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Enantioselective Total Synthesis of (−)-Maoecrystal V

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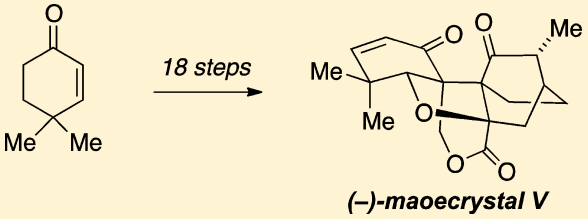
Supporting Information

ABSTRACT: The enantioselective synthesis of maoecrystal V, a cytotoxic polycyclic diterpene, is described. Key reactions in the synthesis include an intramolecular Heck reaction, an oxidative cycloetherification, and an intermolecular Diels−Alder reaction to forge the carbocyclic core in a concise and stereoselective manner. Late-stage amine and C−H oxidation is used to install the final functional groups required to complete the synthesis.



INTRODUCTION

The *Isodon* species of plants produce a staggering array of terpene natural products that are biosynthetically derived from the common *ent*-kaurene nucleus (**1**, Figure 1).[1] One such terpene, maoecrystal V (**2**), possesses a unique structure that shares little resemblance to its biogenic progenitor (i.e., **1**).[2]

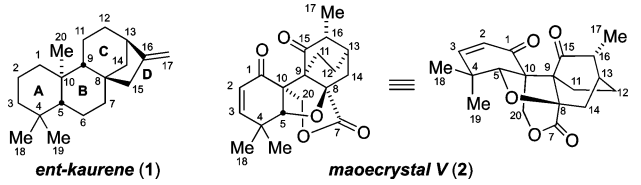


Figure 1. *ent*-Kaurene (**1**) and maoecrystal V (**2**).

First isolated from *Isodon eriocalyx* by Sun and co-workers in 1994, maoecrystal V's structure was tentatively assigned on the basis of NMR and MS spectral data, but was not reported at that time due to uncertainty surrounding the assignment. Such was the peculiarity of its structure that it was not until 2004 that maoecrystal V (**2**) was disclosed in the literature thanks to unambiguous structural assignment via single crystal X-ray diffraction.[2] Maoecrystal V (**2**), a nor-C6-diterpene, possesses a unique structure that has undergone substantial reorganization from **1** such that it contains vicinal quaternary stereocenters at C9 and C10, a highly strained cyclic ether between C5 and C8, a spirocyclic lactone, and a bicyclo[2.2.2]octane ring system. Moreover, maoecrystal V (**2**) was shown to possess potent and selective cytotoxic activity against HeLa cells (IC_{50} = 60 nM).

The combination of its complex structure and compelling biological profile has made maoecrystal V (**2**) a popular target for total synthesis,[3,4] but to date only three successful total syntheses of racemic maoecrystal V have been reported (Figure 2).[5]

In 2010, Yang and co-workers reported the first total synthesis of **2** by a concise approach that utilized an intramolecular Diels−Alder reaction of lactone **3** to forge the cyclic ether, lactone, and bicyclo[2.2.2]octane nucleus of **2** in a single step.[5a] Danishefsky and Peng's synthesis of maoecrystal V (**2**), which was reported in 2012, made use of an intramolecular Diels−Alder reaction of

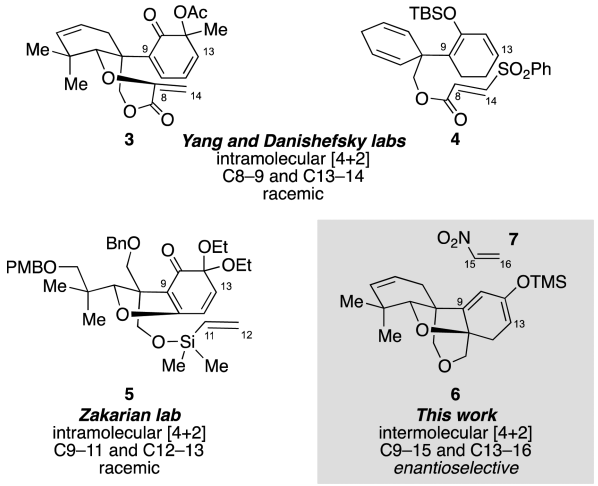


Figure 2. Diels−Alder reactions toward maoecrystal V (**2**).

ester **4** to also forge the C8−C9 and C13−C14 bonds of the bicyclo[2.2.2]octane ring system.[5b] Zakarian and co-workers, however, constructed the bicyclo[2.2.2]octane core through generation of the C9−C11 and C12−C13 bonds by a silicon-tethered intramolecular Diels−Alder reaction of vinyl silane **5**.[5c] We now wish to report the results of our own work toward maoecrystal V (**2**) that led to construction of the critical bicyclo[2.2.2]octane nucleus by way of an alternative intermolecular Diels−Alder reaction of diene **6** and nitroethylene (**7**) that forms the C9−C15 and C13−C16 bonds. These efforts have now culminated in a concise enantioselective total synthesis of maoecrystal V (**2**).[6]

RESULTS AND DISCUSSION

In 2010, our group reported an approach to maoecrystal V (**2**) that successfully constructed the bicyclo[2.2.2]octane ring system by an intermolecular Diels−Alder reaction with nitro-

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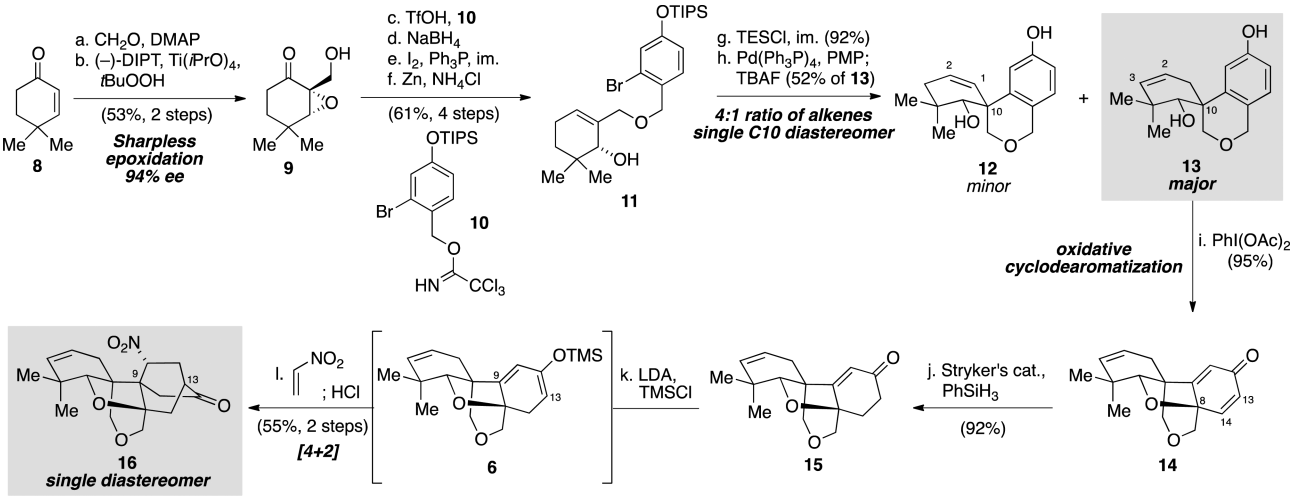
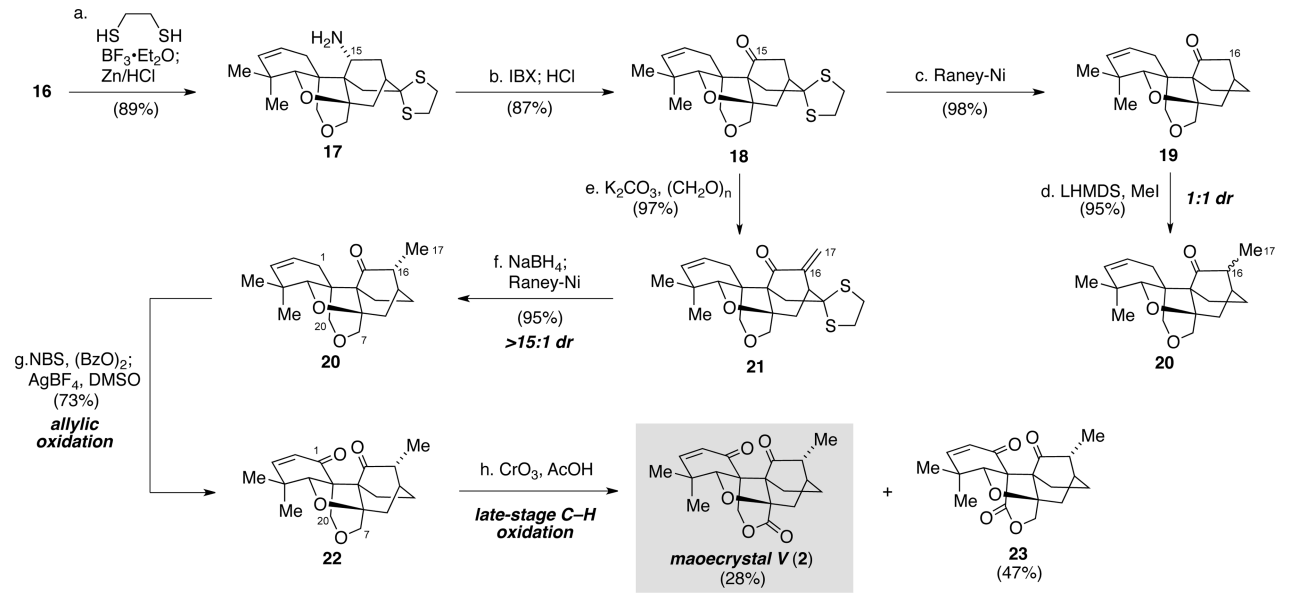
Scheme 1[a]



