CHAPTER 2

Efforts toward the Rapid Construction of the Cortistatin A Carbocylic Core[1]

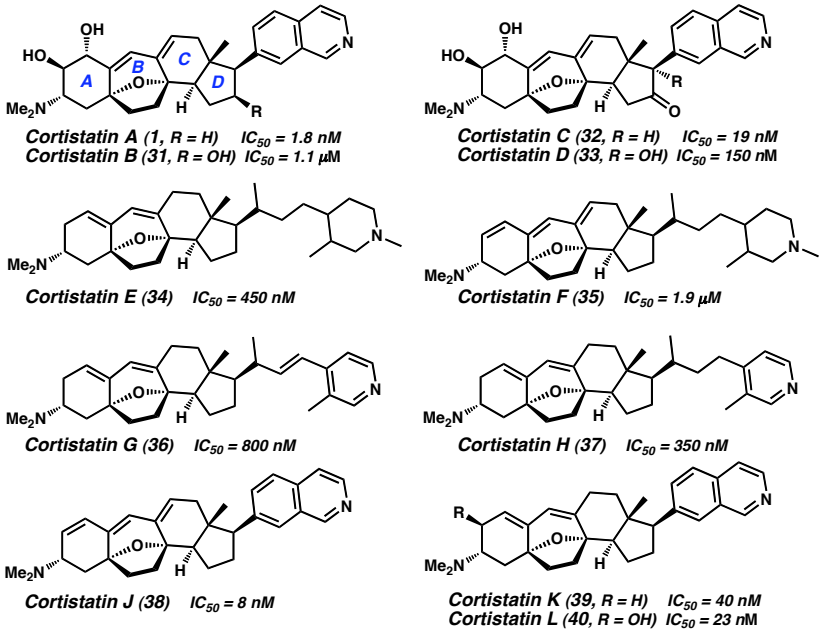
2.1 INTRODUCTION

The discovery of novel anti-angiogenic agents has become an active area of drug therapy research given their therapeutic applications in the treatment of cancer, autoimmune diseases, macular degeneration, and other diseases.[1] A series of unique *abeo*-9(10,19)-androstane-type steroidal alkaloids were isolated from the marine sponge *Corticium simplex* in 2006 and 2007,[2] some of which possessed significant anti-angiogenic activity (Figure 2.1). The most potent member, cortistatin A (**1**), demonstrated a highly selective growth inhibition of human umbilical vein endothelial cells (IC_{50} = 1.88 nM, selectivity index > 3000) with relatively no general toxicity toward other cell types. The biological activity, as well as the intriguing molecular structure of **1**

[1] This work was performed in collaboration with Drs. Corinne Baumgartner and Qi (Charles) Liu.

has led to several total syntheses[3] and efforts toward the construction of the cortistatin A core.[4]

Figure 2.1 Cortistatin family of natural products

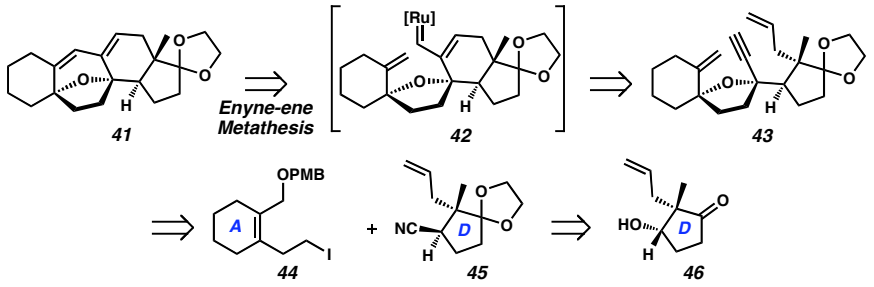


2.2 SYNTHETIC APPROACH OF CORTISTATIN A CORE

2.2.1 Retrosynthetic Analysis

In our approach to the synthesis of cortistatin A (**1**), we envisioned that the [6,7,6,5] core could arise via an intramolecular tandem enyne-ene metathesis (Scheme 2.1).[5] To examine the feasibility of such a step, we focused on the synthesis of alkynyl diene **43** as a model precursor for the key enyne-ene metathesis to give pentacyclic model diene **41**. Alkynyl diene **43** could arise from alkyl iodide **44** and nitrile **45**. Nitrile **45**, in turn, could be derived from ketone **46**, which has been synthesized in enantiopure form,[6] thus providing a direct route for an asymmetric synthesis of the cortistatin A carbocyclic core.

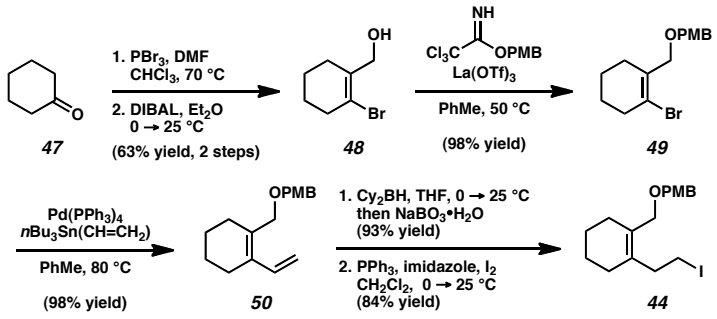
Scheme 2.1 Retrosynthetic analysis of cortistatin A core



2.2.2 Synthesis of A-ring Portion of Cortistatin A Core

Our synthesis of the A-ring portion of cortistatin A commenced from cyclohexanone **47,** which was converted to the allylic alcohol **48** through treatment with PBr_3 and DMF followed by a DIBAL reduction of the resulting aldehyde (Scheme 2.2).[7] PMB protection of the allylic alcohol yielded ether **49**, which was coupled to vinyltributylstannane to afford diene **50**. Hydroboration of diene **50** and subsequent exposure of the resultant primary alcohol to triphenylphosphine and iodine produced iodide **44**.

Scheme 2.2 Synthesis of A-ring

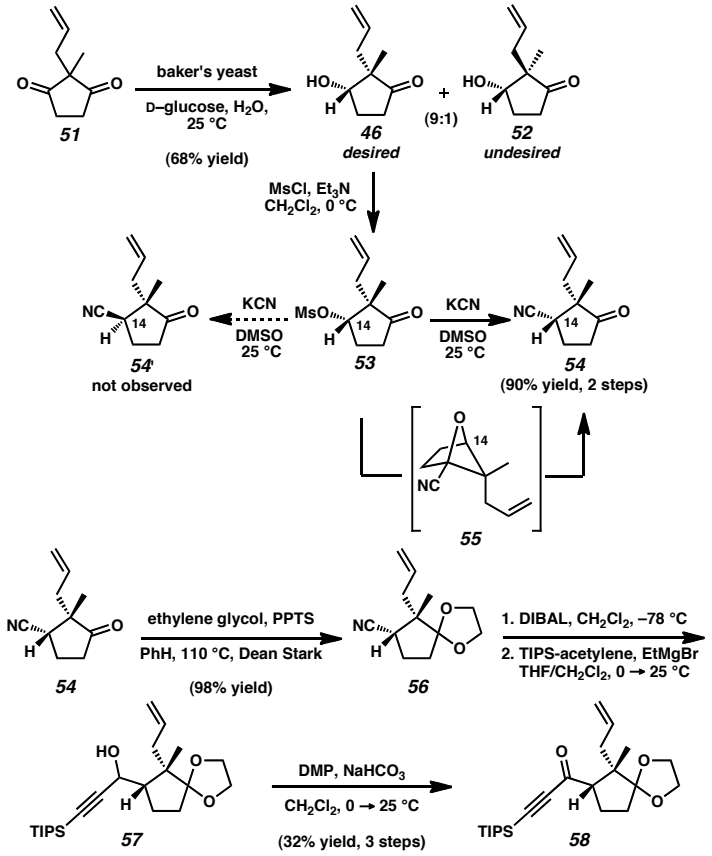


2.2.3 Synthesis of D-ring Portion of Cortistatin A Core

With the A-ring precursor **44** in hand, we set out to make the D-ring portion in an asymmetric manner (Scheme 2.3). Treatment of dione **51** with baker's yeast provided a 9:1 mixture of chromatographically separable alcohols **46** and **52**.[5] We envisioned that subjecting the major product alcohol **46**[8] to S_N2 displacement conditions would install the final carbon of the D-ring moiety and set the desired absolute and relative stereochemistry. However, mesylation of alcohol **46** followed by treatment with potassium cyanide in DMSO surprisingly afforded nitrile **54**, a product with net retention of stereochemistry at C(14). This unexpected result was confirmed via NOESY correlations of alcohol **46**, alcohol **52**, and nitrile **54** and by x-ray diffractometry of crystalline compounds derived from alcohol **46** and nitrile **54**.[9,10] A possible explanation for this unexpected outcome is that the mechanism proceeds via oxetane **55**, which is postulated to arise from reversible cyanohydrin formation of mesylate **53**.

