) in 4 mL of CH_2Cl_2 was added dropwise. The RM was stirred at reflux for an additional 16 h and then cooled to 0 °C. The RM was treated with 2-acetoxyisobutyryl chloride (2.9 g, 11.8 mmol). The RM was stirred at rt for 1 h, and then solvent was evaporated. Anhydrous methanol (35 mL) was added to RM and the mixture cooled to 0 °C. Anhydrous potassium carbonate (2.51 g, 18.2 mmol) was added and then the mixture stirred at rt for 40 min. RM was poured into an ice/water mixture (6 mL) and then extracted with CH_2Cl_2 (10 × 10 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 13:1

hexane/ethyl acetate mixture to give allylic epoxide **14** (1.9 g, 11.06 mmol, 79%): R_f = 0.83 (3:1 hexane:EtOAc); $[\alpha]_D^{25}$ = +22.5 (c = 1.5, CH_2Cl_2). For spectral data, see ***ent*-14**.

*(3aR,5aR,6aR,6bR)-2,2-Dimethyl-3a,5a,6a,6b-tetrahydrooxireno-[2′,3′:3,4]benzo[1,2-d][1,3]dioxole (**ent-14**).* (1) Epoxy diol **12** (202 mg, 1 mmol) in *N,N*-dimethylformamide dimethyl acetal (0.8 mL) was vigorously stirred at rt in an argon atmosphere for 16 h. The excess acetal was evaporated under reduced pressure and then acetic anhydride (1 mL) added to the same flask. The RM was vigorously stirred at 120 °C for 3.5 h and then allowed to cool to rt. RM was filtered over silica gel, washed with CH_2Cl_2 (4 mL), and then concentrated under reduced pressure. The residue was subjected to flash chromatography with a 13:1 hexane/ethyl acetate mixture to give *ent*-allylic epoxide ***ent*-14** (120 mg, 0.71 mmol, 71%): R_f = 0.83 (3:1 hexane:EtOAc); $[\alpha]_D^{25}$ = −22.1 (c = 1.5, CH_2Cl_2). For spectral data, see the next paragraph.

(2) Epoxy alcohol **16** (186 mg, 1 mmol) in THF (1 mL) was treated with triethylamine (182 mg, 1.8 mmol) and mesyl chloride (155 mg, 1.35 mmol) at 0 °C for 5 min and then stirred at rt for 40 min. DBU (274 mg, 1.8 mmol) was added to the RM and stirred at rt for 2 h. The RM was diluted with CH_2Cl_2, quenched with an ice/water mixture, and then extracted with CH_2Cl_2 (2 × 3 mL). Combined extracts were dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 13:1 hexane/ethyl acetate mixture to give *ent*-allylic epoxide ***ent*-14** (159 mg, 0.71 mmol, 94%): R_f = 0.83 (3:1 hexane:EtOAc); $[\alpha]_D^{25}$ = −22.1 (c = 1.5, CH_2Cl_2): IR (film) ν_{max} 3010, 2986, 1379, 1370, 1243, 1167, 1068, 1052, 1000, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (ddd, J = 10.0, 4.0, 1.6, 1H), 5.74 (dd, J = 10.0, 1.2, 1H), 4.72 (dt, J = 6.8, 1.2, 1H), 4.40 (dt, J = 7.2, 1.6, 1H), 3.49 (dd, J = 3.6, 2.4, 1H), 3.28 (dd, J = 3.6, 2.0, 1H), 1.34 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.06 (CH), 123.46 (CH), 110.54 (C), 70.81 (CH), 70.74 (CH), 49.20 (CH), 46.50 (CH), 27.79 (CH_3), 25.96 (CH_3); HRMS (FAB) calcd for $C_9H_{13}O_3$ $[M + H]^+$ 169.0865, found 169.0870. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.10.