[a]*Reagents and conditions:* (a) CH_2O, sodium dodecyl sulfate, DMAP, H_2O, 71%; (b) 1.5 equiv of (−)-diisopropyltartrate, 1.45 equiv of Ti(*i*PrO)$_4$, *t*BuOOH, 4 Å MS, 74%, 94% ee; (c) TfOH, **10**, 87%; (d) $NaBH_4$, 87%; (e) Ph_3P, I_2, imidazole, 76%; (f) Zn, NH_4Cl, 0 °C, 93%; (g) TESCl, imidazole, 92%; (h) 3 mol % $Pd(Ph_3P)_4$, PMP, 125 °C; TBAF, 52% of **13**; (i) $PhI(OAc)_2$, $NaHCO_3$, $(CF_3)_2CHOH$–DCM, 95%; (j) 3 mol % Stryker's cat., $PhSiH_3$, 92%; (k) LDA, TMSCl; (l) **7**, BHT, PhH; HCl/THF, 55% from **15**.

Scheme 2. [a]



[a]*Reagents and conditions:* (a) 1,2-ethanedithiol, BF_3·Et_2O; then Zn/HCl, 89%; (b) IBX, DMSO; 1 N HCl, 87%; (c) Raney Ni, MeOH, reflux, 98%; (d) LHMDS, MeI, 95%, 1:1 dr; (e) K_2CO_3, $(CH_2O)_n$, DMF, 97%; (f) $NaBH_4$, MeOH; then Raney Ni, reflux, 95%, >15:1 dr; (g) NBS, benzoylperoxide, CCl_4, 80 °C; then $AgBF_4$, DMSO, 73%; (h) CrO_3/AcOH, DCM, reflux, 28% (**2**) + 47% (**23**).

ethylene (**7**).[4f] This first strategy called for late-stage installation of the cyclic ether by formation of the C5 carbon–oxygen bond from a pre-existing C8 hydroxyl group, which was ultimately unsuccessful. Subsequent model studies indicated that, even if the C5 carbon–oxygen bond was formed in this "east-to-west" manner, it would most likely possess the incorrect stereochemistry.[4k] After considering these results, we designed a new approach that would maintain the successful intermolecular Diels–Alder reaction but install the C5 stereochemistry early and form the cyclic ether by the alternative "west-to-east" direction.

Our synthesis commenced from 4,4-dimethylcyclohexenone (**8**, Scheme 1), which was subjected to a Baylis–Hillman reaction[7] and a Sharpless asymmetric epoxidation to produce ketone **9** in good yield and with high optical purity (94% ee).[8] Benzylation of **9** with trichloroimidate **10**[9] followed by reductive fragmentation of the epoxide delivered the allylic alcohol **11** in 61% yield. Construction of the critical C10 spirocyclic quaternary stereocenter was achieved through a completely diastereoselective Heck reaction,[10] which first necessitated protection of the secondary alcohol as a triethylsilyl ether.[11] Thus, protection of alcohol **11** with TESCl followed by treatment with 3 mol % $Pd(Ph_3P)_4$ gave rise to 2,3-alkene **13** as the major product along with the 1,2-alkene **12** (4:1 ratio of **13**:**12**). Both silyl groups were cleaved during this process by quenching the reaction mixture with TBAF after full consumption of the starting material was observed, and in this way, alkene **13** was obtained in

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52% yield as a single isomer after chromatography. Formation of the 2,3−alkene as the major product from this Heck reaction may be rationalized by olefin isomerization to the more thermodynamically stable isomer by reinsertion of the intermediate Pd−hydride complex formed following initial spirocyclization.[12]

We next turned our attention to construction of the critical THF ring, which we envisioned forming by an intramolecular oxidative cyclodearomatization.[13] Ultimately, we found that treatment of phenol **13** with $PhI(OAc)_2$ in a mixture of $(CF_3)_2CHOH$ and DCM provided the desired dienone **14** in 95% yield. Curiously, exposure of the 1,2-alkene isomer **12** to the same conditions led to exclusive benzylic oxidation, an outcome that highlights the nuanced effects the A-ring alkene has on conformation and reactivity. Conjugate reduction of the less hindered 13,14-alkene using Stryker's catalyst[14] delivered enone **15** in 92% yield and set the stage for the key Diels−Alder cycloaddition. Enone **15** was converted to the unstable enol ether **6**, which was exposed to nitroethylene (**7**) without purification. Care had to be taken to avoid fragmentation of the ether ring to regenerate phenol **13** under the reaction conditions, yet under optimized conditions we were able to obtain cycloadduct **16** as a single regio- and stereoisomer (55% yield from enone **15**).

With the carbocyclic framework of maoecrystal V installed in a concise and selective fashion we focused our efforts toward the required late-stage functional group manipulations and C−H oxidations necessary to deliver the natural product (Scheme 2). Early attempts to delete the C12 ketone within **16** through Clemmenson and Wolff−Kishner reductions or via the corresponding tosyl hydrazone were met with issues of low yields, poor reproducibility, and/or significant decomposition. Ultimately, conversion of ketone **16** to the dithiane followed by in situ reduction of the nitro function provided C15 amine **17** in 89% yield. Oxidation of the amine within **17** to the corresponding imine with IBX,[15] followed by hydrolysis, provided ketone **18** in 87% yield. Subsequent desulfuration with Raney Ni[16] then gave rise to ketone **19** in high yield (98% yield).

Alkylation of **19** with methyl iodide delivered ketone **20** in 95% yield as a 1:1 mixture of inseparable isomers. The poor selectivity we obtained for this reaction led us to devise an alternative strategy that first involved generation of the exocyclic enone **21** from ketone **18** by means of an aldol condensation with paraformaldehyde (97% yield). We anticipated that reduction of the exocyclic 16,17-alkene within **21** would proceed with high levels of facial selectivity due to the steric hindrance imparted by the dithiane group, which having served its role as a blocking group would be removed subsequently. In the event, sequential treatment of enone **21** with $NaBH_4$ followed by Raney Ni in one pot facilitated smooth conjugate reduction and desulfurization to deliver ketone **20** in 95% yield and with >15:1 diastereoselectivity.

