

# Symmetry-Driven Total Synthesis of Myrioneurinol

Jake M. Aquilina, Myles W. Smith\*

*Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas,  
TX 75390, United States.*

\*myles.smith@utsouthwestern.edu

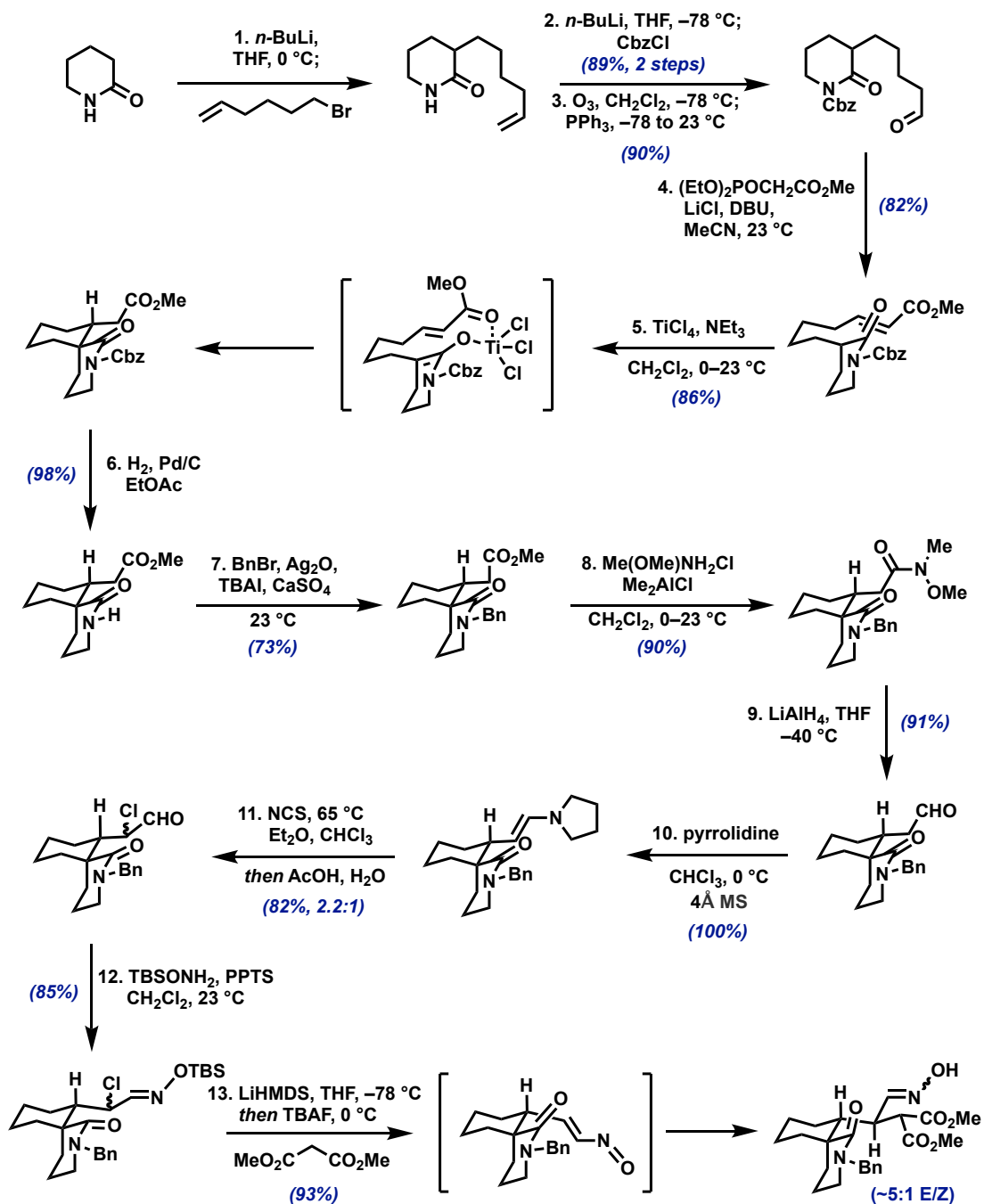
<b>1. General Information.....</b>	<b>2</b>
<b>2. Synthetic Schemes for Weinreb's, Ma's and Our Myrioneurinol Syntheses.....</b>	<b>3</b>
<b>3. Alternate Approaches to Reductive Amination Precursor.....</b>	<b>7</b>
<b>4. Experimental Procedures.....</b>	<b>9</b>
<b>5. Details for Single Crystal X-ray Analyses of 18, 20 and (–)-18.....</b>	<b>31</b>
<b>6. References.....</b>	<b>37</b>
<b>7. NMR Spectra.....</b>	<b>38</b>