*(3aR,4S,7aS)-2,2-Dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]-dioxol-4-ol (**15**).* To a suspension of LAH (139.5 mg, 3.675 mmol) in anhydrous diethyl ether (5 mL) at 0 °C was added dropwise allylic epoxide **14** (595 mg, 3.5 mmol) in ether (5 mL). The RM was heated to reflux for 5 h and 30 min and then cooled to 0 °C. The RM was carefully quenched with chilled water (1 mL) and then filtered through Celite. The ether layer was washed with a 15% NaCl solution (2 × 5 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give **15** (583.40 mg, 3.43 mmol, 98%): R_f = 0.2 (silica gel, 3:1 hexane:ethylacetate); $[\alpha]_D^{25}$ = +143 (c = 1.78, $CHCl_3$). For spectral data, see ***ent*-15**.

*(3aS,4R,7aR)-2,2-Dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]-dioxol-4-ol (**ent-15**).*[21] To a suspension of LAH (139.5 mg, 3.675 mmol) in anhydrous diethyl ether (5 mL) at 0 °C was added dropwise allylic epoxide ***ent*-14** (595 mg, 3.5 mmol) in ether (5 mL). The RM was heated to reflux for 5 h and 30 min and then cooled to 0 °C. The RM was carefully quenched with chilled water (1 mL) and then filtered through Celite. The ether layer washed with a 15% NaCl solution (2 × 5 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give ***ent*-15** (583.40 mg, 3.43 mmol, 98%): R_f = 0.2 (silica gel, 3:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −146 (c = 1.35, $CHCl_3$); IR (film) ν_{max} 3037, 2986, 1378, 1244, 1217, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.82 (m, 2H), 4.60−4.58 (m, 1H), 3.95 (dd, J = 8.4, 6.2, 1H), 3.78−3.75 (m, 1H), 2.45 (d, J = 10.8, 1H), 2.39 (dt, J = 10.0, 5.0, 2H), 2.01 (dddd, J = 10, 4.6, 2.6, 1.4, 1H) 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3 (CH), 124.3 (CH), 109.2 (C), 79.4 (CH), 72.7 (CH), 69.3 (CH), 30.8 (CH_2), 28.4 (CH_3), 25.9 (CH_3); HRMS (EI) calcd for $C_9H_{14}O_3$ 170.0943, found 170.0938.

*(3aR,4S,5aR,6aR,6bS)-2,2-Dimethylhexahydrooxireno[2′,3′:3,4]-benzo[1,2-d][1,3]dioxol-4-ol (**16**).* To a suspension of LAH (79.7 mg, 2.1 mmol) in anhydrous diethyl ether (3 mL) at 0 °C was added dropwise allylic epoxide **14** (338 mg, 2 mmol) in ether (3 mL). The RM was heated to reflux for 5 h and 30 min and then cooled to 0 °C. The RM was carefully quenched with chilled water (1 mL) and then filtered through Celite. The ether layer was washed with a 15% NaCl solution (2 × 5 mL), dried ($MgSO_4$), and concentrated. The residue proceeded to the next step without purification. The residue was dissolved in CH_2Cl_2 (3 mL) at rt, and then *m*-CPBA (690.3 mg, 4 mmol) was added and the mixture stirred overnight. The RM was quenched with saturated $NaHCO_3$ (2 mL). The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give **16** (324 mg, 1.74 mmol, 87%): R_f = 0.6 (silica gel, 3:1 hexane:ethyl acetate); IR (film) ν_{max} 3505, 2989, 2932, 1425, 1378, 1228, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (d, J = 6.0, 1H), 4.30−4.28 (m, 1H), 3.90 (dt, J = 6.4, 3.6, 1H), 3.39 (dd, J = 2.4, 1.2, 1H), 3.19 (d, J = 3.6, 1H), 2.95 (d, J = 11.2, 1H), 2.27−2.25 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.9 (C), 74.5 (CH), 70.4 (CH), 64.6 (CH), 53.2 (CH), 53.0 (CH), 27.6 (CH_2), 25.4 (CH_3), 25.3 (CH_3); HRMS (EI) calcd for $C_9H_{14}O_4$ 186.0892, found 186.0898.