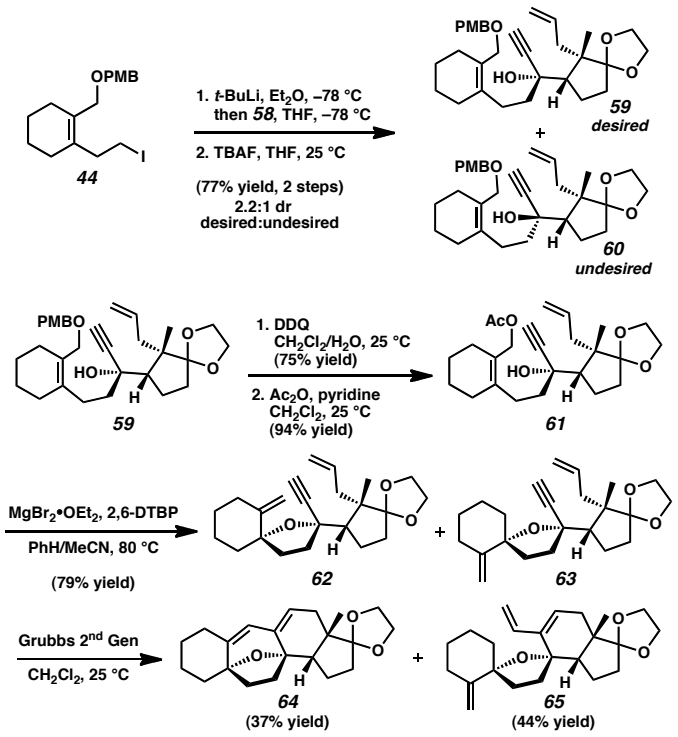
Despite this unusual result, we wished to continue the synthesis of the model system due to our interest in testing the enyne-ene metathesis. To advance ketone **54**, we protected the ketone as the acetal to give **56**. Nitrile **56** was then reduced to the aldehyde and after treatment with TIPS-acetylene and EtMgBr, afforded alcohol **57** as a mixture of diastereomers. Alcohol **57** was oxidized with Dess-Martin periodinane (DMP) to give ketone **58**.

Scheme 2.3 Asymmetric synthesis of D-ring piece



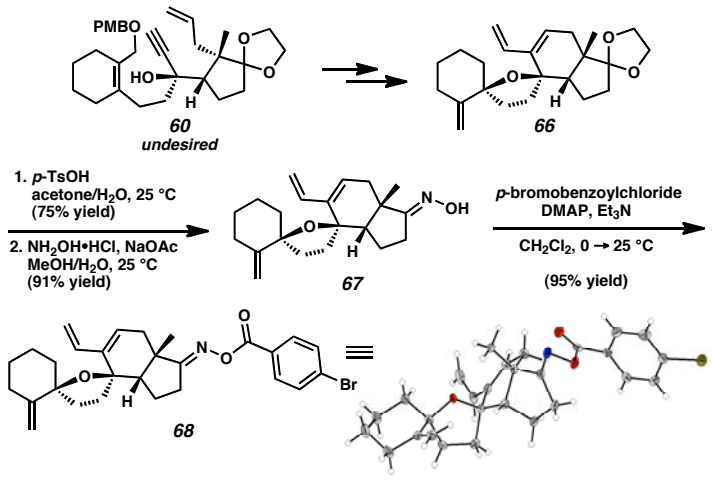
With our A-ring (**44**) and epi-D-ring (**58**) precusors in hand, we then coupled the two together by treating vinyl iodide **44** with *t*-BuLi and adding the resultant lithio species to ketone **58** (Scheme 2.4). Subsequent TIPS cleavage with TBAF gave a 2.2:1 mixture of the desired alcohol **59** (Felkin-Anh product) and the undesired alcohol **60**. After separation by column chromatography, PMB ether **59** was converted to allylic acetate **61**. Treatment of **61** with $MgBr_2$ gave the substituted tetrahydrofurans **62** and **63**, which were inseparable by column chromatography. Nonetheless, subjection of the mixture of **62** and **63** to Grubbs second-generation catalyst produced the desired enyne-ene metathesis product **64**, which contains the desired [6,7,6,5]-core, in 37% yield and the enyne metathesis product **65** in 44% yield.

Scheme 2.4 Enyne-ene metathesis



We planned to establish the absolute and relative stereochemistry of our metathesis products via derivatization to give compounds suitable for x-ray crystallography analysis. Attempts to convert the enyne-ene product **64** or the enyne product **65** to crystalline compounds were not successful. However, we were able to derivatize the undesired alcohol **60** by proceeding through a similar route as outlined in Scheme 2.4 for **59** to ultimately afford enyne product **66**. Enyne product **66** was then transformed to oxime **67**, which was acylated with *p*-bromobenzoylchloride to furnish **68**, a compound that was amenable to x-ray diffraction (Scheme 2.5). As a result, we were able to assign the relative and absolute stereochemistry of enyne product **66** and thereby, the relative and absolute stereochemistry of enyne-ene product **64** as well.[11]

Scheme 2.5 Determination of relative and absolute stereochemistry



2.3 CONCLUSION

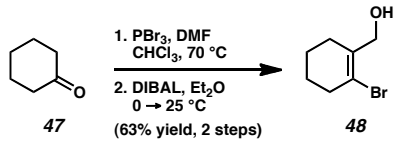
Herein, we have established the enyne-ene metathesis as a rapid method for the construction of the carbocylic core of cortistatin A. We have also reported an unusual reaction in which an attempted S_N2 displacement of a secondary mesylate on our five-membered D-ring piece gave a product with retention of stereochemistry. Further studies directed toward the synthesis of cortistatin A and related analogs are underway and will be reported in due course.

2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel OD-H column (250 mm x 4.6 mm, 5 mm particle size, 0.8 mL/min flow rate) obtained from Daicel Chemical Industries, Ltd. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using either a 100 mm or 50 mm path-length cell. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

2.4.2 Preparative Procedures and Spectroscopic Data



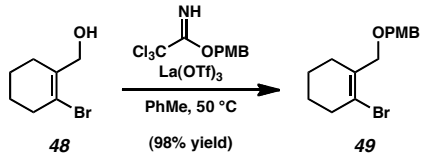
47 *48*

(2-Bromocyclohex-1-enyl)methanol (**48**).[7]

The allylic alcohol was synthesized according to a similar procedure.[12] To a solution of DMF (7.4 mL, 95.0 mmol, 3.0 equiv) in $CHCl_3$ (25 mL) was added PBr_3 (8.1 mL, 86.0 mmol, 2.7 equiv) dropwise at 0 °C. The mixture was stirred at 70 °C for 30 min, then cyclohexanone (**47**) (3.3 mL, 32.0 mmol, 1.0 equiv) was added dropwise over 30 min. After the resulting dark red solution was stirred at 70 °C for 1.5 h, it was poured into 4 M aq NaOAc (40 mL). Solid NaOH was added to the mixture to adjust the pH to 7.0 and the aqueous layer was extracted with hexanes. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was used in the next step without further purification. R_f = 0.80 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 2.77-2.72 (m, 2H), 2.30-2.25 (m, 2H), 1.80-1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 143.9, 128.6, 39.1, 25.2, 24.5, 21.3; IR (Neat Film NaCl) 2937, 1681, 1619, 1449, 1340, 1208, 972 cm^{-1}.