## 1. General Information

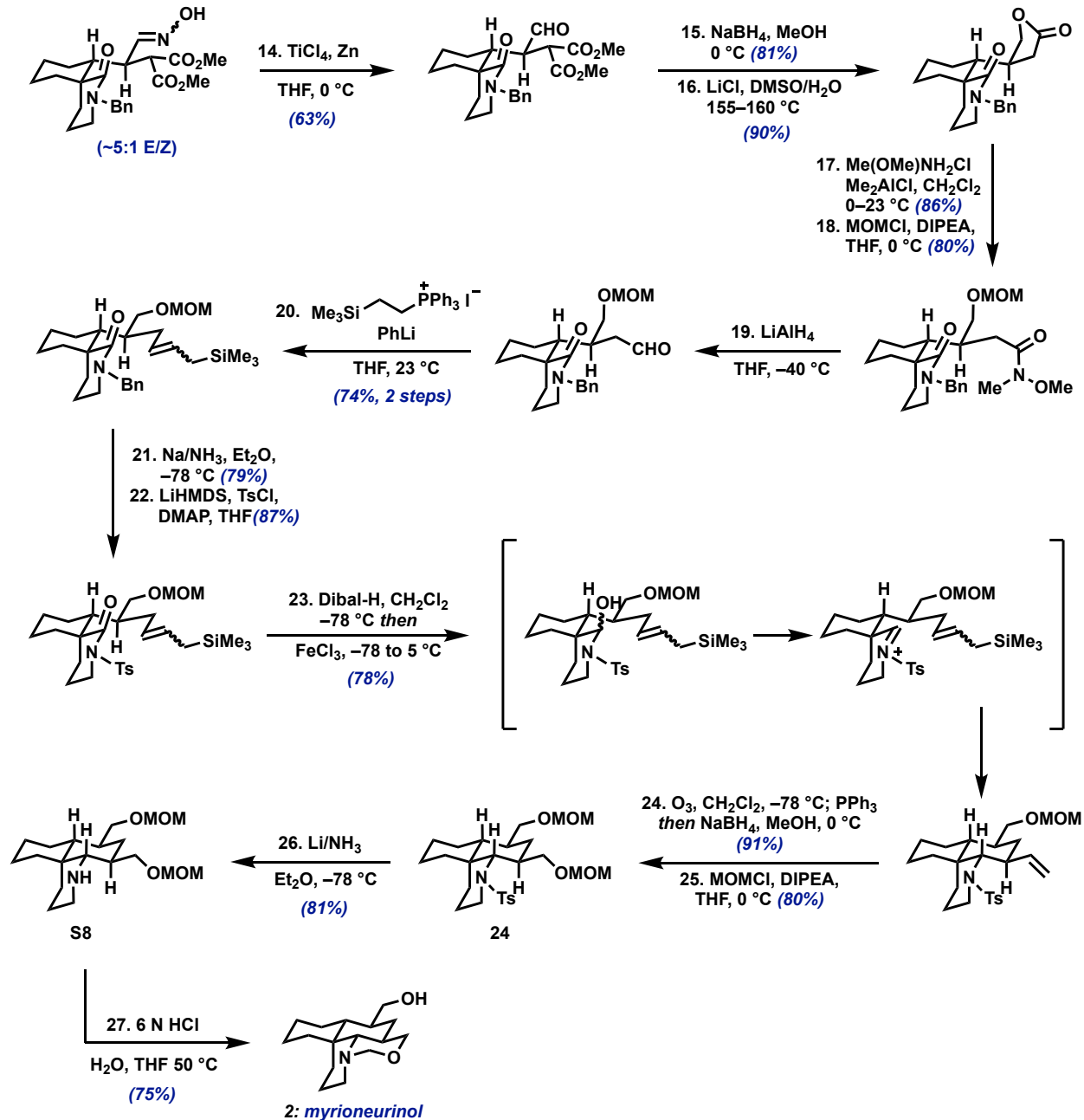
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Dry methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), tetrahydrofuran (THF), diethyl ether ( $\text{Et}_2\text{O}$ ), and toluene (PhMe) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; *N,N*-dimethylformamide (DMF) and methanol (MeOH) were purchased in anhydrous form from Sigma–Aldrich or Acros and used as received; acetonitrile (MeCN), dioxane, acetic acid (AcOH), and 1,2-dimethoxyethane (DME) were purchased from Fisher, Oakwood, or TCI and used as received. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F<sub>254</sub>) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.25 mm E. Merck silica gel plates (60 F<sub>254</sub>). SiliCycle silica gel (60 Å, academic grade, particle size 40–63  $\mu\text{m}$ ) was used for flash column chromatography. NMR spectra were recorded on Varian MR400, Bruker AN400 and AN600 instruments and calibrated using residual undeuterated solvent as an internal reference (for  $\text{CDCl}_3$ ,  $^1\text{H} = \delta$  7.26 and  $^{13}\text{C} = \delta$  77.16). The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent. High-resolution mass spectrometric data (ESI) were acquired on Shimadzu 9030 qTOF mass spectrometer in positive ion mode (UT Arlington) or on a SCIEX TripleTOF 6600 High Resolution Accurate Mass System (UT Southwestern Metabolomics Core Facility). Optical rotation data were recorded on a Rudolph Research Analytical Autopol® IV Polarimeter.

## 2. Chemical Synthesis Schemes

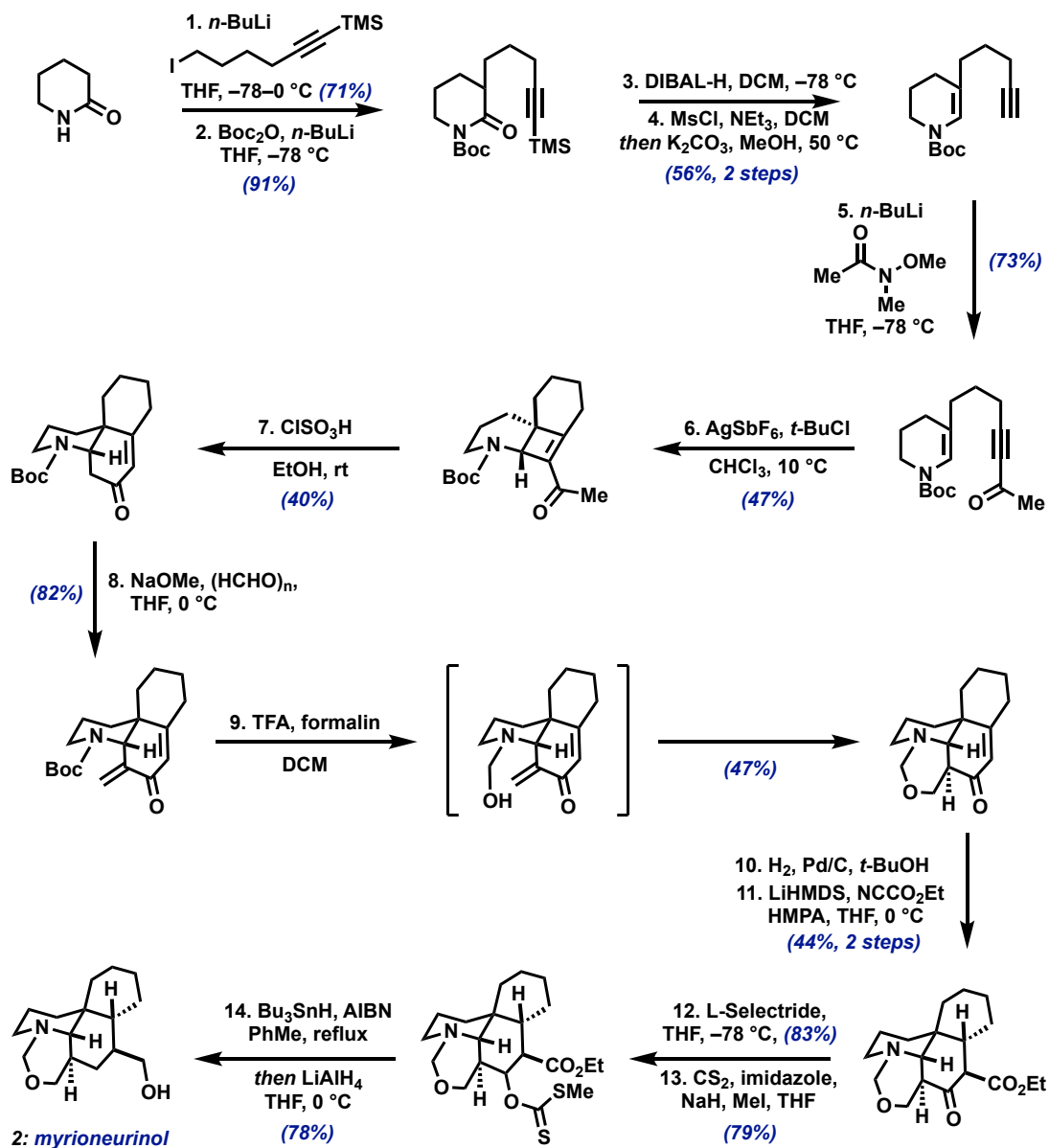
Scheme S1. Weinreb synthesis of oxime precursor to **2**.<sup>1</sup>