*(3aS,4R,5R,7S,7aR)-4,7-Dihydroxy-2,2-dimethylhexahydrobenzo-[d][1,3]dioxole-5-carbonitrile (**17**).* To epoxy alcohol **16** (558 mg, 3 mmol) in anhydrous THF (10 mL) was added LiCN (396 mg, 12 mmol), and then the mixture was stirred at reflux for 14 h. The RM was left to cool, and saturated aqueous potassium carbonate (3 mL) and ether (10 mL) were added. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 1:1 hexane/ethyl acetate mixture to give **17** (588 mg, 2.76 mmol, 92%): R_f = 0.2 (1:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −39.2 (c = 0.73, $CHCl_3$); IR (film) ν_{max} 3419, 2989, 2249, 1383, 1244, 1222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25−4.23 (m, 1H), 4.15−4.14 (m, 1H), 4.10−4.07 (m, 1H), 3.85−3.81 (m, 1H), 3.0−2.94 (m, 1H), 2.12−2.09 (m, 2H), 1.5 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.3 (CN), 109.9 (C), 78.6 (CH), 76.7 (CH), 72.2 (CH), 65.8 (CH), 30.3 (CH), 28.6 (CH_2), 28.0 (CH_3), 26.0 (CH_3); HRMS (EI) calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.1007.

*(3aS,4R,5R,7S,7aR)-5-Cyano-2,2-dimethylhexahydrobenzo[d]-[1,3]dioxole-4,7-diyl Diacetate (**18**).* To epoxy alcohol **16** (558 mg, 3 mmol) in anhydrous THF (10 mL) was added LiCN (396 mg, 12 mmol), and then the mixture was stirred at reflux for 14 h. The RM was left to cool. Then TEA (455 mg, 4.5 mmol), DMAP (10 mg), and Ac_2O (408.3 mg, 4 mmol) were sequentially added, and the mixture was stirred for 15 h at rt. Water (2 mL) and ether (10 mL) were added to quench the reaction. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give **18** (802 mg, 2.7 mmol, 90%): R_f = 0.80 (1:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −72.3 (c = 1.72, $CHCl_3$); IR (film) ν_{max} 2988, 2936, 2247, 1748, 1443, 1374 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.4 (dd, J = 6.2, 3.0, 1H), 5.23 (dd, J = 11.2, 7.2, 1H), 4.12−4.04 (m, 2H), 2.90 (td, J = 10.8, 4.8, 1H), 2.20−2.07 (m, 8H), 1.55 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (CO), 169.0 (<u>C</u>O), 118.0 (<u>C</u>N), 110.6 (C), 76.4 (CH), 75.3 (CH), 71.2 (CH), 67.0 (CH), 28.6 (CH), 27.7 (CH_2), 27.6 (CH_3), 26.4 (CH_3), 20.9 (CH_3), 20.7 (CH_3); HRMS (ESI) calcd for $C_{14}H_{20}O_6N$ $[M + H]^+$ 298.1291, found 298.1300.

*(3aR,4S,7aS)-6-Cyano-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[d][1,3]dioxol-4-yl Acetate (**19**).* To epoxy alcohol **16** (558 mg, 3 mmol) in anhydrous THF (10 mL) was added LiCN (396 mg, 12 mmol), and then the mixture was stirred at reflux for 14 h. The RM was left to cool. Then TEA (455 mg, 4.5 mmol), DMAP (10 mg), and Ac_2O (408.3 mg, 4 mmol) were sequentially added, and the mixture was stirred for 15 h at rt. Then DBU (1.6 g, 10.5 mmol) was added and the mixture stirred for 13 h at 45 °C. Water (2 mL) and ether (10 mL) were added to quench the reaction. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give **19** (633 mg, 2.67 mmol, 89%): R_f = 0.22 (hexane:ethyl acetate); $[\alpha]_D^{25}$ = +33.5 (c = 1.72, $CHCl_3$); IR (neat) ν_{max} 2989, 2936, 2222, 1747, 1429, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55−6.53 (m, 1H), 5.23−5.20 (m, 1H), 4.65−4.63 (m, 1H), 4.22 (t, J = 5.6, 1H), 2.67 (ddt, J = 17.6, 4.2, 1.9, 1H), 2.31 (dd, J = 17.7, 4.9, 1H), 2.06 (s,