With the C15 ketone and C17 methyl groups in place, the remaining obstacles were incorporation of the C1 ketone and C7 lactone. Yang and co-workers had shown in their synthesis of maoecrystal V (**2**) that the C1 ketone could be introduced through a four-step sequence of a related compound involving initial allylic bromination at C1, with subsequent manipulations involving trapping with TEMPO, N−O bond cleavage, and oxidation of the allylic alcohol.[5a] Utilizing this key precedent, we devised a one-pot allylic bromination/Kornblum oxidation[17] procedure that provided the C1 ketone directly from the alkene. Exposure of **20** to NBS and benzoylperoxide provided the intermediate allylic bromide, which was not isolated but instead treated with $AgBF_4$ and dimethyl sulfoxide to provide ketone **22** in 73% yield.

Completion of the synthesis would now require oxidation at C7 to deliver the requisite lactone present within maoecrystal V (**2**). We had anticipated that the C7 and C20 methylene groups would be the most activated positions for this challenging late-stage C−H functionalization.[18] Earlier efforts showed that electronic factors appear to dominate this oxidation; compound **20**, which lacks the electron withdrawing C1 ketone, gave rise to the C20 lactone exclusively when treated with CrO_3 and AcOH.[19] This high selectivity for the wrong isomer is most likely enhanced by additional deactivation of C7 by the THF oxygen. We speculated that the presence of the C1 ketone within **22** would deactivate the C20 carbon and provide access to the desired C7 lactone. This line of reasoning proved fruitful, as we found that treatment of **22** with CrO_3 and AcOH provided synthetic (−)-maoecrystal V (**2**, 28% yield), whose spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS, $[\alpha]_D$) were in excellent agreement with that reported for the natural sample.[2] Although the isomeric C20 lactone **23** was also formed (47% yield) during the final oxidation, pentacyclic ether **22** is one of the most complex substrates utilized in late-stage C−H oxidation en route to a natural product and further highlights the powerful utility of such reactions.

■ CONCLUSION

The enantioselective synthesis of maoecrystal V (**2**) reported herein proceeded in 18 steps from commercially available 4,4-dimethylcyclohexenone (**8**) and made use of numerous powerful transformations. Key to the success of the synthesis was the sequential use of a Heck spirocyclization, an oxidative cyclodearomatization, and an intermolecular Diels−Alder reaction to convert benzyl ether **11** into the pentacyclic carbocycle **16**. This rapid escalation in carbogenic complexity then allowed for a series of efficient redox adjustments, including two late-stage C−H oxidations to forge the C1 and C7 carbonyl groups and thus deliver the natural product. The efficiency of our approach, coupled with an ability to access either enantiomer of the natural product, will allow full exploration of maoecrystal V's medicinal potential.

■ EXPERIMENTAL SECTION

General Methods. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring unless otherwise stated. Methanol, benzene, ether, THF, and DCM were purified by passage through a bed of activated alumina. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230−400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, *p*-anisaldehyde, or $KMnO_4$ stain. Germanium ATR infrared spectra were recorded using a Bruker Tensor 37. All ^{1}H NMR spectra were recorded on a Varian Inova 500 (500 MHz), Varian Inova 400 (400 MHz), or Bruker Advance III 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Two-dimensional NMR experiments were run on a Bruker Advance III 500 (500 MHz). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad; integration; coupling constant(s) in Hz). Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Inova 500 (125 MHz), Varian Inova 400 (400 MHz), or Bruker Advance III 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). Mass spectral data were obtained on an Agilent 6210 time-of-flight LC/MS and a Thermo Finnegan Mat 900 XL high resolution magnetic sector.

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Experimental Procedures. *Compound* ***9***. To a flame-dried round-bottom flask equipped with a stir bar and activated 4 Å molecular sieves were added titanium(IV) isopropoxide (16.6 mL, 56 mmol), (−)-diisopropyl D-tartrate (11.2 mL, 57.6 mmol), and anhydrous dichloromethane (130 mL). The resulting mixture was cooled to −20 °C, and 2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (5.92 g, 38.4 mmol)[7] was added as a solution in anhydrous dichloromethane (30 mL). The resulting solution was allowed to stir at −20 °C for 30 min, after which it was cooled further to −30 °C. *tert*-Butyl hydroperoxide (~5.5 M solution in nonane, 20.9 mL, 115.2 mmol) was added dropwise to the reaction mixture, and the resulting solution was allowed to warm to −20 °C and stirred for 36 h, at which point TLC analysis of the crude mixture showed full conversion. The reaction mixture was quickly filtered through Celite, and the filtrate was cooled to −20 °C and quenched with iron(II) sulfate heptahydrate (32 g) and 10% aqueous tartaric acid (200 mL). The mixture was then allowed to warm to room temperature, and the two layers were separated. The aqueous layer was extracted with dichloromethane three times, and the combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was purified using silica gel chromatography using hexanes:ethyl acetate (19:1 → 2:1) to give **9** (4.83 g, 28.4 mmol, 74% yield) as a clear oil: IR (neat) 3424, 1701, 2960, 2872, 1090, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (dd, J = 12.8, 6.7 Hz, 1H), 3.82 (dd, J = 12.8, 3.8 Hz, 1H), 3.22 (d, J = 1.3 Hz, 1H), 2.43 (ddd, J = 18.8, 6.3, 3.2 Hz, 1H), 2.30 (d, J = 6.7 Hz, 1H), 2.20 (ddd, J = 18.8, 11.6, 6.9 Hz, 1H), 1.87 (ddd, J = 13.6, 11.6, 6.3 Hz, 1H), 1.34 (dddd, J = 13.6, 6.9, 3.3, 1.3 Hz, 1H), 1.19 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 67.9, 61.6, 60.5, 33.9, 31.0, 30.4, 27.5, 23.2; $[\alpha]_D$ = +75 (c 1.3, $CHCl_3$). HRMS (ESI) Calcd for $C_9H_{14}O_3$ $[M + H]^+$: 170.0943. Found: 170.0933. The enantiopurity of **9** was determined to be 94% ee by conversion to the corresponding Mosher ester; see Supporting Information for details.

Compound ***11***. To a flame-dried flask equipped with a stir bar was added **9** (14.4 g, 84.6 mmol), **10** (83 g, 169 mmol), and anhydrous ether (330 mL). Anhydrous trifluoromethanesulfonic acid (75 μL, 0.846 mmol) was added to the reaction solution, and the resulting mixture was allowed to stir for several hours, at which point TLC analysis of the crude mixture showed full conversion. The reaction mixture was quenched with saturated sodium bicarbonate, and the two layers were separated. The organic layer was dried over magnesium sulfate and then was concentrated to 1/3 of the original volume and filtered through a cotton plug. The filtrate was diluted with hexanes, and the resulting mixture was filtered again. The resulting filtrate was concentrated and purified by silica gel chromatography using hexanes:ethyl acetate (99:1 → 96:4) to give benylated adduct (37.5 g, 73.3 mmol, 87% yield) as a clear oil: IR (neat) 2946, 2867, 1709, 1600, 1491, 1284, 1105, 935, 883, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 4.56 (d, J = 12.5 Hz, 1H), 4.51 (d, J = 12.5 Hz, 1H), 4.11 (d, J = 11.6 Hz, 1H), 3.66 (d, J = 11.6 Hz, 1H), 3.35 (d, J = 1.2 Hz, 1H), 2.45 (ddd, J = 18.4, 6.1, 3.3 Hz, 1H), 2.21 (ddd, J = 18.4, 11.6, 6.8 Hz, 1H), 1.88 (ddd, J = 13.6, 11.6, 6.1 Hz, 1H), 1.37 (dddd, J = 13.6, 6.8, 3.4, 1.3 Hz, 1H), 1.28−1.22 (m, 6H), 1.09 (d, J = 7.0 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 156.3, 130.1, 129.6, 124.1, 123.2, 118.9, 72.8, 67.6, 66.6, 61.1, 34.0, 31.0, 30.7, 27.6, 23.3, 18.0, 12.8; $[\alpha]_D$ = +16 (c 1.5, $CHCl_3$). HRMS (ESI) Calcd for $C_{25}H_{39}BrO_4Si$ $[M + H]^+$: 510.1801. Found: 510.1802.