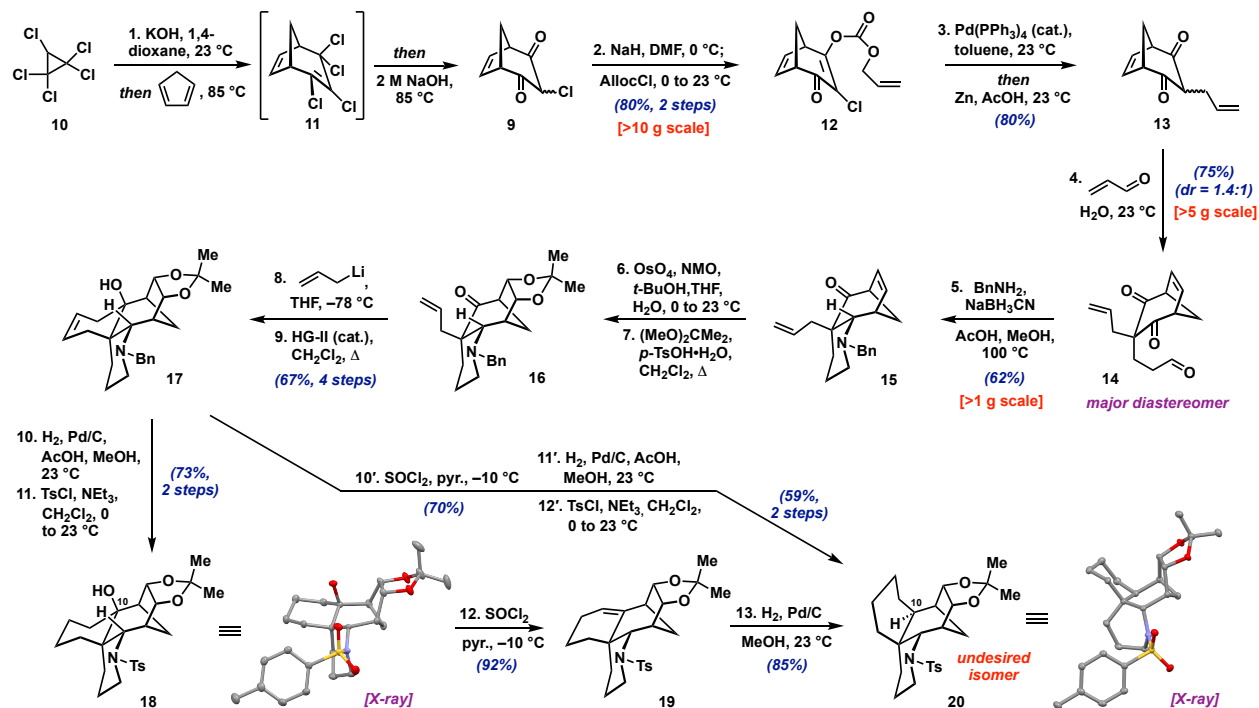
**Scheme S2.** Weinreb's completion of (±)-myrioneurinol (**2**).<sup>1</sup>



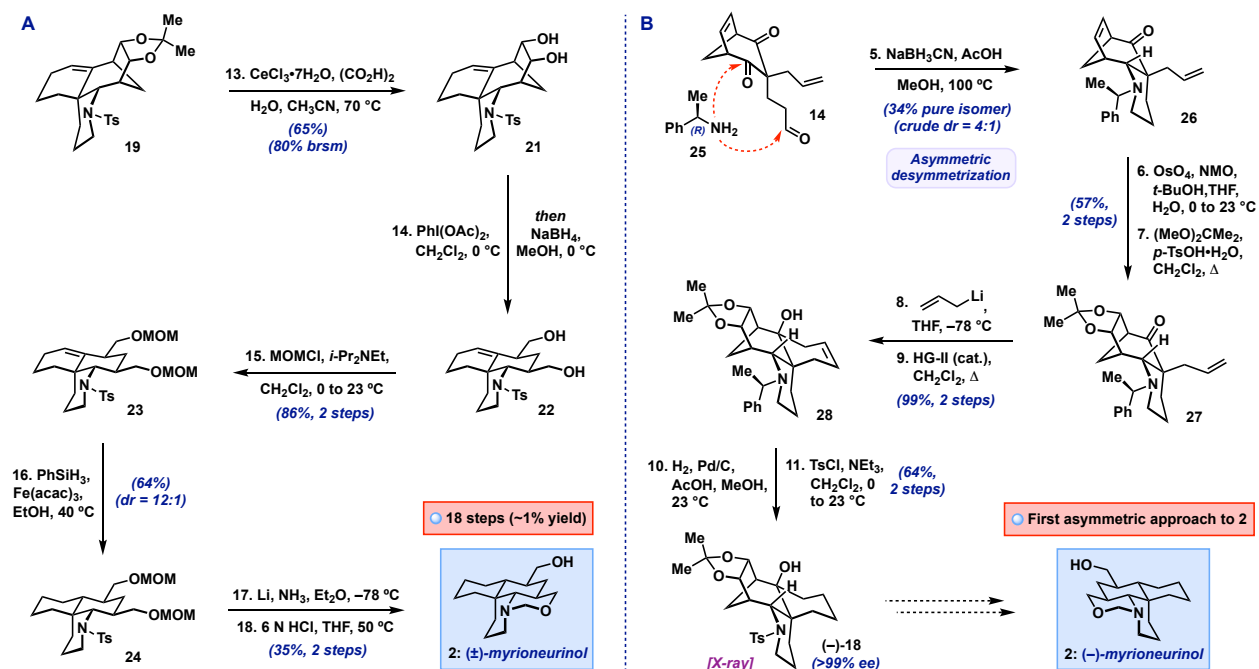
**Scheme S3.** Ma's synthesis of (±)-myrioneurinol (**2**).<sup>2</sup>



**Scheme S4.** Our synthesis of tetracyclic alkene **19**.

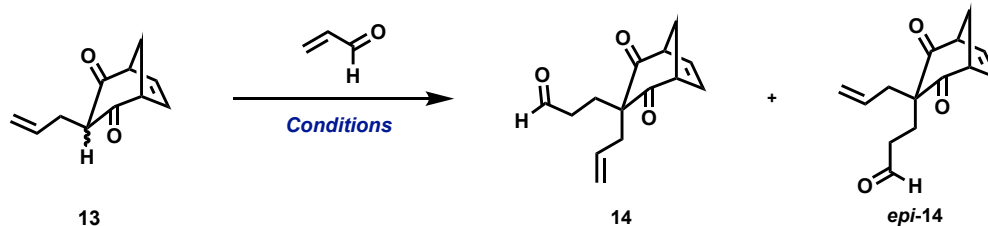


**Scheme S5.** (A) Completion of (±)-myrioneurinol (**2**). (B) Formal synthesis of (–)-*ent*-myrioneurinol (**2**) via preparation of enantioenriched (–)-**18**.