3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 140.6, 117.8, 111.3, 110.5, 72.5, 70.7, 68.0, 28.1, 27.7, 26.0, 20.0; HRMS (ESI) calcd for $C_{12}H_{16}O_4N$ $[M + H]^+$ 238.1079, found 238.1071.

(+)-Shikimic acid (1). To the solution of vinyl nitrile (119 mg, 0.5 mmol) in a 1:1 methanol/water mixture (3 mL) was added sodium hydroxide (2 mmol). The RM was stirred at reflux for 3 h. Then 2 N HCl was slowly added to neutralize the mixture at rt. The RM was concentrated and furthur evaporated with absolute ethanol (2 × 4 mL). Anhydrous methanol (4 mL) and Dowex 50 W x-8 resin were added to the resiude in the same flask. After the mixture had been stirred for 10 h, the resin was filtered off and concentrated to afford shikimic acid. A sample was recrystallized from ethanol ether to furnish (+)-shikimic acid (74 mg, 0.43 mmol, 85%), whose physical properties are identical to those of the reported compound.[2b,d]

*2-[(3aR,4S,5S,7aS)-4-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-yl]malononitrile (**20**).* Sodium ethoxide (918.7 mg, 13.5 mmol) was added to malanonitrile (905 mg, 13.7 mmol) in anhydrous ethanol (3 mL) at 0 °C. After the mixture had been stirred for 5 min, allylic epoxide (504 mg, 3 mmol) in anhydrous ethanol (3 mL) was added and the mixture stirred for 30 min at 0 °C. Chilled water (2.5 mL) and CH_2Cl_2 were added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 × 2.5 mL). Combined organic layers were dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 1:1 hexane/ethyl acetate mixture to give substrate **20**: R_f = 0.58 (1:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −10.74 (*c* = 0.7, $CHCl_3$); IR (neat) ν_{max} 2990, 2920, 2251, 2249, 1380, 1216, 1158, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, *J* = 7.0, 3.0, 1H), 5.92 (d, *J* = 9.6, 1H), 4.68−4.66 (m, 1H), 4.39 (d, *J* = 3.6, 1H), 4.05 (dd, *J* = 8.0, 7.0, 1H), 3.59−3.54 (m, 1H), 2.86 (br s, 1H), 2.72 (d, *J* = 9.2, 1H), 1.5 (s, 3H), 1.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9 (CH), 125.9 (CH), 112.1 (C), 110.7 (C), 110.4 (C), 78.5 (CH), 72.4 (CH), 70.3 (CH), 42.5 (CH), 28.0 (CH), 25.6 (CH_3), 23.9 (CH_3); HRMS (EI) calcd for $C_{12}H_{14}O_3N_2$ 234.1004, found 234.1002.