The crude product was dissolved in Et_2O (60 mL) and the solution was cooled to 0 °C. DIBAL (5.7 mL, 32.0 mmol, 1.0 equiv) was added slowly, and the mixture was stirred at 25 °C for 12 h. The reaction was quenched with H_2O (1.5 mL), 3 M aq NaOH (1.5 mL) and H_2O (3.0 mL), and stirred vigorously for 20 min. Na_2SO_4 (ca. 20 g) was added, and the mixture was stirred for an additional 1 h. The white solid was removed by filtration and the filtrate was concentrated to afford a yellow oil, which was purified by flash chromatography (4:1 hexanes/EtOAc) to give **48** as a clear oil (3.85 g, 63% yield

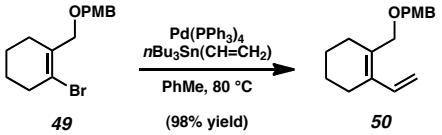
over 2 steps). R_f = 0.30 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 2H), 2.52-2.50 (m, 2H), 2.28-2.24 (m, 2H), 1.69 (quintet, *J* = 3.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 121.0, 66.1, 36.9, 29.0, 24.9, 22.5.



48 *49*

1-(((2-Bromocyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (**49**).

To a solution of **48** (1.01 g, 5.29 mmol, 1.0 equiv) in toluene (21 mL) was added 4-methoxybenzyl 2,2,2-trichloroacetimidate[13] (2.24 g, 7.93 mmol, 1.5 equiv) and $La(OTf)_3$ (164 mg, 0.28 mmol, 0.053 equiv). The mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **49** as a colorless oil (1.60 g, 98% yield). R_f = 0.40 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.90-6.84 (m, 2H), 4.41 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 2.52-2.49 (m, 2H), 2.24-2.20 (m, 2H), 1.71-1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 133.5, 130.8, 129.6, 122.3, 114.0, 73.2, 72.0, 55.5, 37.1, 29.2, 25.0, 22.5; IR (Neat Film NaCl) 2934, 2858, 2836, 1613, 1586, 1513, 1464, 1332, 1302, 1246, 1173, 1112, 1077, 1037, 972, 820 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}BrO_2$ $[M]^+$: 310.0568, found 310.0563.

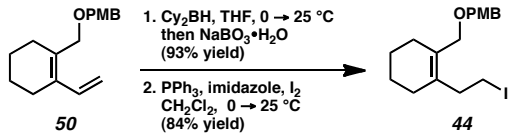


49 *50*

1-Methoxy-4-(((2-vinylcyclohex-1-enyl)methoxy)methyl)benzene (**50**).

A Schlenk flask was charged with $Pd(PPh_3)_4$ (281 mg, 0.24 mmol, 0.1 equiv), evacuated and refilled with Ar. **49** (755 mg, 2.44 mmol, 1.0 equiv) in toluene (10 mL)

and tributyl(vinyl)tin (1.0 mL, 3.41 mmol, 1.4 equiv) were added. The mixture was stirred at 80 °C for 2 d. The reaction mixture was concentrated, and the crude residue was purified by flash chromatography (hexanes → 99:1 → 98:2 hexanes/EtOAc) to give **50** as a colorless oil (618 mg, 98% yield). R_f = 0.50 (99:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.90-6.88 (m, 2H), 6.83 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.20 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.42 (s, 2H), 4.09 (s, 2H), 3.81 (s, 3H), 2.23-2.21 (m, 4H), 1.68-1.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 134.4, 133.9, 133.1, 130.9, 129.6, 114.0, 112.3, 71.9, 69.1, 55.5, 29.3, 25.3, 22.8, 22.7; IR (Neat Film NaCl) 3088, 2999, 2930, 2857, 2835, 1698, 1637, 1613, 1586, 1514, 1464, 1357, 1302, 1248, 1173, 1136, 1064, 1037, 986, 896, 820 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1623.



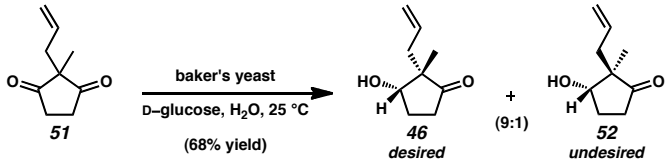
1-(((2-(2-Iodoethyl)cyclohex-1-enyl)methoxy)methyl)-4-methoxybenzene (**44**).

A round bottom flask was cooled to 0 °C and charged with BH_3•THF (3.6 mL, 1 M in THF, 3.54 mmol, 1.5 equiv). Cyclohexene (0.73 mL, 7.20 mmol, 3.05 equiv) was added and the mixture was allowed to warm to 25 °C over 30 min. Then **50** (610 mg, 2.36 mmol, 1.0 equiv) in THF (5 mL) was added at 0 °C, and the mixture was allowed to warm to 25 °C over 5 h. The reaction was quenched with $NaBO_3$•H_2O (4.48 g, 44.9 mmol, 19 equiv) in H_2O (20 mL), and the mixture was stirred at 25 °C for 12 h. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 → 7:1 → 5:1 hexanes/EtOAc) to give 2-(2-((4-

methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol as a colorless oil (608 mg, 93% yield). R_f = 0.20 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.88-6.86 (m, 2H), 4.43 (s, 2H), 3.88 (s, 2H), 3.79 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.66 (br s, 1H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.10 (br s, 2H), 2.01 (br s, 2H), 1.61-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 133.9, 130.9, 130.3, 129.9, 114.0, 72.6, 70.2, 60.5, 55.5, 36.8, 29.8, 29.5, 23.2, 23.1; IR (Neat Film NaCl) 3401, 2998, 2929, 2858, 2835, 1664, 1613, 1586, 1514, 1464, 1442, 1365, 1352, 1302, 1249, 1174, 1138, 1110, 1038, 821 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1811.

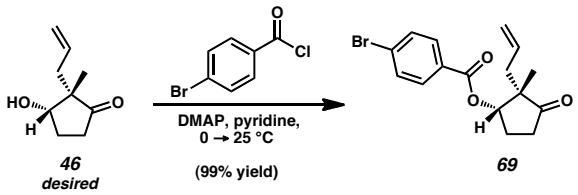
To a solution of PPh_3 (527 mg, 2.01 mmol, 1.5 equiv) and imidazole (273 mg, 4.02 mmol, 3.0 equiv) in CH_2Cl_2 (8 mL) was added I_2 (544 mg, 2.14 mmol, 1.6 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then 2-(2-((4-methoxybenzyloxy)methyl)cyclohex-1-enyl)ethanol (370 mg, 1.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added, and the mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 16 h. After addition of 5% aq $Na_2S_2O_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 95:5 → 9:1 hexanes/EtOAc) to give **44** as a pale yellow oil (436 mg, 84% yield). R_f = 0.50 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.41 (s, 2H), 3.89 (s, 2H), 3.80 (s, 3H), 3.12 (t, *J* = 8.5 Hz, 2H), 2.60 (t, *J* = 8.5 Hz, 2H), 2.07 (br s, 2H), 2.01 (br s, 2H), 1.60-1.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 135.1, 131.0, 130.7, 129.6, 114.0, 72.2, 69.8, 55.5, 38.2, 29.5, 28.5, 23.0, 22.9, 4.6; IR (Neat Film NaCl) 2998, 2927, 2855,

2833, 1612, 1586, 1513, 1463, 1354, 1302, 1248, 1172, 1134, 1068, 1037, 820 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{23}IO_2$ $[M]^+$: 386.0743, found 386.0733.