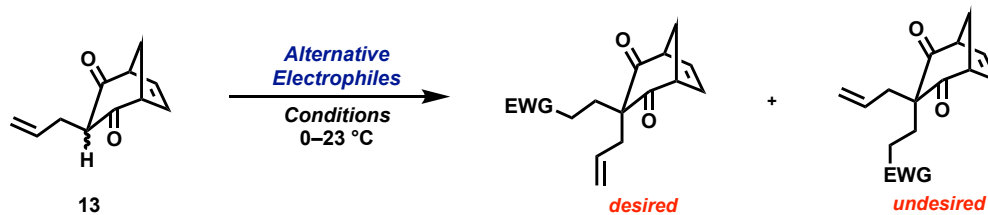
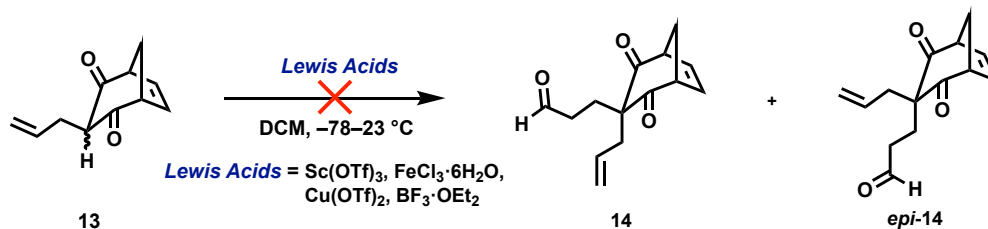
### 3. Alternate Approaches to Reductive Amination Precursor

(i) Attempts to improve diastereoselectivity in Michael addition of **13**:



Entry	Solvent	Base	dr (14: <i>epi</i> -14)	Entry	Solvent	Base <sup>c</sup>	dr (14: <i>epi</i> -14)
1	H <sub>2</sub> O	–	1.4:1.0	12	H <sub>2</sub> O/dioxane (9:1)	–	1.3:1.0 <sup>b</sup>
2	DCM	–	NR <sup>a</sup>	13	H <sub>2</sub> O/CH <sub>3</sub> CN (9:1)	–	1.3:1.0 <sup>b</sup>
3	THF	–	NR <sup>a</sup>	14	H <sub>2</sub> O/MeNO <sub>2</sub> (9:1)	–	1.4:1.0 <sup>b</sup>
4	CH <sub>3</sub> CN	–	NR <sup>a</sup>	15	H <sub>2</sub> O/MeNO <sub>2</sub> (1:1)	–	1.4:1.0 <sup>b</sup>
5	PhMe	–	NR <sup>a</sup>	16 <sup>d</sup>	<i>t</i> -BuOH:THF (1:5)	KOtBu	0.7:1.0
6	DMF	–	1.3:1.0	17 <sup>d</sup>	THF	KHMDS	0.8:1.0
7	Ether	–	NR <sup>a</sup>	18 <sup>d</sup>	THF	LiHMDS	0.8:1.0
8	IPA	–	1.2:1.0	19	DMF	NEt <sub>3</sub>	1.0:1.0
9	Neat	–	NR <sup>a</sup>	20	DMF	DBU	1.0:1.0
10	H <sub>2</sub> O/DMF (9:1)	–	1.3:1.0	21	DMF	Cs <sub>2</sub> CO <sub>3</sub>	1.0:1.0
11	H <sub>2</sub> O/DMF (1:1)	–	1.1:1.0	22 <sup>e</sup>	DMF	–	0.8:1.0

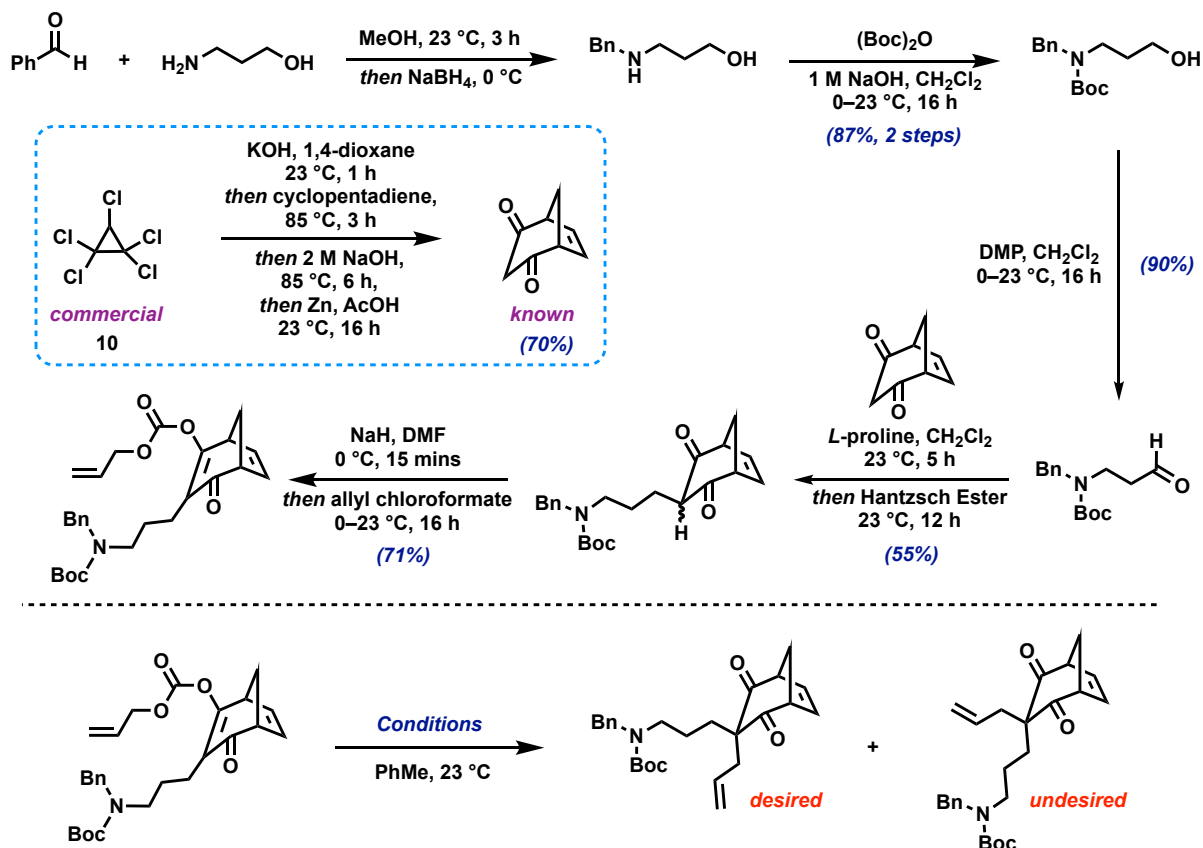
<sup>a</sup>NR = No reaction; <sup>b</sup>Byproduct formation; <sup>c</sup>Typically 0.1 equiv; <sup>d</sup>–78 to 0 °C; <sup>e</sup>–50 °C