To a stirred suspension of the above prepared benzyl ether (18.1 g, 35.4 mmol) in methanol (120 mL) at 0 °C was added sodium borohydride (2.28 g, 60.3 mmol) in small portions. After the mixture was stirred for 1 h, it showed full conversion by TLC. The reaction mixture was quenched with saturated ammonium chloride, and the mixture was concentrated. The resulting residue was diluted with water and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was purified by silica gel chromatography using hexanes:ethyl acetate (19:1 → 9:1) to give a mixture of the corresponding alcohols (15.5 g, 30.3 mmol, 87% yield) as a clear oil: IR (neat) 3453, 2945, 2867, 1600, 1491, 1284, 935, 883, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) **major** δ 7.25 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.2, 2.2 Hz, 1H), 4.56 (s, 2H), 4.16−4.11 (m, 1H), 3.76 (d, J = 10.8 Hz, 1H), 3.60 (d, J = 10.8 Hz, 1H), 2.89 (s, 1H), 2.48 (d, J = 7.0 Hz, 1H), 1.61−1.50 (m, 2H), 1.46−1.33 (m, 1H), 1.30−1.18 (m, 4H), 1.12−1.07 (m, 21H), 1.01 (s, 3H); ^1H NMR ($CDCl_3$, 500 MHz) **minor** δ 7.26 (d, J = 8.2 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.15 (d, J = 10.8 Hz, 2H), 4.16−4.11 (m, 1H), 3.31 (d, J = 11.0 Hz, 1H), 3.18−3.11 (m, 1H), 2.65 (s, 1H), 1.79 (dtd, J = 12.5, 6.2, 3.3 Hz, 1H), 1.46−1.33 (m, 1H), 1.30−1.18 (m, 5H), 1.12−1.07 (m, 18H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 156.4, 131.1, 130.3, 129.5, 129.2, 124.4, 124.2, 123.9, 123.4, 119.0, 74.0, 73.0, 72.9, 72.7, 68.0, 67.1, 66.6, 65.2, 62.4, 31.1, 30.2, 30.0, 29.8, 26.9, 26.8, 26.3, 26.1, 25.4, 18.0, 12.8; $[\alpha]_D$ = −7.5 (c 0.3, $CHCl_3$). HRMS (ESI) Calcd for $C_{25}H_{41}BrO_4Si$ $[M + H]^+$: 512.1957. Found: 512.1966.

To a flame-dried round-bottom flask equipped with a stir bar was added the mixture of alcohols (15 g, 29.2 mmol), triphenylphosphine (8.4 g, 32.1 mmol), imidazole (4.47 g, 65.7 mmol), and dry dichloromethane (120 mL). The resulting solution was allowed to cool to 0 °C and stirred for 5 min. Iodine (11.1 g, 43.8 mmol) was added dropwise as a solution in dry dichloromethane (530 mL), and the reaction mixture was allowed to warm to room temperature and stirred for 3 h, at which point TLC analysis of the crude mixture indicated full conversion. The reaction mixture was cooled in ice and was quenched with 5% aqueous sodium thiosulfate. The two layers were separated, and the aqueous layer was diluted with water and extracted three times with dichloromethane. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was purified through silica plug using hexanes:ethyl acetate (9:1) to afford the corresponding iodides (13.8 g, 22.1 mmol, 76% yield) as a yellow oil: IR (neat) 2945, 2867, 1600, 1491, 1283, 1105, 934, 883, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) **major** δ 7.32 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.4, 2.5 Hz, 1H), 4.84 (t, J = 3.1 Hz, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 12.3 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 3.43 (d, J = 11.2 Hz, 1H), 2.77 (s, 1H), 1.71−1.60 (m, 2H), 1.47−1.38 (m, 1H), 1.33−1.18 (m, 4H), 1.14−1.02 (m, 24H); ^1H NMR (500 MHz, $CDCl_3$) **minor** δ 7.26 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.4, 2.5 Hz, 1H), 4.72 (t, J = 6.1 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.00 (d, J = 10.6 Hz, 1H), 3.23 (s, 1H), 3.12 (d, J = 10.6 Hz, 1H), 2.11−2.04 (m, 2H), 1.94−1.82 (m, 1H), 1.33−1.18 (m, 4H), 1.14−1.02 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 156.3, 130.5, 130.4, 129.8, 129.5, 124.3, 124.1, 123.5, 123.3, 118.9, 73.8, 73.6, 73.0, 72.6, 72.5, 65.2, 63.9, 62.4, 34.5, 33.7, 31.7, 30.7, 30.5, 30.1, 29.5, 29.2, 27.6, 26.6, 26.5, 25.9, 18.1, 12.8; $[\alpha]_D$ = +6.3 (c 0.5, $CHCl_3$). HRMS (ESI) Calcd for $C_{25}H_{40}BrIO_3Si$ $[M + H]^+$: 622.0975. Found: 622.0971.

To a solution of the iodides (21.7 g, 34.8 mmol) in 95% EtOH (380 mL) at 0 °C was added activated zinc dust (11.4 g, 174 mmol) and saturated ammonium chloride (40 mL). The reaction mixture was allowed to stir for 1 h, at which point the analysis of the crude mixture by TLC showed full conversion. The reaction mixture was filtered through Celite, and the filtrate was quenched with saturated sodium bicarbonate. The resulting mixture was extracted with ethyl acetate six times. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. No further purification was necessary, and **11** (16.0 g, 32.2 mmol, 93% yield) was isolated as a clear oil: IR (neat) 3483, 2945, 2867, 1599, 1491, 1283, 936, 883, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.3, 2.4 Hz, 1H), 5.79 (t, J = 3.6 Hz, 1H), 4.51 (d, J = 1.9 Hz, 2H), 4.16 (d, J = 10.8 Hz, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.77 (s, 1H), 2.56 (bs, 1H), 2.21−1.94 (m, 2H), 1.59 (dt, J = 13.8, 6.9 Hz, 1H), 1.41−1.17 (m, 4H), 1.10 (d, J = 7.5 Hz, 18H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 135.1, 130.2, 129.6, 128.4, 124.0, 123.3, 118.8, 74.6, 74.5, 71.4, 33.4, 31.1, 25.1, 23.4, 23.0, 17.8, 12.6; $[\alpha]_D$ = +28 (c 0.5, $CHCl_3$). HRMS (ESI) Calcd for $C_{25}H_{41}BrO_3Si$ $[M + H]^+$: 496.2008. Found: 496.2011. The optical purity of **11** was determined to be 94% ee by HPLC using a Chiralcel OD-H column, hexanes:isopropanol = 97.3, flow rate = 1.20 mL/min. (*R*)-enantiomer (major): retention time = 3.76 min. (*S*)-enantiomer (minor): retention time = 4.11 min.

Compound ***12*** *and* ***13***. To a flame-dried round-bottom flask equipped with a stir bar was added **11** (16.0 g, 32.1 mmol), imidazole

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(6.57 g, 96.5 mmol), DMAP (789 mg, 6.4 mmol), and anhydrous DMF (100 mL). To the resulting solution was added chlorotriethylsilane (8.1 mL, 48.2 mmol) dropwise, and the reaction mixture was allowed to stir at room temperature for several hours, at which point the analysis of the crude mixture by TLC showed full conversion. The reaction mixture was quenched with brine, diluted with water, and extracted six times with hexanes. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was passed through a silica plug using hexanes to give the TES ether (18 g, 30 mmol, 92% yield) as a clear oil.