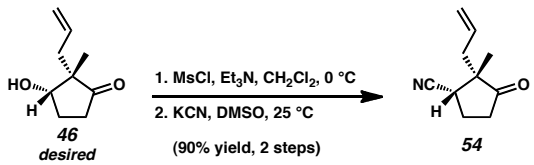
(2*S*, 3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone (**46**).[6]

To a solution of D-glucose (30.0 g) in H_2O (200 mL) was added dry active baker's yeast (20.0 g) at 35 °C. The suspension was stirred open to the air at 33 °C for 45 min. Dione **51** (1.71 g, 11.2 mmol, 1.0 equiv) was added dropwise, and the mixture was vigorously stirred at 25 °C for 5 d. The mixture was filtered over Celite, and the Celite was washed with H_2O and CH_2Cl_2. The filtrate was diluted with H_2O and extracted with CH_2Cl_2 in a continuous extractor for 48 h. The organic phase was concentrated and the crude residue was purified by flash chromatography (9:1 → 7:1 → 3:1 hexanes/EtOAc) to afford separated diastereoisomers **46** and **52** (1.16 g, 68% yield, 9 : 1 dr). **46** was isolated as a colorless oil. R_f = 0.27 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.17-5.10 (m, 2H), 4.13-4.10 (m, 1H), 2.51-2.43 (m, 1H), 2.37-2.16 (m, 4H), 1.97 (dddd, *J* = 13.0, 9.5, 9.5, 3.5 Hz, 1H), 1.90 (s, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.9, 134.6, 118.4, 77.7, 53.4, 35.7, 34.3, 28.0 20.0; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O_2$ $[M]^+$: 154.0994, found 154.0993; $[\alpha]_D^{24.6}$ +98.4° (*c* 1.01, $CHCl_3$, >99% ee). Analytical chiral HPLC assay with the benzoate of **46**: Chiralcel OD-H column, 1:9 2-propanol:hexanes, 0.8 mL/min, λ = 254 nm, isocratic method. **46-benzoate**: t_{fast} = 13.93 min (**(+)-46-benzoate**), t_{slow} = 15.51 min (**(–)-46-benzoate**). Enantioenriched **46-benzoate**: t_{fast} = 13.93 min (**(+)-46-benzoate**, >99%) (the trace corresponding to **(–)-46-benzoate** was below the threshold of detection).



(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentyl 4-bromobenzoate (**69**).

To a suspension of alcohol **46** (150 mg, 0.97 mmol, 1 equiv) and DMAP (11.9 mg, 0.097 mmol, 0.1 equiv) in pyridine (9 mL) cooled to 0 °C, *p*-bromobenzoylchloride (320 mg, 1.46 mmol, 1.5 equiv) was added. The reaction was allowed to gradually warm to 25 °C and quenched with water after 18 hours. The reaction mixture was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (hexanes → 90:10 hexanes/EtOAc) to afford **69** (335 mg, 99% yield) as a white solid. MP: 55-57 °C; R_f = 0.52 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 5.72 (dddd, J = 17.0, 10.5, 7.5, 7.5 Hz, 1H), 5.37 (m, 1H), 5.04-4.99 (m, 2H), 2.49-2.33 (comp. m, 5H), 2.20 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 165.0, 133.1, 132.1, 131.2, 128.9, 128.6, 118.8, 79.9, 52.4, 35.9, 34.1, 25.9, 20.1; IR (Neat Film NaCl) 3076, 2976, 1742, 1721, 1590, 1484, 1398, 1271, 1113, 1102, 1012, 756 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{17}O_3Br$ [M^+]: 336.0361, found 336.0350; $[\alpha]_D^{25.0}$ +162.2° (*c* 0.61, $CHCl_3$).

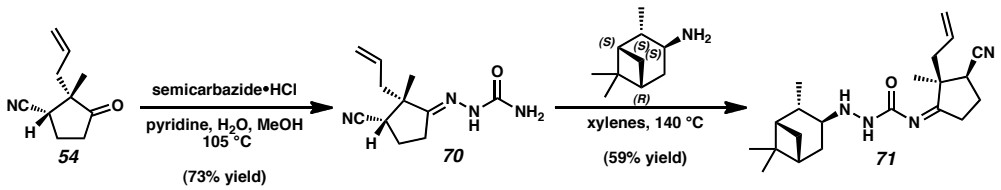


(1*S*, 2*S*)-2-allyl-2-methyl-3-oxocyclopentanecarbonitrile (**54**).

To a solution of **46** (805 mg, 5.22 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added MsCl (0.8 mL, 10.4 mmol, 2.0 equiv) and Et_3N (1.5 mL, 10.4 mmol, 2.0 equiv) at 0 °C.

The mixture was stirred at 0 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the crude mesylate was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dddd, J = 11.4, 8.7, 7.2, 7.2 Hz, 1H), 5.16-5.10 (m, 2H), 5.02 (m, 1H), 3.05 (s, 3H), 2.45-2.28 (m, 6H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 132.5, 119.2, 85.9, 52.4, 38.8, 35.4, 33.7, 26.4, 19.7; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{17}SO_4$ $[M]^+$: 233.0848, found 233.0844.

The resulting yellow oil was dissolved in DMSO (16 mL), KCN (680 mg, 10.4 mmol, 2.0 equiv) was added, and the mixture was stirred at 25 °C for 5 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 6:1 hexanes/EtOAc) to give **54** (765 mg, 90% yield) as a yellow oil. R_f = 0.33 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.21-5.15 (m, 2H), 2.94-2.90 (m, 1H), 2.52-2.21 (m, 6H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 131.8, 120.4, 119.4, 51.2, 39.1, 38.4, 35.5, 23.5, 21.2; IR (Neat Film NaCl) 3079, 2978, 2917, 2848, 2240, 1743, 1640, 1457, 1406, 1378, 1298, 1268, 1196, 1148, 1111, 1049, 994, 923 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{13}NO$ $[M]^+$: 163.0997, found 163.0997; $[\alpha]_D^{24.3}$ +46.8° (*c* 0.80, $CHCl_3$).

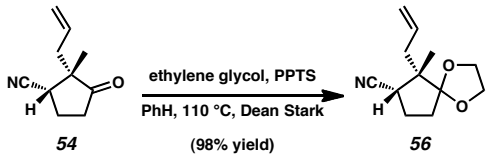


(Isopinocampheylamine)-semicarbazone 71.

Semicarbazide•HCl (51.2 mg, 0.46 mmol, 1.5 equiv) was added to a solution of ketone **54** (50 mg, 0.31 mmol, 1 equiv) in pyridine (2.7 mL), water (1.3 mL), and MeOH (0.4 mL). The reaction mixture was heated to 105 °C for 1 h and then cooled to 25 °C. After addition of water, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH) to afford the semicarbazone **70** (49.7 mg, 73% yield) as a white solid. R_f = 0.53 (10:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, MeOD) δ 5.87 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.12 (m, 2H), 3.00 (m, 1H), 2.57-2.36 (m, 4H), 2.31 (m, 1H), 2.17 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.8, 133.2, 119.5, 117.8, 40.7, 39.1, 25.4, 24.9, 22.1; IR (Neat Film NaCl) 3215, 1691, 1490 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{17}N_4O$ $[M+H]^+$: 221.1402, found 221.1408; $[\alpha]_D^{25.0}$ +60.5° (*c* 0.615, MeOH).