*(3aR,4S,5R,7aS)-Methyl 4-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole-5-carboxylate (**21**).* Sodium ethoxide (918.7 mg, 13.5 mmol) was added to malanonitrile (905 mg, 13.7 mmol) in anhydrous ethanol (3 mL) at 0 °C. After the mixture had been stirred for 5 min, allylic epoxide (504 mg, 3 mmol) in anhydrous ethanol (3 mL) was added and the mixture stirred for 30 min at 0 °C. Chilled water (2.5 mL) and CH_2Cl_2 were added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 × 2.5 mL). Combined organic layers were dried ($MgSO_4$) and concentrated. Crude residue **20** was taken in anhydrous methanol (10 mL) at 0 °C. Cs_2CO_3 (1.47 g, 4.5 mmol) and magnesium bis(monoperoxy phthalate) (1.9 g, 3.9 mmol) were added, and the mixture was stirred for 10 min. The RM was filtered through silica gel and concentrated. The residue was subjected to flash chromatography with a 1:1 hexane/ethyl acetate mixture to give substrate **21** (554 mg, 2.43 mmol, 81%): R_f = 0.45 (1:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = 15.33 (*c* = 0.6, $CHCl_3$); IR (neat) ν_{max} 3461, 2987, 2931, 1736, 1638, 1255, 1211 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dt, *J* = 10, 3.0, 1H), 5.88 (d, *J* = 10, 1H), 4.62−4.61 (m, 1H), 4.11−4.04 (m, 1H), 3.93 (t, *J* = 9.0, 1H), 3.77 (s, 3H), 3.10 (d, *J* = 9.2, 1H), 3.01 (br s, 1H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C), 127.4 (CH), 125.7 (CH), 110.0 (C), 78.1 (CH), 72.2 (CH), 70.4 (CH), 52.5 (CH), 48.0 (CH_3), 28.1 (CH_3), 25.7 (CH_3); HRMS (ESI) calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.0993.

*(3aR,4S,5S,5aR,6aR,6bS)-Methyl 4-Hydroxy-2,2-dimethylhexahydrooxireno[2′,3′:3,4]benzo[1,2-d][1,3]dioxole-5-carboxylate (**22**).* To methyl ester **21** (342 mg, 1.5 mmol) in dichloroethane (5 mL) were added *m*-CPBA (518 mg, 3 mmol) and butylated hydroxytoluene (33 mg, 0.15 mmol). The RM was refluxed for 14 h and then quenched with sodium bicarbonate. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 4:1 hexane/ethyl acetate mixture to give substrate **22** (320 mg, 1.31 mmol, 87%): R_f = 0.83 (1:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −36.13 (*c* = 6.3, $CHCl_3$); IR (neat) ν_{max} 2989, 2940, 1732, 1440, 1380 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, *J* = 5.9, 1H), 4.45−4.41 (m, 1H), 4.31 (ddd, *J* = 5.6, 4.0, 1.4, 1H), 3.77 (ddt, *J* = 3.8, 2.4, 1.4, 1H), 3.71 (s, 3H), 3.32 (d, *J* = 3.7, 1H), 3.30 (t, *J* = 2.8, 1H), 3.14 (d, *J* = 11.6, 1H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 110.4 (C), 74.1 (CH), 70.2 (CH), 66.6 (CH), 53.4 (CH_3), 53.1 (CH), 52.0 (CH), 42.5 (CH), 26.6 (CH_3), 25.4 (CH_3); HRMS (ESI) calcd for $C_{11}H_{17}O_6$ $[M + H]^+$ 245.1025, found 245.1017.

*(3aR,4S,7R,7aS)-Methyl 4,7-Dihydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxole-5-carboxylate (**23**).* DBU (152 mg, 1.0 mmol) was added to substrate **22** (244 mg, 1 mmol) in methanol (2 mL) at rt. After the mixture had been stirred for 3 h, water (1 mL) and CH_2Cl_2 (2 mL) were added. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 1:1 hexane/ethyl acetate mixture to give substrate **23** (234 mg, 0.96 mmol, 96%): R_f = 0.33 (1:1 hexane:ethyl aceate); IR (neat) ν_{max} 3483, 2981, 1720, 1645, 1441, 1374 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 5.2, 1H), 4.72 (s, 1H), 4.56 (dd, *J* = 6.8, 2.8, 1H), 4.47 (dd, *J* = 7.2, 2.8, 1H), 4.34 (s, 1H), 3.80 (s, 3H), 3.65 (s, 1H), 3.09 (s, 1H), 1.31 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3 (C), 142.0 (C), 134.3 (CH), 108.8 (C), 77.8 (CH), 77.3 (CH), 66.7 (CH), 65.6 (CH), 52.3 (CH_2), 26.3 (CH_3), 24.2 (CH_3); HRMS (ESI) calcd for $C_{11}H_{16}O_6Na$ $[M + Na]^+$ 267.0845, found 267.08442.