Entry	Solvent	Electrophile	Base <sup>c</sup>	Result	Entry	Solvent	Electrophile	Base <sup>c</sup>	Result (des:undes)
1	H <sub>2</sub> O	$\text{CH}_2=\text{CHCN}$	–	NR <sup>a</sup>	5	DMF	$\text{CH}_2=\text{CHN}(\text{S}^+\text{O}^-t\text{Bu})$	Cs <sub>2</sub> CO <sub>3</sub>	1.3:1.0
2	THF	$\text{CH}_2=\text{CHCN}$	NEt <sub>3</sub>	NR <sup>a</sup>	6	DMF	$\text{CH}_2=\text{CHN}(\text{H})(\text{Ts})$	Cs <sub>2</sub> CO <sub>3</sub>	CM <sup>b</sup>
3	H <sub>2</sub> O	$\text{CH}_2=\text{CHCO}_2\text{Me}$	–	NR <sup>a</sup>					
4	THF	$\text{CH}_2=\text{CHCO}_2\text{Me}$	NEt <sub>3</sub>	NR <sup>a</sup>					

<sup>a</sup>NR = No reaction; <sup>b</sup>CM = Complex mixture; <sup>c</sup>Typically 0.1 equiv.

(ii) Alternate Tsuji–Trost route to reductive amination precursor:

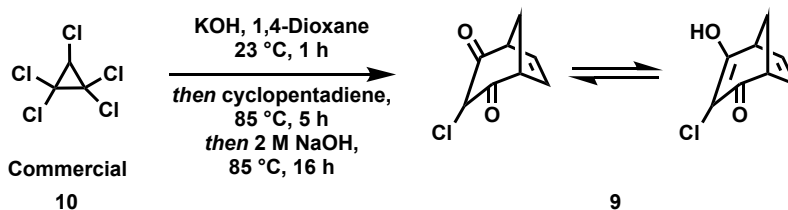


Entry	Catalyst	Ligand	dr (des:undes)
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	1.5:1.0
2	Pd <sub>2</sub> (dba) <sub>3</sub>	SPhos	1.5:1.0
3	Pd <sub>2</sub> (dba) <sub>3</sub>	DPEPhos	1.4:1.0
4	Pd <sub>2</sub> (dba) <sub>3</sub>	PCy <sub>3</sub>	NR <sup>a</sup>
5	Pd <sub>2</sub> (dba) <sub>3</sub>	P( <i>o</i> -tol) <sub>3</sub>	1.1:1.0
6	Pd <sub>2</sub> (dba) <sub>3</sub>	P(OPh) <sub>3</sub>	1.2:1.0
7	Pd <sub>2</sub> (dba) <sub>3</sub>	P(2-furyl) <sub>3</sub>	1.5:1.0
8	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	1.4:1.0
9	Pd <sub>2</sub> (dba) <sub>3</sub>	P(C <sub>6</sub> H <sub>3</sub> (CF <sub>3</sub> )) <sub>3</sub>	CM <sup>b</sup>
10	Pd <sub>2</sub> (dba) <sub>3</sub>	( <i>R,R</i> )-Naphthyl-Trost	1.0:1.6
11	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	NR <sup>a</sup>
12	[Pd(allyl)Cl] <sub>2</sub>	PPh <sub>3</sub>	NR <sup>a</sup>
13	[Ir(COD)Cl] <sub>2</sub>	BINOL phosphoramidite	1.1:1.0
14	[Ir(COD)Cl] <sub>2</sub>	P(OPh) <sub>3</sub>	CM <sup>b,c</sup>

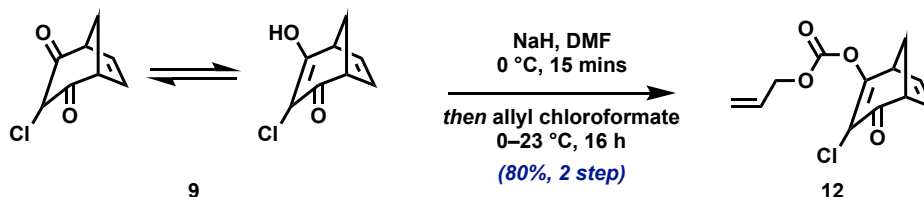
<sup>a</sup>NR = No Reaction; <sup>b</sup>CM = Complex Mixture; <sup>c</sup>Byproduct Formation



#### 4. Experimental Procedures



**Chlorodiketone 9.** Following a literature procedure,<sup>3</sup> powdered KOH (377 mg, 6.7 mmol, 1.4 equiv) was added to a solution of pentachlorocyclopropane (**10**, 1.21 g, 4.8 mmol, 1.0 equiv; either commercial technical grade or freshly prepared and distilled) in 1,4-dioxane (5 mL) under argon and the mixture left to stir at room temperature for 1 h. Freshly distilled cyclopentadiene (887  $\mu$ L, 22.4 mmol, 4.7 equiv) was added dropwise, the reaction vessel was capped and heated to 85 °C for 5 h. Aqueous 2 M NaOH solution (28 mL) was then added and the reaction left to heat at 85 °C overnight (~16 h). The reaction was then cooled, acidified to pH 1–2 with 6 M HCl (~8 mL), transferred to a separatory funnel, diluting with water (10 mL) and EtOAc (40 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2  $\times$  40 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude **9**, which exists as a mixture of enol and keto forms, matches literature NMR data and is taken forward without further purification.



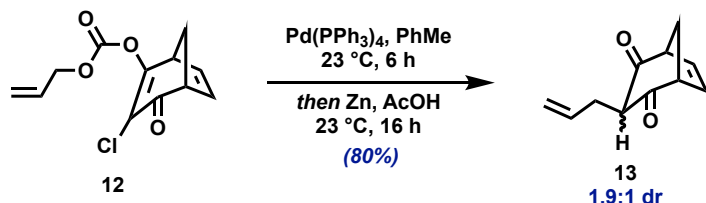
**O-Acylation product 12.** A crude mixture of enol and keto forms of **9** (~4.8 mmol, 1.0 equiv) was dissolved in dry DMF (15 mL) then cooled to 0 °C. Sodium hydride (60%, 240 mg, 6.0 mmol, 1.25 equiv) was added directly to the solution. After 15 min, allyl chloroformate (638  $\mu$ L, 6.0 mmol, 1.25 equiv) added dropwise and the reaction was allowed to warm to room temperature overnight (~16 h). Upon completion, determined by TLC, the reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (~15 mL) and transferred to a separatory funnel, diluting with water (30 mL) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The layers were separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  30 mL). The combined organic layers were then combined and washed with water (3  $\times$  30 mL) to remove any excess DMF. The organic layer was then dried (NaSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 5–35%) to give *O*-Alloc enol product **12** (968 mg, 80% over 2 steps) as a yellow oil. [Note: When this reaction sequence was conducted on 26.3 g of pentachlorocyclopropane **10**, 71% of **12** was obtained over the 2 steps. Alloc protection can also be performed using *i*-Pr<sub>2</sub>NEt (1.25 equiv) in CH<sub>2</sub>Cl<sub>2</sub> instead of NaH in DMF in comparable yields]