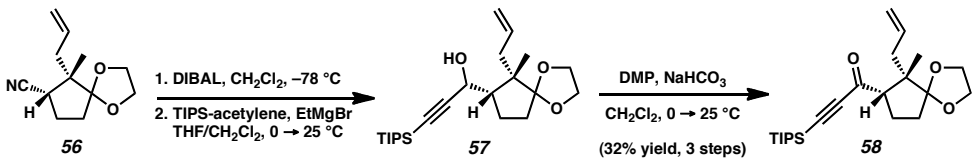
To a solution of the semicarbazone **70** (30 mg, 0.136 mmol, 1 equiv) in xylenes (1.3 mL) was added (1*S*, 2*S*, 3*S*, 5*R*)-(+)-isopinocampheylamine (27.5 uL, 0.163 mmol, 1.2 equiv). The reaction mixture was refluxed for 18 hours. Upon cooling, the reaction mixture was concentrated and purified by column chromatography (100:1 → 1:100 hexanes/EtOAc) to give **71** as a light brown solid (28.5 mg, 59% yield). MP: 230-232 °C from $CDCl_3$; R_f = 0.67 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 5.92 (d, *J* = 9.0 Hz, 1H), 5.80 (dddd, *J* = 17.5, 15.0, 7.5, 7.5 Hz, 1H), 5.21-5.14 (m, 2H), 4.17 (m, 1H), 2.74 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.63-2.52 (m, 2H), 2.45-2.40 (m, 4H), 2.30-2.17 (m, 2H), 1.97 (m, 1H), 1.86-1.83 (m, 2H), 1.60 (ddd, *J* = 13.5, 6.0, 2.5 Hz, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 1.13 (d, *J* = 7.5 Hz, 3H), 1.05 (s, 3H), 0.92 (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.1, 132.8, 119.5, 119.5, 48.4, 48.4, 48.0, 46.7, 41.8, 41.0,

40.0, 38.5, 37.9, 35.4, 28.2, 25.9, 25.4, 23.5, 23.5, 20.9; IR (Neat Film NaCl) 3414, 3192, 3080, 2911, 1669, 1659, 1534 cm $^{-1}$; HRMS (EI+) *m/z* calc'd for $C_{21}H_{32}ON_4$ [M^+]: 356.2576, found 356.2584; $[\alpha]_D^{25.0}$ +96.3 (c 1.09, $CHCl_3$).



(6*S*,7*S*)-6-allyl-6-methyl-1,4-dioxaspiro[4.4]nonane-7-carbonitrile (**56**).

To a solution of **54** (800 mg, 4.90 mmol, 1.0 equiv) in benzene (49 mL) was added PPTS (308 mg, 1.23 mmol, 0.25 equiv) and ethylene glycol (1.9 mL, 34.3 mmol, 7.0 equiv). The flask was fitted with a Dean-Stark trap, and the mixture was refluxed at 110 °C for 2 d. The volatiles were removed, and the crude residue was purified by flash chromatography (95:5 → 9:1 hexanes/EtOAc) to give **56** (997 mg, 98% yield) as a pale yellow oil. R_f = 0.42 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1H), 5.19-5.14 (m, 1H), 5.11-5.08 (m, 1H), 4.00-3.94 (m, 2H), 3.93-3.88 (m, 2H), 2.75-2.72 (m, 1H), 2.47 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.28 (ddt, *J* = 14.0, 7.0, 1.5 Hz, 1H), 2.17-2.08 (m, 1H), 2.04-1.96 (m, 2H), 1.93-1.86 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 121.5, 118.6, 118.0, 65.7, 65.1, 49.1, 37.8, 37.3, 32.7, 23.8, 19.9; IR (Neat Film NaCl) 3077, 2979, 2916, 2888, 2849, 2237, 1639, 1462, 1439, 1380, 1310, 1290, 1202, 1173, 1148, 1132, 1043, 1005, 950, 928 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{18}NO_2$ [M+H]$^+$: 208.1338, found 208.1331; $[\alpha]_D^{26.4}$ +78.0° (*c* 0.85, $CHCl_3$).



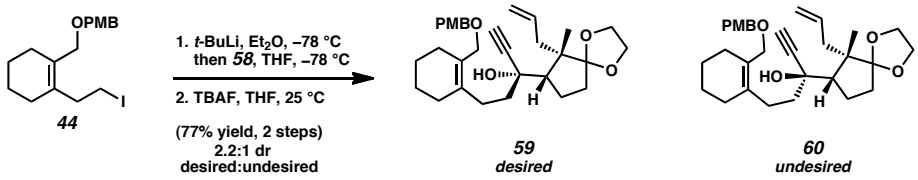
Compound 58.

To a solution of **56** (500 mg, 2.41 mmol, 1.0 equiv) in CH_2Cl_2 (23 mL) was added DIBAL (3.6 mL, 1 M in CH_2Cl_2, 3.62 mmol, 1.5 equiv) at –78 °C. The mixture was stirred at –78 °C for 1 h. Rochelle's salt (7.5 mL) was added and the mixture was stirred at 25 °C for 40 min. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude product was used in the next step without further purification.

The resulting colorless oil was dissolved in CH_2Cl_2 (12 mL) and added to a solution of TIPS-acetylene (3.2 mL, 14.5 mmol, 6.0 equiv) and ethylmagnesium bromide (3.2 mL, 3.0 M in Et_2O, 9.64 mmol, 4.0 equiv) in THF (29 mL) at 0 °C. The mixture was allowed to warm to 25 °C slowly and stirred at 25 °C for 24 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 → 9:1 hexanes/EtOAc) to give **57** as a mixture of two diastereomers.

To a solution of **57** in CH_2Cl_2 (10 mL), DMP (601 mg, 1.43 mmol, 1.0 equiv) and $NaHCO_3$ (132 mg, 1.57 mmol, 1.1 equiv) were added at 0 °C. The mixture was allowed to warm to 25 °C over 2 h and stirred at 25 °C for 10 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (98:2 hexanes/EtOAc) to give **58** as a colorless oil (298 mg, 32% yield over 3 steps). R_f = 0.60 (9:1 hexanes/EtOAc); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 4.99-4.95 (m, 2H), 3.95-3.88 (m, 4H), 3.00 (t, *J* = 9.0 Hz, 1H), 2.38-2.26 (m, 2H), 2.11 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.96-1.89 (m, 1H), 1.79-1.70 (m, 2H), 1.22 (s, 3H), 1.17-1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 135.7, 119.7, 117.6, 105.9, 96.7, 66.0, 64.5, 60.7, 50.6, 37.8, 32.0, 20.4, 19.6, 18.8, 11.4; IR (Neat Film NaCl) 3075, 2945, 2867, 2146, 1665, 1463, 1384, 1346, 1307, 1201, 1126, 1074, 1044, 998, 950, 917, 883 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{38}O_3Si$ $[M]^+$: 390.2590, found 390.2585; $[\alpha]_D^{19.1}$ +44.5° (*c* 1.03, $CHCl_3$).



Compounds 59 and 60.

To a solution of **44** (159 mg, 0.41 mmol, 1.5 equiv) in Et_2O (4.2 mL), *t*-BuLi (0.63 mL 0.88 mmol, 3.2 equiv) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 30 min. A solution of **58** (107 mg, 0.27 mmol, 1.0 equiv) in THF (2.7 mL) was added, and the mixture was stirred at –78 °C for 1 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (9:1 hexanes/EtOAc) to give the tertiary alcohol as a mixture of two diastereomers.

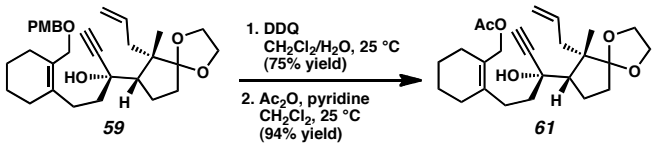
To a solution of this alcohol (147 mg, 0.23 mmol, 1.0 equiv) in THF (2.3 mL), TBAF (0.27 mL, 1 M in THF, 1.2 equiv) was added at 25 °C. The mixture was stirred at 25 °C for 1 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The

filtrate was concentrated, and the residue was purified by flash chromatography (8:1 → 1:1 hexanes/EtOAc) to give separated diastereomers **59** and **60** as colorless oils (104 mg, 77% yield, 2.2:1 dr).