To a flame-dried flask equipped with a stir bar and a condenser was added the TES ether (1.85 g, 3.02 mmol) and anhydrous DMF (32.6 mL). To this mixture under nitrogen was added 1,2,2,6,6-pentamethylpiperidine (654 μL, 3.62 mmol) and $Pd(PPh_3)_4$ (105 mg, 3 mol %), and the resulting solution was heated to 126 °C and was allowed to stir for 6 days, at which point no further conversion was observed when the reaction mixture was analyzed by TLC. The reaction mixture was cooled to room temperature, diluted with anhydrous THF (25 mL), and further cooled to 0 °C. Tetrabutylammonium fluoride (1 M solution in THF, 7.5 mL, 7.5 mmol) was added dropwise, and the resulting mixture was heated to 72 °C and allowed to stir for several hours, at which point the analysis of the crude mixture by TLC showed full conversion. The reaction mixture was then quenched by saturated ammonium chloride and 1.0 N HCl. The resulting mixture was extracted six times with ethyl acetate, and the combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was purified by silica gel chromatography using hexanes:ethyl acetate (9:1 → 3:1) to give **13** (1.25 mmol, 325 mg, 52% yield) and **12** (0.31 mmol, 81.7 mg, 13% yield) as white solids.

13: IR (neat) 3329, 3017, 2960, 2872, 1612, 1505, 1467, 1292, 1179, 1097, 998, 819, 731 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 6.89 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 8.3, 2.4 Hz, 1H), 5.56 (dd, J = 10.1, 2.6 Hz, 1H), 5.50 (ddd, J = 10.0, 5.3, 1.8 Hz, 1H), 4.66 (d, J = 13.5 Hz, 1H), 4.59 (d, J = 14.0 Hz, 1H), 4.15 (s, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.93 (dd, J = 11.1, 2.1 Hz, 1H), 2.52 (dd, J = 17.9, 5.3 Hz, 1H), 2.20 (dd, J = 17.9, 2.4 Hz, 1H), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 157.5, 142.4, 138.5, 128.3, 126.2, 122.4, 114.3, 113.2, 79.7, 69.7, 69.6, 43.8, 39.4, 38.9, 31.7, 23.1; $[\alpha]_D$ = −75 (c 0.3, MeOH). HRMS (ESI) Calcd For $C_{16}H_{20}O_3$ $[M + H]^+$: 260.1412. Found: 260.1406.

12: IR (neat) 3356, 2952, 2872, 1611, 1503, 1448, 1286, 1098, 1071, 980, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 2.6 Hz, 1H), 6.64 (dd, J = 9.6, 1.3 Hz, 1H), 5.85 (ddd, J = 9.9, 5.9, 1.9 Hz, 1H), 5.21 (dd, J = 10.0, 2.8 Hz, 1H), 5.06 (s, 1H), 4.81(d, J = 14.3 Hz, 1H), 4.68 (d, J = 14.3 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 3.9 Hz, 1H), 3.79 (d, J = 3.5 Hz, 1H), 3.54−3.42 (m, 1H), 2.14 (d, J = 17.7 Hz, 1H), 1.99 (dd, J = 17.7, 5.9 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 141.6, 129.7, 128.4, 126.1, 125.0, 114.5, 114.2, 85.0, 70.1, 68.3, 43.6, 39.5, 35.7, 29.94, 20.2; $[\alpha]_D$ = −175 (c 0.5, MeOH). HRMS (ESI) Calcd For $C_{16}H_{20}O_3$ $[M + H]^+$: 260.1412. Found: 260.1411.

Compound ***14***. To a flame-dried round-bottom flask equipped with a stir bar was added (diacetoxyiodo)benzene (810 mg, 2.51 mmol), sodium bicarbonate (486 mg, 5.79 mmol), 1,1,1,3,3,3-hexafluoroisopropanol (10.8 mL), and anhydrous dichloromethane (2.7 mL). The resulting suspension was cooled to −10 °C, and **13** (500 mg, 1.93 mmol) was added as a solution in 1,1,1,3,3,3-hexafluoroisopropanol (5.4 mL) and anhydrous dichloromethane (2.7 mL) at a rate of 0.17 mL/min. The resulting mixture was allowed to stir for an additional 10 min, at which point the analysis of the crude mixture by TLC showed full conversion. The reaction mixture was quenched with water and extracted three times with dichloromethane. The combined organic layer was dried over anhydrous magnesium sulfate and was concentrated. The crude residue was purified by chromatography on silica gel that was neutralized with triethylamine and was eluted with hexanes:ethyl acetate (9:1 → 7:3) to give **14** (475 mg, 1.84 mmol, 95% yield) as a yellow oil: IR (neat) 3013, 2964, 2848, 1683, 1653, 1104, 811, 726, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.98 (d, J = 10.0 Hz, 1H), 6.31 (dd, J = 10.0, 1.6 Hz, 1H), 5.95 (d, J = 1.6 Hz, 1H), 5.55−5.35 (m, 2H), 4.34 (d, J = 10.9 Hz, 1H), 4.09 (d, J = 10.4 Hz, 1H), 3.83 (s, 1H), 3.44 (d, J = 11.8 Hz, 1H), 3.34 (d, J = 10.4 Hz, 1H), 2.28 (d, J = 17.9 Hz, 1H), 1.99 (dd, J = 17.6, 4.3 Hz, 1H), 1.33 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.8, 167.0, 142.6, 137.4, 132.4, 120.2, 113.9, 90.7, 78.9, 72.9, 46.4, 37.5, 31.1, 27.6, 22.0; $[\alpha]_D$ = −111 (c 0.5, $CHCl_3$). HRMS (ESI) Calcd for $C_{16}H_{18}O_3$ $[M + H]^+$: 258.1256. Found: 258.1249.

Compound ***15***. To a flame-dried flask equipped with a stir bar was added **14** (271 mg, 1.05 mmol), phenylsilane (259 μL, 2.1 mmol), and dry benzene (18 mL). The reaction mixture was cooled to 5 °C, and (triphenylphosphine)copper hydride hexamer (62 mg, 3 mol %) was added as a solution in anhydrous benzene (2 mL) dropwise. The resulting solution was allowed to stir for 3 h at 5 °C, at which point the analysis of the crude mixture by TLC indicated full conversion. The reaction mixture was quenched by saturated aqueous ammonium chloride. The two layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude residue was purified by silica gel chromatography using hexanes:ethyl acetate (7:3) to give **15** (252 mg, 0.97 mmol, 92% yield) as a white solid: IR (neat) 3013, 2959, 2846, 1682, 1636, 1560, 1471, 1272, 1103, 952, 808, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.73 (d, J = 0.8 Hz, 1H), 5.50 (dd, J = 10.1, 2.5 Hz, 1H), 5.45 (ddd, J = 9.9, 5.0, 1.7 Hz, 1H), 4.26 (d, J = 11.0 Hz, 1H), 3.97 (d, J = 10.7 Hz, 1H), 3.95 (d, J = 10.6 Hz, 1H), 3.75 (d, J = 1.2 Hz, 1H), 3.40 (dd, J = 11.1, 1.3 Hz, 1H), 2.66−2.42 (m, 1H), 2.43−2.12 (m, 4H), 1.91 (ddd, J = 17.3, 5.1, 0.9 Hz, 1H), 1.31 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.8, 169.5, 137.7, 120.2, 114.4, 87.4, 78.4, 76.4, 73.1, 47.1, 37.3, 35.5, 31.3, 30.3, 27.6, 22.0; $[\alpha]_D$ = −185 (c 0.7, $CHCl_3$). HRMS (ESI) Calcd for $C_{16}H_{20}O_3$ $[M + H]^+$: 260.1412. Found: 260.1403.