**Physical properties:** Yellow oil;

**R<sub>f</sub>** = 0.38 (silica gel, 30% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>12</sub>H<sub>11</sub>ClO<sub>4</sub> [M + H]<sup>+</sup> 255.0419; Found 255.0413;

**$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.79 (dd,  $J = 5.2, 3.0$  Hz, 1H), 6.23 (dd,  $J = 5.2, 3.3$  Hz, 1H), 5.94 (ddt,  $J = 17.2, 10.5, 5.9$  Hz, 1H), 5.41 (dq,  $J = 17.2, 1.4$  Hz, 1H), 5.33 (dq,  $J = 10.4, 1.2$  Hz, 1H), 4.72 (dt,  $J = 5.9, 1.3$  Hz, 2H), 3.59–3.56 (m, 1H), 3.54–3.51 (m, 1H), 2.66 (d,  $J = 10.4$  Hz, 1H), 2.49 (dt,  $J = 10.4, 4.6$  Hz, 1H);  
 **$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  191.3, 168.5, 150.3, 141.9, 132.7, 130.4, 120.4, 113.9, 70.2, 56.2, 50.4, 47.5.



**Allyl Diketone 13.** A solution of **12** (1.077 g, 4.240 mmol, 1.0 equiv) in dry toluene (20 mL) was degassed for 30 min by argon sparge.  $\text{Pd(PPh}_3)_4$  (196 mg, 0.170 mmol, 4 mol%) was then added and the reaction stirred at room temperature under argon for 6 h, at which point TLC showed consumption of starting material. The intermediate chloro-diketone was treated with zinc powder (1.39 g, 21.3 mmol, 5.0 equiv) and acetic acid (7 mL) and the reaction was left to stir at room temperature overnight (16 h). The reaction mixture was filtered through a Celite pad and the filtrate was then acidified to pH 1–2 with 6 M HCl and extracted with EtOAc ( $3 \times 20$  mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–30%) to give allyl diketone **13** (597 mg, 80%) as a pale-yellow oil. [**Note:** When this reaction sequence was conducted in a stepwise fashion on 5.16 g of **12**, a similar yield (80%) of **13** was obtained over two steps. This involved filtering the crude  $\text{Pd(PPh}_3)_4$  reaction mixture through a silica plug (rinsing with 40% EtOAc/hexanes), concentration, redissolution in 1,4-dioxane, and subjection to Zn/AcOH reduction]

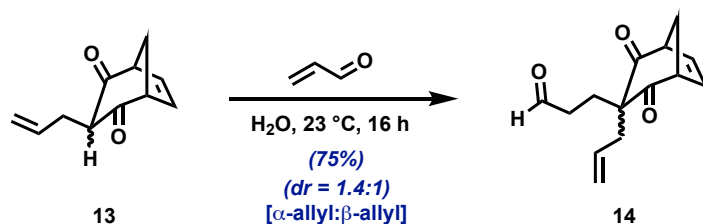
**Physical properties:** Pale yellow oil;

**$R_f$**  = 0.30 (silica gel, 30% EtOAc/hexanes);

**MS** (ESI): Calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_2$   $[\text{M} + \text{H}]^+$  177.0916; Found 177.0911;

**$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.29–6.25 (m,  $2\text{H}_{\text{minor}}$ ), 6.03 (d,  $J = 2.0$  Hz,  $2\text{H}_{\text{major}}$ ), 5.61 (ddt,  $J = 17.3, 10.1, 7.2$  Hz,  $1\text{H}_{\text{minor}}$ ), 5.45 (ddt,  $J = 17.1, 10.1, 7.1$  Hz,  $1\text{H}_{\text{major}}$ ), 5.03 (dq,  $J = 17.1, 1.5$  Hz,  $1\text{H}_{\text{minor}}$ ), 4.99–4.94 (m,  $1\text{H}_{\text{major}} + 1\text{H}_{\text{minor}}$ ), 4.89 (ddt,  $J = 10.1, 2.1, 1.1$  Hz,  $1\text{H}_{\text{major}}$ ), 3.65 (t,  $J = 5.1$  Hz,  $1\text{H}_{\text{minor}}$ ), 3.47 (dd,  $J = 5.0, 2.1$  Hz,  $2\text{H}_{\text{major}}$ ), 3.37 (d,  $J = 5.0$  Hz,  $2\text{H}_{\text{minor}}$ ), 3.31 (td,  $J = 4.8, 1.2$  Hz,  $1\text{H}_{\text{major}}$ ), 2.62–2.58 (m,  $3\text{H}_{\text{major}}$ ), 2.56 (d,  $J = 12.2$  Hz,  $1\text{H}_{\text{major}}$ ), 2.55–2.51 (m,  $1\text{H}_{\text{minor}}$ ), 2.37 (dtd,  $J = 12.2, 4.9, 1.3$  Hz,  $2\text{H}_{\text{minor}}$ ), 2.26 (d,  $J = 12.4$  Hz,  $1\text{H}_{\text{minor}}$ ); [**Note:** where possible, individual signals for the major and minor diastereomers are indicated]

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  203.8 (minor), 201.4 (major), 136.2 (major), 134.3 (minor), 133.8 (major), 133.7 (minor), 118.3 (minor), 117.7 (major), 59.6 (major), 57.3 (minor), 55.6 (minor), 55.2 (major), 36.9 (minor), 35.6 (major), 29.6 (minor), 28.8 (major). [**Note:** where possible, individual signals for the major and minor diastereomers are indicated]



**Aldehyde 14.** A suspension of allyl diketone **13** (4.35 g, 24.7 mmol, 1.0 equiv) in deionized water (200 mL) was sonicated (~20 s) and then degassed for 20 min by argon sparge. Acrolein (2.5 mL, 37.4 mmol, 1.51 equiv) was added dropwise to the sparged solution, then the reaction flask was sealed and allowed to stir vigorously at room temperature overnight (16 h). After transferring to a separatory funnel, the aqueous reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 150 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography ( $\text{NEt}_3$ -deactivated silica gel, EtOAc/hexanes, 0–30%) to give aldehyde **14** (4.27 g, 75%) as a mixture of diastereomers (dr = 1.4:1) as a pale yellow oil. [**Note:** Partial separation of the diastereomers of **14** could be achieved by careful silica gel chromatography to yield mixtures enriched (dr = 5–8:1) in the desired, faster-eluting isomer]