*(3aR,4S,7R,7aS)-Methyl 4,7-Dihydroxy-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-5-carboxylate (**24**).* To the suspension of epoxide substrate **22** (976 mg, 4 mmol) and 10% Pd/C (98 mg) in methanol (8 mL) was added DBU (67 mg, 0.44 mmol). The RM was kept in a shaker under a hydrogen pressure of 45 psi for 40 h. The RM was filtered and concentrated. The residue was dissolved in CH_2Cl_2 and washed with water (3 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with a 1:1 hexane/ethyl acetate mixture to give diol **24** (929 mg, 3.76 mmol, 94%): R_f = 0.30 (1:1 hexane:ethyl acetate); IR (neat) ν_{max} 2944, 1725, 1644, 1446, 1379, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, *J* = 3.6, 1H), 4.15−4.12 (m, 2H), 3.92 (dd, *J* = 10.0, 7.6, 1H), 3.71 (s, 3H), 3.09 (br b, 1H), 2.77 (td, *J* = 10.0, 6.2, 1H), 2.20 (s, 1H), 1.98−1.95 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 109.4, 79.0, 78.1, 72.5, 66.5, 52.0, 41.7, 30.0, 27.9, 26.0; HRMS (ESI) calcd for $C_{11}H_{19}O_6$ $[M + H]^+$ 247.1182, found 247.1173.

*(3aR,4S,7R,7aS)-5-(Methoxycarbonyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-4,7-diyl Diacetate (**25**).* To diol substrate **24** (864.5 mg, 3.5 mmol) in THF (7 mL) were added triethylamine (885 mg, 8.75 mmol), DMAP (42.75 mg, 0.35 mmol), and acetic anhydride (786 mg, 7.7 mmol), and the mixture was stirred for 3 h and 40 min. The RM was quenched with a saturated aqueous solution of sodium bicarbonate (2 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with a 2:1 hexane/ethyl acetate mixture to give diacetate **25**: R_f = 0.62 (1:1 hexane:ethyl acetate); IR (neat) ν_{max} 3478, 2988, 1746, 1441, 1375, 1228, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34−5.33 (m, 1H), 5.24 (dd, *J* = 11.0, 7.0, 1H), 4.11 (d, *J* = 5.2, 2H), 3.65 (s, 3H), 2.74 (td, *J* = 11.6, 3.2, 1H), 2.14 (ddd, *J* = 15.2, 12.1, 3.4, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.99 (dt, *J* = 7.2, 3.2, 1H), 1.54 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.7, 169.3, 110.1, 75.6, 72.9, 68.1, 65.8, 52.2, 41.0, 27.62, 27.58, 26.4, 20.99, 20.86; HRMS (ESI) calcd for $C_{15}H_{22}O_8$ 330.1315, found 330.1311.

*(3aR,7R,7aS)-Methyl 7-Acetoxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxole-5-carboxylate (**26**).*[22−24] To diol substrate **24** (864.5 mg, 3.5 mmol) in THF (7 mL) were added triethylamine (885 mg, 8.75 mmol), DMAP (42.75 mg, 0.35 mmol), and acetic anhydride (786 mg, 7.7 mmol), and the mixture was stirred for 3 h and 40 min. Then DBU (959 mg, 6.3 mmol) was added and the mixture stirred for 10 h. The RM was quenched with a saturated aqueous solution of sodium bicarbonate (2 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give vinyl ester **26**: R_f = 0.68 (2:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −59 (*c* = 0.4, $CDCl_3$); IR (neat) ν_{max} 1724, 1657, 1438, 1373, 1237, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dt, *J* = 3.4, 1.7,

1H), 5.13 (td, J = 6.6, 4.8, 1H), 4.72–4.69 (m, 1H), 4.20 (t, J = 6.4, 1H), 3.75 (s, 3H), 2.76 (dd, J = 17.6, 4.8, 1H), 2.32 (ddt, J = 17.9, 6.7, 1.6, 1H), 2.04 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 166.4, 134.2, 129.5, 110.0, 74.0, 71.9, 70.0, 52.1, 27.8, 26.5, 26.0, 21.1; HRMS (ESI) calcd for $C_{13}H_{18}O_6Na$ [M + Na]$^+$ 293.1001, found 293.0996.