Compound ***16***. To a solution of **15** (135 mg, 0.52 mmol) in THF (5.2 mL) at −78 °C was added TMSCl (99 μL, 0.78 mmol) followed by LDA (1.0 M in THF, 0.57 mmol, 1.1 equiv) dropwise. After addition of the reagents, the reaction was deemed complete by TLC. The solution was concentrated to 1/4 volume under vacuum at room temperature, and then hexanes (4 mL) were added to precipitate a solid. The mixture was stirred for 5−10 min and filtered with a pipet filled with Celite, washed with hexanes, and concentrated under vacuum for at least 30 min to yield an oil. To a solution of the above oil and BHT (2,6-di-*tert*-butyl-4-methylphenol) (15%, 17 mg) in benzene (14.8 mL) under N_2 at 5 °C was added nitroethylene (**7**) in benzene (5.0 M, 10 equiv, 1.04 mL) in 10 min. The clear solution was then stirred at room temperature for 24 h after which time hexanes were added to precipitate a solid that was removed by filtration. The filtrate was concentrated to give an oil, which was then dissolved in THF (5 mL) and cooled to 0 °C. The silyl ether was removed by slowly adding 1 N HCl (∼1 equiv). Water was added, and the mixture was extracted with DCM three times, dried over Na_2SO_4, and purified by flash chromatography on silica gel with hexanes:ethyl acetate (10:1 → 7:2) to give **16** as an oil (95 mg, 55% yield): IR (neat) 2956, 2924, 1730, 1550, 1336, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (t, J = 8.4 Hz, 1H), 5.41 (d, J = 10.4 Hz, 1H), 5.34 (dd, J = 10.4, 4.2 Hz, 1H), 4.31 (s, 1H), 3.91 (d, J = 12.4 Hz, 1H), 3.71 (d, J = 12.4 Hz, 1H), 3.64 (d, J = 12.4 Hz, 1H), 3.57 (d, J = 19.1 Hz, 1H), 3.46 (d, J = 12.4 Hz, 1H), 2.86 (d, J = 19.1 Hz, 1H), 2.75 (ddd, J = 14.0, 10.1, 4.1 Hz, 1H), 2.55 (m, 1H), 2.23 (dd, J = 13.7, 8.0 Hz, 1H), 2.00 (d, J = 18.0 Hz, 1H), 1.97 (d, J = 15.0 Hz, 1H), 1.60−1.64 (m, 1H), 1.52 (dd, J = 17.7, 5.1 Hz, 1H), 1.21 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 136.0, 121.3, 88.8, 80.8, 79.3, 70.5, 65.9, 51.1, 45.4, 42.3, 37.1, 35.5, 32.2, 32.0, 31.0, 26.7, 21.3; $[\alpha]_D$ = −40 (c 0.5, $HCCl_3$). HRMS (ESI) Calcd for $C_{18}H_{24}NO_5$ $[M + H]^+$ 334.1649. Found: 334.1661.

Compound ***17***. Boron trifluoride−diethyl ether complex (78 μL, 0.63 mmol) was added over a period of 40 min to a solution of **16** (70 mg, 0.21 mmol) and 1,2-ethanedithiol (0.7 mL, 8.4 mmol) in anhydrous benzene (2.5 mL) at 0 °C. The mixture was then stirred for 20 min at 0 °C after which time TLC analysis indicated that the reaction was complete. The mixture was concentrated under reduced pressure to give a yellow solid, which was dissolved in EtOH/THF (3.6 mL/1.2 mL). Activated zinc powder (166 mg, 2.55 mmol) was added to the solution portionwise, followed by the dropwise addition of 20% HCl (0.93 mL, 6.3 mmol). The mixture was then stirred for 10 min and then filtered to

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remove the zinc. Ethyl acetate (5 mL) was added to the filtrate followed by saturated $NaHCO_3$ solution and Na_2CO_3 powder to adjust the pH to ~10. The mixture was filtered to remove the solid. The filtrate was extracted using ethyl acetate three times. The organic layer was separated and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with DCM:ethyl acetate:MeOH (50:40:2) provided **17** as foam (70 mg, 89% yield): IR (neat) 3373, 2923, 2857, 1465, 1112, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (d, J = 2.5 Hz, 2H), 4.31 (d, J = 12.1 Hz, 1H), 4.10 (s, 1H), 3.77 (d, J = 11.8 Hz, 1H), 3.63 (dd, J = 16.1, 11.3 Hz, 2H), 3.48 (d, J = 12.1 Hz, 1H), 3.42 (ddd, J = 11.4, 6.6, 4.4 Hz, 1H), 3.35−3.26 (m, 2H), 3.22−3.16 (m, 1H), 2.91 (d, J = 15.6 Hz, 1H), 2.85−2.76 (m, 2H), 2.36 (ddd, J = 13.9, 10.6, 3.1 Hz, 1H), 1.98 (p, J = 3.0 Hz, 1H), 1.81 (dd, J = 14.1, 3.0 Hz, 1H), 1.75 (dd, J = 14.4, 2.0 Hz, 1H), 1.68 (dt, J = 14.5, 3.5 Hz, 1H), 1.55−1.47 (m, 1H), 1.39 (s, 2H), 1.20 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 122.3, 88.7, 80.8, 73.6, 68.5, 65.6, 49.1, 44.7, 43.3, 41.4, 40.4, 38.6, 38.4, 37.2, 34.2, 32.6, 29.6, 21.6; $[\alpha]_D$ = −28 (c 0.3, $HCCl_3$). HRMS (ESI) Calcd for $C_{20}H_{30}NO_2S_2$ $[M + H]^+$: 380.1712. Found: 380.1717.

Compound ***18***. A solution of IBX (67 mg, 0.24 mmol) in DMSO (0.6 mL) was added to a solution of **17** (70 mg, 0.19 mmol) in DMSO/THF (1.75 mL/1.2 mL) at 5 °C over 1 h. The solution was then stirred at 5 °C for 40 min. The mixture was directly filtered through a short silica gel plug and washed with hexanes:ethyl acetate (7:2 v:v). The collected filtrate was concentrated to give the imine as a solid, which was dissolved in a minimal volume of EtOH (0.5 mL) and water (1.5 mL). The solid precipitate dissolved upon the addition of 1 N HCl (~1.0 equiv). The resulting solution was heated to 104 °C for 20 min, during which time a white solid precipitated gradually. After cooling to room temperature, the mixture was extracted with dichloromethane by three times. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column with hexanes:ethyl acetate (7:2) to give ketone **18** as a white solid (60 mg, 87% yield): IR (neat) 2922, 2853, 1718, 1463, 1141, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (ddd, J = 10.0, 4.8, 1.7 Hz, 1H), 5.36 (dd, J = 10.2, 2.0 Hz, 1H), 4.36 (d, J = 12.3 Hz, 1H), 4.17 (s, 1H), 3.74 (d, J = 12.1 Hz, 1H), 3.57 (d, J = 12.2 Hz, 1H), 3.56 (d, J = 12.0 Hz, 1H), 3.53−3.41 (m, 2H), 3.41−3.31 (m, 2H), 3.26 (d, J = 16.1 Hz, 1H), 3.21−3.14 (m, 1H), 3.02 (dt, J = 19.6, 2.7 Hz, 1H), 2.50 (dd, J = 19.6, 2.9 Hz, 1H), 2.43 (d, J = 16.1 Hz, 1H), 2.38−2.36 (m, 1H), 2.07 (dd, J = 14.7, 1.9 Hz, 1H), 2.02 (dt, J = 14.9, 3.4 Hz, 1H), 1.41 (dd, J = 18.0, 5.0 Hz, 1H), 1.19 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 136.0, 122.2, 87.0, 79.8, 72.2, 67.1, 65.8, 57.4, 45.3, 43.6, 43.0, 41.1, 40.7, 38.9, 36.6, 34.1, 32.0, 26.4, 21.8; $[\alpha]_D$ = +47 (c 0.8, $HCCl_3$). HRMS (ESI) Calcd for $C_{20}H_{27}O_3S_2$ $[M + H]^+$: 379.1396. Found: 379.1425.