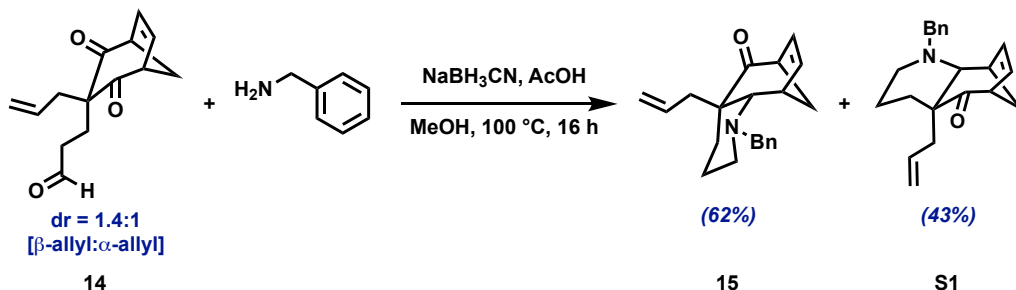
**Physical properties:** Pale yellow oil;

$R_f$  = 0.27 (silica gel, 20% EtOAc/hexanes);

**MS** (ESI): Calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_3$   $[\text{M} + \text{H}]^+$  233.1172; Found 233.1176;

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.67 (s, 1 $\text{H}_{\text{major}}$ ), 9.61 (s, 1 $\text{H}_{\text{minor}}$ ), 6.25 (d,  $J$  = 2.0 Hz, 2 $\text{H}_{\text{minor}}$ ), 6.11 (d,  $J$  = 2.0 Hz, 2 $\text{H}_{\text{major}}$ ), 5.62 (ddt,  $J$  = 17.5, 10.2, 7.5 Hz, 1 $\text{H}_{\text{minor}}$ ), 5.32 (ddt,  $J$  = 17.6, 10.4, 7.4 Hz, 1 $\text{H}_{\text{major}}$ ), 5.15–5.02 (m, 2 $\text{H}_{\text{minor}}$ ), 4.97–4.87 (m, 2 $\text{H}_{\text{major}}$ ), 3.43 (td,  $J$  = 5.0, 1.9 Hz, 2 $\text{H}_{\text{major}}$  + 2 $\text{H}_{\text{minor}}$ ), 2.77 (d,  $J$  = 12.4 Hz, 1 $\text{H}_{\text{major}}$ ), 2.69 (d,  $J$  = 12.4 Hz, 1 $\text{H}_{\text{minor}}$ ), 2.55 (t,  $J$  = 7.1 Hz, 2 $\text{H}_{\text{major}}$ ), 2.52–2.38 (m, 3 $\text{H}_{\text{major}}$  + 3 $\text{H}_{\text{minor}}$ ), 2.24–2.16 (m, 2 $\text{H}_{\text{minor}}$ ), 2.11–2.02 (m, 2 $\text{H}_{\text{major}}$  + 2 $\text{H}_{\text{minor}}$ ); [**Note:** where possible, individual signals for the major and minor diastereomers are indicated]

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  205.2 (major), 204.6 (minor), 201.0 (major), 200.8 (minor), 135.4 (major), 134.6 (minor), 132.8 (minor), 132.3 (major), 120.0 (major), 118.7 (minor), 64.3 (major), 63.6 (minor), 55.4 (minor), 55.3 (major), 42.5 (major), 40.5 (minor), 39.9 (major), 39.0 (minor), 35.5 (minor), 34.9 (major), 30.1 (minor), 30.1 (major). [**Note:** where possible, individual signals for the major and minor diastereomers are indicated]



**Double reductive amination products 15 and S1.** To a microwave vial containing a solution of aldehyde diastereomers **14** (1.108 g, 4.8 mmol, 1.0 equiv) in dry MeOH (10 mL) under argon was added benzylamine (612  $\mu\text{L}$ , 5.6 mmol, 1.2 equiv), glacial acetic acid (267  $\mu\text{L}$ , 4.7 mmol, 1.0

equiv, dropwise), and NaBH<sub>3</sub>CN (881 mg, 14.0 mmol, 3.0 equiv). The reaction vial was then sealed and heated at 100 °C overnight (16 h). After cooling to room temperature, the reaction was quenched with NaHCO<sub>3</sub> (8 mL), diluted with EtOAc (20 mL) and H<sub>2</sub>O (10 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–20%) to give desired double reductive amination product **15** (533 mg, 62% based on β-allyl **14**) and undesired diastereomer **S1** (262 mg, 43% based on α-allyl **14**) both as colorless oils.

**Physical properties for desired 15:** Colorless oil;

**R<sub>f</sub>** = 0.29 (silica gel, 20% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>21</sub>H<sub>25</sub>NO [M + H]<sup>+</sup> 308.2011; Found 308.2009;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.34–7.28 (m, 4H), 7.25–7.21 (m, 1H), 6.16 (dd, *J* = 5.4, 3.1 Hz, 1H), 5.75 (dd, *J* = 5.4, 3.2 Hz, 1H), 5.50–5.37 (m, 1H), 4.91–4.83 (m, 2H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.58 (d, *J* = 13.7 Hz, 1H), 3.15 (t, *J* = 3.7 Hz, 1H), 3.10 (dd, *J* = 5.1, 3.2 Hz, 1H), 2.75–2.63 (m, 3H), 2.53–2.42 (m, 3H), 2.12–1.99 (m, 2H), 1.79–1.65 (m, 1H), 1.63–1.57 (m, 1H), 1.44 (dt, *J* = 14.0, 4.7 Hz, 1H);

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 207.0, 141.3, 139.7, 135.6, 129.7, 128.7, 128.4, 127.1, 117.6, 59.4, 58.7, 54.0, 52.8, 45.5, 41.1, 37.5, 36.0, 33.5, 22.0.

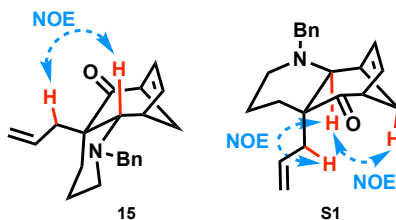
**Physical properties for undesired S1:** Colorless oil;