Compound 59: R_f = 0.31 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 6.87-6.85 (m, 2H), 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.04 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.01-4.98 (m, 1H), 4.40 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.80 (s, 3H), 3.35 (s, 1H), 2.63 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.55-2.50 (m, 1H), 2.49 (s, 1H), 2.30 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.22 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.08-2.01 (m, 5H), 1.85-1.54 (m, 10H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 138.4, 136.1, 131.2, 129.7, 128.3, 119.8, 115.8, 114.0, 87.6, 74.8, 71.9, 71.3, 70.0, 65.4, 64.5, 55.5, 54.0, 49.1, 41.5, 37.8, 31.3, 30.1, 28.3, 28.3, 23.3, 23.2, 22.7, 19.9; IR (Neat Film NaCl) 3436, 3294, 3065, 2929, 2879, 2836, 1997, 1633, 1612, 1584, 1514, 1462, 1302, 1248, 1173, 1140, 1070, 1036, 1006, 949, 907, 821 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3133; $[\alpha]_D^{23.7}$ +6.4° (*c* 1.02, $CHCl_3$).

Compound 60: R_f = 0.39 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.88-6.86 (m, 2H), 6.16 (dddd, *J* = 17.0, 10.0, 7.5, 6.5 Hz, 1H), 5.05 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.99 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.41 (ABq, *J* = 11.5 Hz, 2H), 4.00-3.87 (m, 6H), 3.82 (s, 3H), 2.68 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.52 (s, 1H), 2.52-2.48 (m, 1H), 2.45 (s, 1H), 2.34-2.25 (m, 2H), 2.12-1.96 (m, 5H), 1.90-1.85 (m, 1H), 1.80-1.57 (m, 9H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 138.4, 136.4, 131.0, 129.7, 128.4, 119.9, 116.1, 114.0, 86.4, 75.6, 74.4, 72.0, 70.1, 65.8, 64.2, 55.5, 55.3, 49.6, 42.5, 37.4, 31.8, 30.0, 28.6, 27.6, 23.3, 23.2, 23.0, 21.7; IR (Neat Film NaCl) 3436, 3302, 2930, 2884, 2832, 1995, 1638, 1613, 1514, 1458, 1302, 1248, 1174, 1141, 1068, 1037,

1003, 951, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_5$ $[M+H]^+$: 495.3110, found 495.3124; $[\alpha]_D^{23.5}$ +32.3° (*c* 0.98, $CHCl_3$).

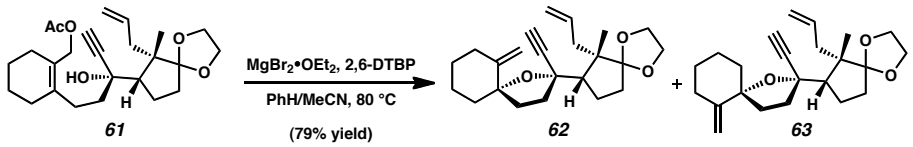


Acetate 61.

To a solution of **59** (65 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (13 mL) and H_2O (1.3 mL) was added DDQ (45 mg, 0.20 mmol, 1.5 equiv). The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (3:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (37 mg, 75% yield). R_f = 0.11 (4:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.05-4.98 (m, 2H), 4.11 (ABq, *J* = 11.5 Hz, 2H), 3.97-3.86 (m, 4H), 3.47 (br s, 1H), 2.62 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.58 (s, 1H), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.36 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H), 2.24 (ddd, *J* = 12.0, 12.0, 5.5 Hz, 1H), 2.14-1.99 (m, 5H), 1.88-1.54 (m, 11H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.3, 130.7, 119.8, 115.9, 87.4, 75.0, 71.4, 65.4, 64.5, 63.1, 54.0, 49.2, 41.4, 37.7, 31.2, 29.9, 28.1, 28.1, 23.3, 23.3, 22.6, 19.9; IR (Neat Film NaCl) 3401, 3304, 3070, 2919, 2884, 1995, 1724, 1636, 1459, 1434, 1377, 1318, 1274, 1246, 1217, 1176, 1138, 1070, 1038, 1003, 982, 937, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2546; $[\alpha]_D^{26.2}$ +12.5° (*c* 0.67, $CHCl_3$).

To a solution of the allylic alcohol (44 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), pyridine (39 μL, 0.48 mmol, 4.0 equiv) and Ac_2O (45 μL, 0.48 mmol, 4.0 equiv)

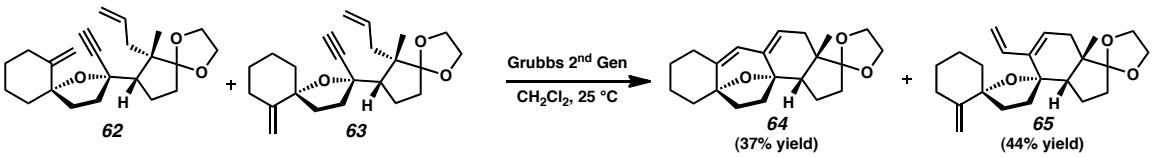
were added. The mixture was stirred at 25 °C for 24 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **61** as a colorless oil (46 mg, 94% yield). R_f = 0.28 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.06-4.98 (m, 2H), 4.59 (ABq, *J* = 11.5 Hz, 2H), 3.98-3.88 (m, 4H), 3.35 (s, 1H), 2.66-2.62 (m, 1H), 2.57 (s, 1H), 2.56-2.52 (m, 1H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 4H), 2.06 (s, 3H), 1.89-1.71 (m, 6H), 1.62-1.55 (m, 5H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 137.9, 126.1, 119.8, 115.9, 87.3, 75.0, 71.2, 65.4, 65.0, 64.5, 54.0, 49.2, 41.5, 37.7, 31.3, 30.1, 28.4, 28.1, 23.1, 23.0, 22.7, 21.4, 19.9; IR (Neat Film NaCl) 3468, 3272, 3069, 2930, 2884, 1735, 1636, 1455, 1436, 1378, 1239, 1176, 1144, 1073, 1023, 952 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M\text{-}OAc]^+$: 357.2430, found 357.2440; $[\alpha]_D^{28.0}$ +4.0° (*c* 0.62, $CHCl_3$).



Compounds 62 and 63.

To a solution of **61** (43 mg, 0.10 mmol, 1.0 equiv) in benzene (5 mL), 2,6-DTBP (0.14 mL 0.62 mmol, 6.0 equiv), $MgBr_2$•OEt_2 (107 mg, 0.41 mmol, 4.0 equiv) and MeCN (1.0 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (hexanes → 199:1 → 99:1 hexanes/EtOAc) to give **62** and **63** as

a mixture of two diastereomers as a colorless oil (29 mg, 79% yield). R_f = 0.45 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23-6.13 (m, 1H), 5.19 (d, *J* = 2.5 Hz, 0.5H), 5.02-4.92 (m, 2H), 4.88 (d, *J* = 2.0 Hz, 0.5H), 4.67 (s, 1H), 3.97-3.86 (m, 4H), 2.56-2.34 (m, 4H), 2.24-1.23 (m, 16H), 1.11 (s, 1.5H), 1.04 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.2, 138.6, 138.5, 120.5, 120.3, 115.5, 115.5, 106.2, 105.4, 88.0, 87.5, 87.3, 86.7, 80.7, 80.1, 74.5, 74.4, 65.9, 65.8, 64.1, 64.1, 55.3, 54.7, 48.8, 48.6, 42.0, 39.9, 38.7, 38.4, 38.4, 38.2, 35.0, 34.9, 34.9, 33.7, 31.7, 31.4, 28.1, 28.0, 25.2, 24.7, 22.0, 21.2, 20.9, 20.7; IR (Neat Film NaCl) 3304, 3071, 2972, 2934, 2879, 2853, 1735, 1649, 1636, 1460, 1446, 1396, 1376, 1315, 1300, 1274, 1217, 1202, 1173, 1145, 1120, 1068, 1046, 1011, 947, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2439.