Compound ***19***. To a solution of the **18** (40 mg, 0.11 mmol) in MeOH (4.6 mL) was added activated Raney Ni (0.94 g, washed four times with MeOH) under N_2. The suspension was heated to reflux for 40 min and then allowed to cool to room temperature. The solid was then removed by filtration over Celite, and the solvent removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with hexanes:ethyl acetate (7:2) provided **19** as a white solid (30 mg, 98% yield): IR (neat) 2923, 2854, 1722, 1464, 1132, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.42 (ddd, J = 10.0, 5.0, 1.9 Hz, 1H), 5.36 (dd, J = 10.0, 1.9 Hz, 1H), 4.23 (s, 1H), 3.83 (d, J = 7.7 Hz, 1H), 3.80 (d, J = 8.0 Hz, 1H), 3.66 (d, J = 12.1 Hz, 1H), 3.53 (d, J = 11.8 Hz, 1H), 3.46 (dt, J = 17.7, 2.3 Hz, 1H), 2.43−2.31 (m, 3H), 2.24 (s, 1H), 1.91−1.77 (m, 2H), 1.73−1.57 (m, 2H), 1.52−1.40 (m, 2H), 1.19 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0, 136.0, 122.4, 86.6, 81.2, 72.3, 66.1, 54.0, 45.4, 42.4, 36.6, 36.5, 32.0, 27.8, 26.4, 22.8, 21.6, 18.7; $[\alpha]_D$ = +44 (c 0.6, $HCCl_3$). HRMS (ESI) Calcd for $C_{18}H_{25}O_3$ $[M + H]^+$: 289.1798. Found: 289.1802.

Compound ***20***. Enone **21** (36 mg, 0.09 mmol) was dissolved in MeOH (1.5 mL), and the solution was cooled to −78 °C. Sodium borohydride powder (10.5 mg, 0.28 mmol) was then added in one portion. The mixture was stirred at −78 °C for 10 min and then at 0 °C for 20 min, after which time TLC analysis indicated complete consumption of the starting material. Raney Ni (850 mg, washed four times with MeOH) was then added and the mixture heated at reflux for 20 min. After cooling, the mixture was filtered through Celite and the filtrate concentrated under reduced pressure. Purification of the residue by silica gel column chromatography with hexanes:ethyl acetate (10:1 → 7:2) afforded ketone **20** as an oil (25 mg, 95% yield, >15:1 stereoselectivity as indicated by ^1H NMR spectroscopy): IR (neat) 2923, 2856, 1717, 1446, 1130, 1029, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.43 (ddd, J = 10.0, 5.0, 1.8 Hz, 1H), 5.36 (dd, J = 10.3, 1.9 Hz, 1H), 4.16 (s, 1H), 3.83 (d, J = 11.8 Hz, 1H), 3.79 (d, J = 12.0 Hz, 1H), 3.64 (d, J = 12.0 Hz, 1H), 3.57−3.50 (m, 2H), 2.40−2.24 (m, 2H), 1.95−2.01 (m, 2H), 1.90 (d, J = 14.2 Hz, 1H), 1.58−1.51 (m, 3H), 1.43 (dd, J = 17.3, 4.5 Hz, 1H), 1.21 (d, J = 7.4 Hz, 3H), 1.20 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 135.9, 122.5, 86.6, 80.8, 72.5, 65.9, 54.4, 48.8, 42.6, 37.9, 36.6, 33.5, 32.0, 26.4, 21.6, 18.8, 18.5, 15.5; $[\alpha]_D$ = +30 (c 0.4, $HCCl_3$). HRMS (ESI) Calcd for $C_{19}H_{27}O_3$ $[M + H]^+$: 303.1955. Found: 303.1959.

Compound ***21***. Finely ground K_2CO_3 (131 mg, 0.95 mmol) and paraformaldehyde (114 mg, 3.8 mmol) was added under N_2 to a solution of **18** (36 mg, 0.1 mmol) in dry DMF. The suspension was then heated for 10 min at 90 °C. After cooling to room temperature, the mixture was poured into cold water and extracted with ethyl acetate three times. The extracts were washed with brine and dried over Na_2SO_4, and the solvent removed under reduced pressure. The residue was subjected to silica gel chromatography with hexanes:ethyl acetate (7:1) to yield **21** as an oil (36 mg, 97% yield): IR (neat) 2924, 1708, 1631, 1440, 1122, 954, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (d, J = 1.2 Hz, 1H), 5.43 (ddd, J = 10.0, 4.9, 1.8 Hz, 1H), 5.39−5.36 (m, 2H), 4.34 (d, J = 12.3 Hz, 1H), 4.25 (s, 1H), 3.77 (d, J = 12.1 Hz, 1H), 3.61−3.52 (m, 3H), 3.51−3.44 (m, 1H), 3.39−3.31 (m, 2H), 3.28 (d, J = 16.0 Hz, 1H), 3.25−3.18 (m, 1H), 2.94 (t, J = 2.9 Hz, 1H), 2.51 (d, J = 16.0 Hz, 1H), 2.17 (dd, J = 14.8, 2.4 Hz, 1H), 2.08 (dd, J = 14.8, 3.5 Hz, 1H), 1.44 (dd, J = 18.1, 5.2 Hz, 1H), 1.20 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 144.6, 136.1, 122.2, 120.7, 86.9, 79.8, 72.2, 66.0, 65.8, 56.9, 51.6, 43.0, 42.3, 41.6, 39.1, 36.6, 34.6, 32.0, 26.5, 21.8; $[\alpha]_D$ = −12 (c 0.3, $HCCl_3$). HRMS (ESI) Calcd for $C_{21}H_{27}O_3S_2$ $[M + H]^+$: 391.1396. Found: 391.1395.

Compound ***22***. To a solution of compound **20** (25 mg, 0.083 mmol) in CCl_4 (1.5 mL) at room temperature under N_2 was added NBS (19 mg, 0.1 mmol) and benzoylperoxide (1 mg, 0.004 mmol). The mixture was heated to reflux for 30 min and then cooled to room temperature, filtered through Celite, and washed with CCl_4. The filtrate was concentrated under vacuum to give yellow foam that was dissolved in dry DMSO (1 mL) at room temperature. A solution of $AgBF_4$ (56 mg, 0.29 mmol) in dry DMSO (0.5 mL) was added dropwise, after which AgBr precipitated immediately. The resulting suspension was stirred for 40 min after which time TLC indicated that the allylic bromide had been consumed. Et_3N (34 μL, 0.25 mmol) was added and the mixture stirred for an additional 2 h. The mixture was filtered and extracted with ethyl acetate three times. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by flash chromatography with hexanes:ethyl acetate (10:1 → 7:3) to afford compound **22** (19 mg, 73% yield) as a white solid: IR (neat) 2925, 1722, 1686, 1283, 1125, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 10.2 Hz, 1H), 5.85 (d, J = 10.2 Hz, 1H), 4.30 (s, 1H), 3.90 (d, J = 12.2 Hz, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.60 (d, J = 11.8 Hz, 1H), 2.49 (dd, J = 13.3, 11.2 Hz, 1H), 2.33 (t, J = 7.4 Hz, 1H), 2.08−1.95 (m, 3H), 1.91 (dt, J = 14.2, 2.1 Hz, 1H), 1.61−1.54 (m, 2H), 1.34 (s, 3H), 1.25 (d, J = 7.4 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 197.7, 156.5, 126.5, 84.0, 81.2, 72.1, 65.3, 56.8, 52.4, 48.1, 38.6, 37.6, 33.5, 30.7, 19.7, 19.6, 18.7, 15.2; $[\alpha]_D$ = −65 (c 0.2, $HCCl_3$). HRMS (ESI) Calcd for $C_{19}H_{25}O_4$ $[M + H]^+$: 317.1747. Found: 317.1748.