(−)-Shikimic Acid (2). To diol substrate **24** (247 mg, 1 mmol) in THF (3 mL) were added triethylamine (253 mg, 2.5 mmol), DMAP (12 mg, 0.1 mmol), and acetic anhydride (225 mg, 2.2 mmol), and the mixture was stirred for 3 h and 40 min. Then DBU (274 mg, 1.8 mmol) was added and the mixture stirred for 10 h. A saturated aqueous solution of sodium bicarbonate (2 mL) and CH_2Cl_2 (4 mL) were added. The organic layer was separated, dried ($MgSO_4$), and concentrated. Aqueous trifluoroacetic acid [3 mL, 70% (v/v)] was added to the residue and the mixture stirred for 12 h at rt. The RM was concentrated with absolute ethanol to afford (−)-shikimic acid **2**. A sample was recystallized from ethanol ether to furnish (−)-shikimic acid (140 mg, 0.8 mmol, 80%), whose physical properties are identical to those of the reported compound.[2d]

(3aR,5aR,6aR,6bR)-Methyl 2,2-Dimethyl-3a,5a,6a,6b-tetrahydro-oxireno[2′,3′:3,4]benzo[1,2-d][1,3]dioxole-5-carboxylate (27). To substrate **22** (244 mg, 1 mmol) in CH_2Cl_2 (4 mL) at 0 °C were added triethylamine (455 mg, 4.5 mmol) and methanesulfonyl chloride (171.84 mg, 1.5 mmol). The RM was stirred at rt for 5 h and 30 min and then quenched with a saturated aqueous solution of sodium carbonate (4 mL). The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 3:1 hexane/ethyl acetate mixture to give **27** (226 mg, 1 mmol, 100%): R_f = 0.78 (2:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −42.286 (c = 0.7, $CHCl_3$); IR (neat) ν_{max} 2992, 2945, 2359, 1724, 1654, 1445, 1378, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, J = 2.0, 1.2, 1H), 4.78 (ddd, J = 7.0, 1.6, 0.8, 1H), 4.55 (dd, J = 6.8, 2.4, 1H), 3.97 (ddd, J = 3.7, 1.6, 0.6, 1H), 3.81 (s, 3H), 3.65–3.63 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 140.0, 127.4, 111.0, 71.2, 70.4, 52.3, 49.3, 46.1, 27.8, 25.8; HRMS (EI) calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0845.

(3aR,7R,7aS)-Methyl 7-Hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxole-5-carboxylate (28).[25] To substrate **27** (226 mg, 1 mmol) in methanol (4 mL) at −55 °C was added $LiBH_4$ (39.2 mg, 1.8 mmol). The reaction temperature was slowly increased to 0 °C over 1 h and then the mixture stirred for 20 h at 0 °C. Then water (2 mL) and CH_2Cl_2 (4 mL) were added. The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography with a 2:1 hexane/ethyl acetate mixture to give **28** (185 mg, 0.81 mmol, 81%): R_f = 0.35 (2:1 hexane:ethyl acetate); $[\alpha]_D^{25}$ = −65.8 (c = 0.43, $CHCl_3$); IR (neat) ν_{max} 3438, 2989, 1716, 1648, 1439, 1378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.36 (q, J = 6.5, 1H), 4.31–4.23 (m, 1H), 3.99 (t, J = 6.7, 1H), 3.74 (s, 3H), 3.13 (dd, J = 16.5, 6.9, 1H), 2.30–2.18 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 140.8, 129.0, 109.3, 80.3, 71.8, 71.2, 52.0, 28.0, 27.3, 25.0; HRMS (ESI) calcd for $C_{11}H_{17}O_4$ [M + H]$^+$ 229.1127, found 229.1123.