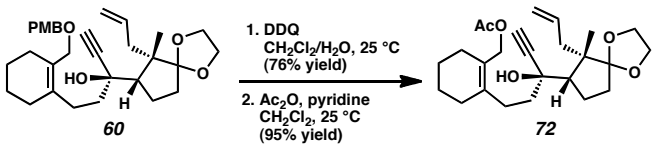
Compounds 64 and 65.

To a solution of **62** and **63** (24 mg, 0.067 mmol, 1.0 equiv) in CH_2Cl_2 (6.5 mL), Grubbs 2nd generation catalyst (8.6 mg, 0.010 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **64** as a beige solid (8.2 mg, 37% yield) and **65** as a colorless oil (10.5 mg, 44% yield).

Compound 64: R_f = 0.47 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.0 Hz, 1H), 5.20 (t, *J* = 4.0 Hz, 1H), 3.95-3.88 (m, 4H), 2.32-2.28 (m, 2H), 2.24-2.12 (m, 3H), 2.05-1.78 (m, 10H), 1.74-1.60 (m, 4H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 137.3, 120.3, 120.1, 117.2, 81.4, 80.7, 65.6, 64.6, 51.0, 46.4, 39.8, 38.9,

35.5, 34.0, 31.7, 31.3, 26.1, 24.4, 23.1, 19.9; IR (Neat Film NaCl) 2919, 2858, 1995, 1727, 1465, 1451, 1427, 1375, 1310, 1279, 1259, 1202, 1175, 1158, 1098, 1070, 1024, 942, 912, 871 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{29}O_3$ $[M+H]^+$: 329.2117, found 329.2122; $[\alpha]_D^{21.3}$ +176.8° (*c* 0.97, $CHCl_3$).

Compound 65: R_f = 0.42 (99:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.85 (t, *J* = 4.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.94 (d, *J* = 2.0 Hz, 1H), 4.67 (s, 1H), 3.92-3.87 (m, 4H), 2.43-2.38 (m, 1H), 2.34-2.24 (m, 2H), 2.16-2.05 (m, 3H), 2.02-1.60 (m, 11H), 1.54-1.48 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 139.8, 136.7, 122.5, 120.5, 113.8, 105.3, 85.4, 84.4, 65.6, 64.6, 51.5, 46.3, 40.4, 36.4, 35.0, 34.0, 33.2, 31.2, 28.6, 24.4, 23.9, 20.9; IR (Neat Film NaCl) 2930, 2853, 1995, 1736, 1648, 1460, 1442, 1372, 1311, 1261, 1200, 1151, 1137, 1078, 1030, 1009, 946, 894 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2445.



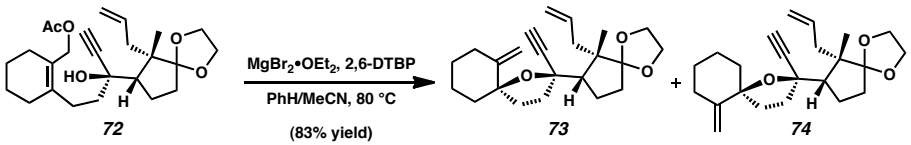
Compound 72.

To a solution of **60** (33 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and H_2O (0.7 mL), DDQ (23 mg, 0.10 mmol, 1.5 equiv) was added. The mixture was stirred at 25 °C for 1 h. After addition of saturated aq $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc) to give the allylic alcohol as a colorless oil (19 mg, 76% yield). R_f = 0.20 (4:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (dddd, *J*

= 17.0, 10.0, 8.0, 6.5 Hz, 1H), 5.09-5.04 (m, 1H), 5.01-4.98 (m, 1H), 4.13 (ABq, *J* = 11.5 Hz, 2H), 3.95-3.86 (m, 4H), 2.68 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.59 (s, 1H), 2.52-2.47 (m, 1H), 2.42-2.32 (m, 1H), 2.31-2.14 (m, 1H), 2.13-1.91 (m, 5H), 1.90-1.55 (m, 12H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 135.5, 130.8, 119.8, 116.4, 86.4, 75.7, 74.5, 65.8, 64.2, 63.2, 55.3, 49.6, 42.5, 37.3, 31.8, 29.9, 28.3, 27.5, 23.3, 23.2, 23.0, 21.6; IR (Neat Film NaCl) 3402, 3305, 3072, 2919, 2884, 1718, 1635, 1459, 1436, 1377, 1320, 1276, 1246, 1216, 1176, 1138, 1070, 1039, 1002, 981, 952, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.2535, found 375.2544; $[\alpha]_D^{26.1}$ +38.6° (*c* 0.62, $CHCl_3$).

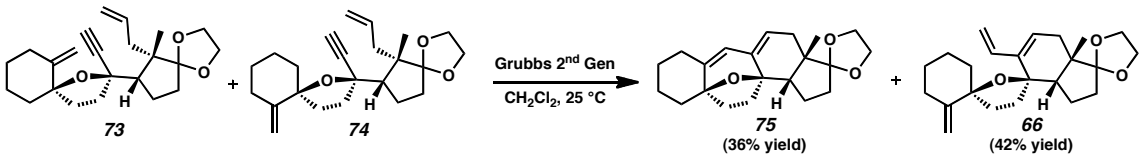
To a solution of the allylic alcohol (18 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), pyridine (15 μL, 0.19 mmol, 4.0 equiv) and Ac_2O (18 μL, 0.19 mmol, 4.0 equiv) were added. The mixture was stirred at 25 °C for 21 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 10% aq HCl, saturated aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (8:1 hexanes/EtOAc) to give **72** as a colorless oil (19 mg, 95% yield). R_f = 0.34 (7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (dddd, *J* = 18.0, 10.0, 8.0, 6.5 Hz, 1H), 5.08-5.04 (m, 1H), 5.01-4.99 (m, 1H), 4.60 (ABq, *J* = 12.0 Hz, 2H), 3.96-3.87 (m, 4H), 2.69 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.58 (s, 1H), 2.54-2.49 (m, 1H), 2.41 (s, 1H), 2.34 (t, *J* = 8.0 Hz, 2H), 2.12 (t, *J* = 9.0 Hz, 1H), 2.06 (s, 3H), 2.05-2.02 (m, 4H), 1.92-1.68 (m, 6H), 1.68-1.57 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.3, 138.0, 126.2, 119.8, 116.3, 86.1, 75.8, 74.4, 65.8, 65.0, 64.2, 55.2, 49.6, 42.6, 37.4, 31.8, 30.1, 28.3, 27.7, 23.1, 22.7, 22.7, 21.6, 21.4; IR (Neat Film NaCl) 3481, 3303, 3071, 2924, 2856, 1736, 1636, 1461, 1436, 1378, 1318, 1239, 1177, 1143, 1075, 1024, 953

cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M\text{-}OAc]^+$: 357.2430, found 357.2426; $[\alpha]_D^{27.9}$ +44.6° (*c* 0.42, $CHCl_3$).



Compounds 73 and 74.