*Maoecrystal V (**2**)*. AcOH (103 μL, 1.8 mmol) was added at room temperature to a suspension of dry CrO_3 (30 mg, 0.3 mmol) and **22** (19 mg, 0.06) in CH_2Cl_2 (1 mL). The suspension was then heated to reflux under N_2 for 12 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the filtrate concentrated under reduced pressure. The solid residue was purified through flash chromatography with hexanes:ethyl acetate (7:1 → 7:3) to yield **2** (5.6 mg, 28% yield) and **23** (9.3 mg, 47% yield) as white solid.

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Maoecrystal V (2): IR (neat) 2963, 1752, 1721, 1683, 1258, 1015, 793 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 6.54 (d, J = 10.1 Hz, 1H), 5.99 (d, J = 10.1 Hz, 1H), 4.73 (d, J = 12.3 Hz, 1H), 4.67 (d, J = 1.3 Hz, 1H), 4.32 (dd, J = 12.3, 1.5 Hz, 1H), 3.29 (dd, J = 14.4, 4.7 Hz, 1H), 2.32 (q, J = 7.2 Hz, 1H), 2.21−2.09 (m, 2H), 1.91−1.86 (m, 1H), 1.78 (d, J = 14.4 Hz, 1H), 1.77−1.70 (m, 1H), 1.54−1.43 (m, 1H), 1.22 (s, 3H), 1.09 (d, J = 7.5 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 211.7, 194.7, 169.5, 156.7, 127.2, 85.5, 84.6, 69.5, 56.9, 52.4, 48.3, 38.3, 34.9, 32.9, 30.4, 18.7, 18.4, 18.3, 15.0; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, J = 10.1 Hz, 1H), 5.95 (d, J = 10.2 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.43 (d, J = 1.2 Hz, 1H), 4.13 (dd, J = 12.5, 1.5 Hz, 1H), 3.19 (dd, J = 14.6, 4.7 Hz, 1H), 2.34 (q, J = 8.0 Hz, 1H), 2.17−2.13 (m, 1H), 2.13−2.06 (m, 2H), 2.01−1.94 (m, 1H), 1.70 (d, J = 14.7 Hz, 1H), 1.67−1.60 (m, 1H), 1.30 (s, 3H), 1.26 (d, J = 7.5 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 194.8, 169.1, 156.7, 127.0, 84.9, 84.1, 69.2, 56.6, 51.9, 48.2, 38.3, 34.5, 32.6, 30.6, 18.6, 18.5, 18.0, 15.1; $[\alpha]_D$ = −96 (c 0.1, MeOH). HRMS (ESI) Calcd for $C_{19}H_{23}O_5$ $[M + H]^+$: 331.1540. Found: 331.1546.

23: IR (neat) 2930, 1730, 1697, 1265, 1042, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (d, J = 10.2 Hz, 1H), 6.11 (d, J = 10.2 Hz, 1H), 4.41 (s, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.30 (d, J = 12.0 Hz, 1H), 2.38 (q, J = 8.7, 7.6 Hz, 1H), 2.22 (ddd, J = 15.0, 11.1, 7.7 Hz, 1H), 2.16 (s, 1H), 2.13−2.04 (m, 1H), 2.01−1.87 (m, 3H), 1.76−1.66 (m, 1H), 1.27 (d, J = 7.5 Hz, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 191.8, 169.1, 155.0, 128.6, 85.8, 80.8, 76.2, 58.5, 55.9, 48.2, 38.6, 36.6, 32.8, 29.1, 20.5, 18.6, 16.9, 15.3; $[\alpha]_D$ = −69 (c 0.3, $HCCl_3$). HRMS (ESI) Calcd for $C_{19}H_{23}O_5$ $[M + H]^+$: 331.1540. Found: 331.1539.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All experimental procedures and complete characterization (NMR, MS, IR, optical rotation) for all new compounds. 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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■ REFERENCES

(1) Sun, H. D.; Huang, S. X.; Han, Q. B. *Nat. Prod. Rep.* **2006**, *23*, 673−698.

(2) Li, S. H.; Wang, J.; Niu, X. M.; Shen, Y. H.; Zhang, H. J.; Sun, H. D.; Li, M. L.; Tian, Q. E.; Lu, Y.; Cao, P.; Zheng, Q. T. *Org. Lett.* **2004**, *6*, 4327−4330.

(3) For recent reviews on the synthesis of maoecrystal V, see: (a) Behara, T. K.; Islam, S. N.; Singh, V. *J. Chem. Sci.* **2013**, *125*, 1301−1314. (b) Lazarski, K. E.; Moritz, B. J.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 10588−10599. (c) Zhang, Y.; Gong, J.; Yang, Z. *Chem. Rec.* **2014**, *14*, 606−622.

(4) For studies toward maoecrystal V, see: (a) Gong, J.; Lin, G.; Li, C. C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770−4773. (b) Krawczuk, P. J.; Schöne, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774−4776. (c) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbont, A. C.; Chen, D. Y.-K. *Chem. Commun.* **2010**, *46*, 70−72. (d) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6586−6587. (e) Singh, V.; Bhalerao, P.; Movin, S. M. *Tetrahedron Lett.* **2010**, *51*, 3337−3339. (f) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010−3013. (g) Baitinger, I.; Mayer, P.; Trauner, D. *Org. Lett.* **2010**, *12*, 5656−5659. (h) Peng, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2011**, *52*, 2104−2106. (i) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, *13*, 1080−1082. (j) Dong, L.; Deng, L.; Lim, Y. H.; Leung, G. Y. C.; Chen, D. Y.-K. *Chem.−Eur. J.* **2011**, *17*, 5887−5781. (k) Lazarski, K. E.; Akpinar, B.; Thomson, R. J. *Tetrahedron Lett.* **2013**, *54*, 635−637. (l) Carberry, P.; Viernes, D. R.; Choi, L. B.; Fegley, M. W.; Chisholm, J. D. *Tetrahedron Lett.* **2013**, *54*, 1734−1737.

(5) (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745−16746. (b) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860−18867. (c) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552−14555.

(6) Zakarian and coworkers have also completed an enantioselective total synthesis of maoecrystal V, see: Lu, P.; Mailyan, A.; Guptil, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, DOI: 10.1021/ja510573v.

(7) Porzelle, A.; Williams, C. M.; Schwartz, B. D.; Gentle, I. R. *Synlett* **2005**, 2923−2926.

(8) Nagasawa, T.; Shimada, N.; Torihata, M.; Kuwahara, S. *Tetrahedron* **2010**, *66*, 4965−4969. Note: No turnover was observed under catalytic conditions.

(9) See the Supporting Information for full details regarding the synthesis of trichloroimidate **10**.

(10) For recent reviews, see (a) Cartney, D. M.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122−5150. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (d) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516.

(11) The Heck reaction on compound **11** produced a 1:1 mixture of alkene isomers **12** and **13** in 54% yield on a 1.0 g scale using 4 mol % Pd.

(12) Semiempirical calculations (PM3) using Spartan indicated that the 2,3-alkene isomer **13** was 0.44 kcal·mol^{-1} more stable than the corresponding 1,2-alkene isomer **12**.

(13) For reviews on hypervalent iodine-mediated oxidative dearomative etherification, see: (a) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467−495. (b) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235−2261. (c) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068−4093.

(14) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627−4630.

(15) (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077−4082. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192−5201.

(16) Cerda-García-Rojas, C. M.; Bucio, M. A.; Román, L. U.; Hernández, J. D.; Joseph-Nathan, P. *J. Nat. Prod.* **2004**, *67*, 189−193.

(17) Ganem, B.; Boeckman, R. K., Jr. *Tetrahedron Lett.* **1974**, *15*, 917−920.

(18) For recent reviews regarding C−H functionalization in the context of total synthesis, see: (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (c) Chen, D. Y. K.; Youn, S. W. *Chem.−Eur. J.* **2012**, *18*, 9452−9474.

(19) (a) Harrison, I. T.; Harrison, S. *Chem. Commun.* **1966**, 752. (b) Fan, Y. C.; Kwon, O. *Org. Lett.* **2012**, *14*, 3264−3267.