(−)-4-epi-Shikimic Acid (3).[6d] To substrate **28** (115 mg, 0.5 mmol) was added aqueous trifluoroacetic acid [2.5 mL, 60% (v/v)], and the mixture was stirred for 12 h. The RM was concentrated with absolute ethanol and recrystallized with an ethanol/ether mixture to give 4-*epi*-shikimic acid (78 mg, 0.45 mmol, 90%), whose physical properties are identical to those of the reported compound. Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.19; H, 5.89.[6d]

(+)-4-epi-Shikimic Acid (4).[6] Preparation **4** from ***ent*-14** is achieved by following the identical experiemental procedure of **3** from **14**, whose physical properties are identical to those of the reported compound. Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.19; H, 5.89.[6d]

(−)-Pinitol (5). To a solution of allylic hydroxyls **9** (300 mg, 1.4 mmol) in CH_2Cl_2 (180 mL) at rt was added a solution of the second-generation Grubbs catalyst (15.6 mg, 0.018 mmol, 0.013 equiv) in CH_2Cl_2 (1 mL). The RM was stirred at reflux for 2 h, and then a solution of CF_3COOH (32 mg, 0.28 mmol) in 0.5 mL of CH_2Cl_2 was added dropwise. The RM was stirred at reflux for an additional 16 h, allowed to reach rt, and then treated with *m*-CPBA (0.48 g, 2.8 mmol). The RM was stirred at rt for 8 h, and then the solvent was evaporated. Methanol (15 mL) and sodium methoxide (9.3 mmol) were added to the residue in the same flask and stirred at reflux for 24 h. The RM was left to cool to rt. Trifluoroacetic acid (2 mL) was added to the same flask and the mixture stirred for 1 day and then concentrated. The residue was subjected to flash chromatography with a 1:4 methanol/dichloromethane mixture to give (−)-pinitol (**5**) (195 mg, 1 mmol, 72%) as a white solid, whose physical properties are identical to those of the reported compound.[7e]

(3aR,4S,5R,7aS)-5-Methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[d][1,3]dioxol-4-ol (29). To a solution of chloro ester **13** (0.3 g, 1.2 mmol) in methanol (5 mL) at rt was added sodium methoxide (0.33 g, 6 mmol). The RM was stirred at reflux for 24 h. Then water (3 mL) and CH_2Cl_2 (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was flash chromatographed with a 5:1 hexane/ethyl acetate mixture to give methoxycyclohexenol **29** (0.23 g, 1.15 mmol, 96%): R_f = 0.34 (1:1 hexane:EtOAc); $[\alpha]_D^{25}$ = +22.9 (c = 1.4, $CHCl_3$); IR (film) ν_{max} 3454, 3041, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.85 (m, 2H), 4.62 (dd, J = 6.8, 3.2, 1H), 4.10 (dd, J = 8.8, 6.8, 1H), 3.67–3.59 (m, 2H), 3.47 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9 (CH), 124.0 (CH), 110.5 (C), 79.7 (CH), 77.6 (CH), 73.3 (CH), 72.4 (CH), 57.2 (CH_3), 28.1 (CH_3), 25.7 (CH_3); HRMS (FAB) calcd for $C_{10}H_{17}O_4$ [M + H]$^+$ 201.1127, found 201.1123.

(+)-Pinitol (6). To a mixture of methoxycyclohexenol **29** (0.1 g, 0.5 mmol) and NMO (0.18 g, 1.5 mmol) in a 1:1 acetone/water mixture (2 mL) was added 0.3 mL of a 0.1 M OsO_4 solution in THF, and the mixture was stirred at rt for 24 h, treated with CF_3COOH (0.37 mL, 5 mmol), and stirred for an additional 24 h. After concentration, the residue was flash chromatographed with a 1:4 MeOH/CH_2Cl_2 mixture to give (+)-pinitol **6** (80 mg, 84%), whose physical properties are identical to those of the reported compound.[7e]

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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