To a solution of **72** (31 mg, 0.08 mmol, 1.0 equiv) in benzene (4 mL), 2,6-DTBP (0.10 mL, 0.45 mmol, 6.0 equiv), $MgBr_2 \bullet OEt_2$ (77 mg, 0.30 mmol, 4.0 equiv) and MeCN (0.6 mL) were added, and the mixture was stirred at 80 °C for 2 d. After addition of brine, the aqueous layer was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 hexanes/EtOAc) to give **73** and **74** as a mixture of two diastereomers as a colorless oil (22 mg, 83% yield). R_f = 0.46 (99:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 0.4H), 5.02-4.91 (m, 2.6H), 4.71 (s, 0.4H), 4.65 (s, 0.6H), 3.97-3.86 (m, 4H), 2.75-2.71 (m, 1H), 2.60-2.54 (m, 1H), 2.47 (s, 0.4H), 2.47 (s, 0.6H), 2.42-2.36 (m, 1H), 2.21-1.29 (m, 16H), 1.12 (s, 1.2H), 1.07 (s, 1.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.4, 138.9, 138.8, 120.0, 119.9, 115.1, 115.1, 106.6, 106.0, 87.9, 87.7, 87.5, 87.1, 81.5, 81.5, 74.7, 74.6, 65.7, 65.7, 64.3, 64.2, 57.2, 56.4, 49.3, 49.3, 42.1, 41.9, 41.6, 40.6, 37.8, 37.5, 34.9, 34.8, 34.5, 33.8, 32.4, 32.4, 28.1, 27.9, 25.2, 24.6, 23.0, 22.9, 22.0, 21.9; IR (Neat Film NaCl) 3302, 3070, 2972, 2935, 2879, 2858, 1649, 1636, 1459, 1446, 1396, 1375, 1298, 1243, 1174, 1137, 1105, 1075, 1050, 1002, 950, 899 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2426.



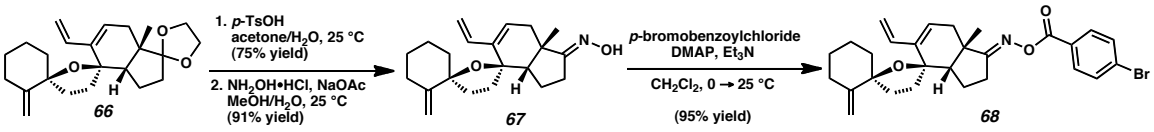
Compounds 75 and 66.

To a solution of **73** and **74** (20 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL), Grubbs 2nd generation catalyst (7 mg, 0.008 mmol, 15 mol%) was added. The mixture was stirred at 25 °C for 2 d. The solvent was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 9:1 hexanes/EtOAc) to give **75** as a white solid (6.7 mg, 36% yield) and **66** as a colorless oil (8.3 mg, 42% yield).

Compound 75: R_f = 0.42 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H), 5.34 (d, *J* = 5.5 Hz, 1H), 3.91-3.88 (m, 4H), 2.31-2.25 (m, 2H), 2.18-2.05 (m, 4H), 1.96-1.70 (m, 10H), 1.61-1.48 (m, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 139.8, 120.1, 119.7, 118.2, 83.4, 79.5, 65.6, 64.6, 49.5, 46.1, 37.4, 35.5, 34.3, 34.0, 31.7, 30.1, 26.2, 24.4, 24.2, 19.5; IR (Neat Film NaCl) 2924, 2853, 1995, 1726, 1623, 1461, 1377, 1310, 1259, 1153, 1072, 1055, 946, 907 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{28}O_3$ $[M]^+$: 328.2039, found 328.2038; $[\alpha]_D^{24.3}$ −159.9° (*c* 0.90, $CHCl_3$).

Compound 66: R_f = 0.42 (99:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (ddd, *J* = 17.0, 11.0, 1.0 Hz, 1H), 5.92 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 5.00 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.69 (s, 1H), 3.96-3.85 (m, 4H), 2.44-2.39 (m, 1H), 2.26 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.15-2.01 (m, 3H), 1.97-1.82 (m, 4H), 1.80-1.73 (m, 2H), 1.70-1.65 (m, 2H), 1.61-1.52 (m, 2H), 1.50-1.43 (m, 2H), 1.31-1.25 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 138.0, 137.0, 124.4, 120.4, 114.2, 105.5, 85.7, 83.0, 65.6, 64.8, 50.2, 44.7, 40.8, 34.9, 34.3, 33.9, 33.2, 31.0, 28.5, 24.7, 23.8, 19.4; IR (Neat Film NaCl) 3079, 2932, 2876, 2858, 1736, 1648,

1619, 1460, 1446, 1374, 1317, 1305, 1263, 1200, 1152, 1087, 1068, 1055, 1021, 1009, 950, 893, 755 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_3$ $[M+H]^+$: 357.2430, found 357.2429; $[\alpha]_D^{24.2}$ +3.1° (*c* 0.93, $CHCl_3$).



Compound 68.

To a solution of **66** (31 mg, 0.09 mmol, 1.0 equiv) in acetone (0.9 mL) was added H_2O (2.4 μL, 0.13 mmol, 1.5 equiv) and *p*-TsOH (3.3 mg, 0.02 mmol, 0.2 equiv) at 25 °C. The mixture was stirred at 25°C for 15 h, and the solvent was concentrated. After addition of EtOAc, the organic phase was washed with saturated aq $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the crude residue was purified by flash chromatography (99:1 → 98:2 hexanes/EtOAc) to afford the desired product that was used directly in the next step.

To the resulting ketone (15 mg, 0.05 mmol, 1.0 equiv) dissolved in MeOH/H_2O (3 mL, 5:1) was added NaOAc (38 mg, 0.45 mmol, 10 equiv) and $NH_2OH•H_2O$ (34 mg, 0.49 mmol, 11 equiv) at 25 °C. The mixture was stirred at 25°C for 14 h, and the solvent was concentrated. After addition of H_2O, the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to give **67**.

To a solution of oxime **67** (14 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL), *p*-bromobenzoylchloride (11 mg, 0.05 mmol, 1.2 equiv), DMAP (1 mg, 0.01 mmol, 0.2 equiv), and Et_3N (12 μL, 0.08 mmol, 2.0 equiv) were added at 0 °C. The mixture was

stirred at 0 °C for 2 h. After addition of saturated aq NH_4Cl, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (99:1 → 98:2 → 95:5 hexanes/EtOAc) to give **68** as a white solid (20 mg, 95% yield). MP: 91-93 °C from ethyl acetate/heptane; R_f = 0.38 (95:5 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.60-7.57 (m, 2H), 6.43 (ddd, *J* = 17.0, 10.5, 1.0 Hz, 1H), 5.89 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.37 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.06 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 2.83 (dd, *J* = 19.5, 8.5 Hz, 1H), 2.67-2.60 (m, 1H), 2.43-2.38 (m, 1H), 2.25 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.20 (d, *J* = 19.0 Hz, 1H), 2.13-2.01 (m, 4H), 1.96-1.75 (m, 4H), 1.71-1.61 (m, 2H), 1.58 (s, 3H), 1.54-1.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 163.5, 154.1, 138.8, 136.4, 132.1, 131.3, 128.6, 128.5, 122.4, 115.0, 105.4, 85.9, 81.8, 53.3, 44.3, 40.8, 34.8, 34.4, 33.9, 32.5, 28.5, 27.4, 24.5, 24.5, 22.4; IR (Neat Film NaCl) 3079, 2932, 2855, 1746, 1648, 1590, 1483, 1447, 1398, 1379, 1320, 1254, 1174, 1069, 1011, 906, 875, 750, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{33}BrO_3N$ $[M+H]^+$: 510.1644, found 510.1644; $[\alpha]_D^{22.9}$ +30.4° (*c* 0.90, $CHCl_3$).

NOTES AND REFERENCES

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(8) The enantiomeric excess of the benzoate derivative of alcohol **46** was determined by chiral HPLC to be >99% ee. See Experimental Section for details.

(9) See Experimental Section for details.

(10) It is worth noting that we did not realize the actual result of our "S_N2" reaction until a much later point in the synthesis. This unexpected result highlights the sometimes unexpected reactivity of individual organic substrates even under conventional reaction conditions.

(11) From this result, the D-ring relative stereochemistry was unambiguously assigned.

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