**R<sub>f</sub>** = 0.31 (silica gel, 20% EtOAc/hexanes);

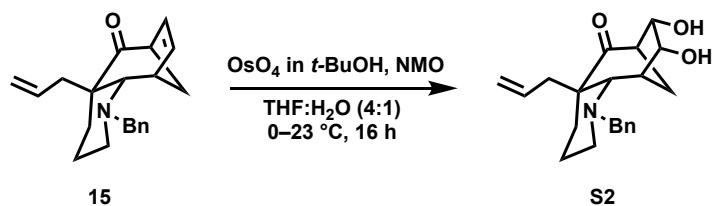
**MS** (ESI): Calcd for C<sub>21</sub>H<sub>25</sub>NO [M + H]<sup>+</sup> 308.2008; Found 308.2008;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.38–7.28 (m, 4H), 7.26–7.20 (m, 1H), 6.35 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.01 (dd, *J* = 5.6, 3.1 Hz, 1H), 5.64 (dddd, *J* = 16.7, 10.5, 9.4, 5.3 Hz, 1H), 5.04–4.95 (m, 2H), 3.74 (AB q, *J* = 19.3, 13.7 Hz, 2H), 3.26 (d, *J* = 3.0 Hz, 1H), 3.18 (dt, *J* = 5.9, 2.9 Hz, 1H), 2.96 (dd, *J* = 4.6, 3.1 Hz, 1H), 2.69 (dd, *J* = 13.2, 9.4 Hz, 1H), 2.51 (ddt, *J* = 13.2, 5.2, 1.5 Hz, 1H), 2.48–2.41 (m, 2H), 2.36 (ddd, *J* = 11.4, 5.8, 4.7 Hz, 1H), 2.26 (td, *J* = 13.4, 5.4 Hz, 1H), 1.78 (d, *J* = 11.3 Hz, 1H), 1.74–1.60 (m, 1H), 1.53–1.44 (m, 2H);

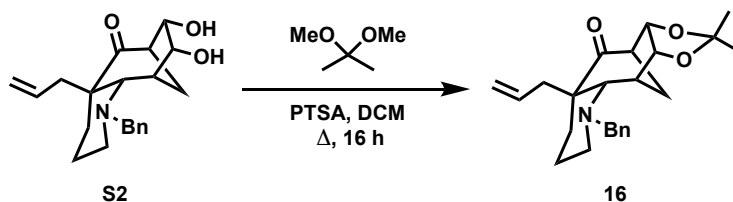
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 212.6, 140.6, 140.1, 136.0, 133.5, 128.5, 128.4, 127.1, 118.4, 60.9, 59.3, 55.5, 52.5, 45.9, 40.8, 40.4, 40.2, 35.4, 23.0.



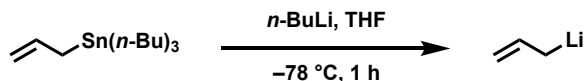
**Figure S1.** NOE studies to determine relative stereochemical assignments of **15** and **S1**.



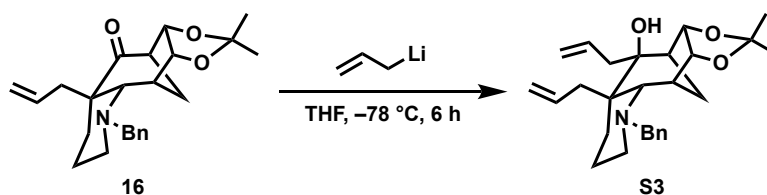
**Diol S2.** *N*-benzyl amine **15** (298 mg, 0.970 mmol, 1.0 equiv) was dissolved in THF (16 mL) and water (4 mL) and cooled to 0 °C under argon. NMO (119 mg, 1.016 mmol, 1.05 equiv) was added to the solution followed by dropwise addition of OsO<sub>4</sub> in *t*-BuOH (2.5 wt.%, 608 μL, 0.0485 mmol, 0.05 equiv). The reaction was allowed to warm to room temperature and stirred overnight (16 h). Upon completion, determined by TLC, the reaction mixture was quenched with saturated Na<sub>2</sub>SO<sub>3</sub> solution (10 mL), allowed to stir for 30 min and transferred to a separatory funnel, diluted with water (10 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product was used directly in the next reaction.



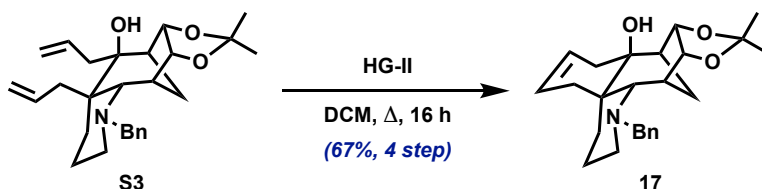
**Acetonide 16.** Crude diol **S2** (~0.970 mmol, 1.0 equiv) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under argon. 2,2-Dimethoxypropane (0.60 mL, 4.88 mmol, 5 equiv) and *p*-TsOH·H<sub>2</sub>O (221 mg, 1.164 mmol, 1.2 equiv) were added and the solution was heated at reflux overnight (16 h). Upon completion, determined by TLC, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and H<sub>2</sub>O (30 mL), transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product was used directly in the next reaction.



**Preparation of allyllithium.** Following a previously reported procedure,<sup>4</sup> in a flame-dried flask containing a magnetic stir bar, allyltributylstannane (3.2 mL, 10.32 mmol, 1.0 equiv) was dissolved in dry THF (24 mL, 0.33 M) then cooled to –78 °C. *n*-Butyllithium (2.5 M in hexanes, 4.13 mL, 10.32 mmol, 1.0 equiv) was added dropwise and the solution stirred for a further 1 h. The formed allyllithium solution (0.33 M) was used in the subsequent allylation.



**Diallyl product S3.** Crude acetone **16** (~0.970 mmol, 1.0 equiv) is dissolved in dry THF (30 mL) under argon and cooled to  $-78\text{ }^{\circ}\text{C}$ . Freshly prepared allyllithium solution (0.33 M, 29.4 mL, 9.70 mmol, 10.0 equiv) was added dropwise and the reaction mixture was allowed to stir for 6–8 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was acidified to pH 1–2 with 0.33 M HCl solution (10 mL), diluted with ether (20 mL) and  $\text{H}_2\text{O}$  (10 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with ether (15 mL). The combined ether layers are washed with additional 0.33 M HCl (15 mL). The combined acidic aqueous layers were then basified using aqueous  $\text{Na}_2\text{CO}_3$  solution until pH >10 and then extracted with EtOAc ( $3 \times 20\text{ mL}$ ). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude diallyl product **S3** was used directly in the next reaction.



**RCM product 17.** Crude diallyl product **S3** (~0.970 mmol, 1.0 equiv) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (40 mL) and sparged with argon for 20 minutes. Hoveyda–Grubbs II catalyst (30.0 mg, 0.048 mmol, 5 mol%) was added and the solution was refluxed overnight. Upon completion, determined by TLC, the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–20%) to give RCM product **17** (257 mg, 67%, 4 steps) as a colorless oil.

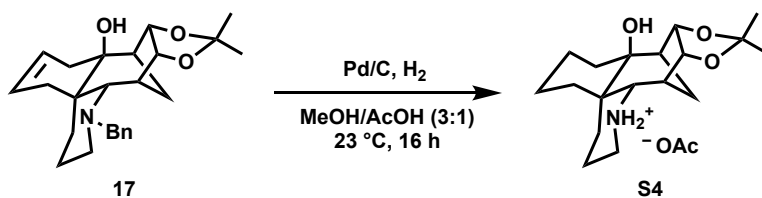
**Physical properties:** colorless oil/foam;

$R_f$  = 0.29 (silica gel, 20% EtOAc/hexanes);

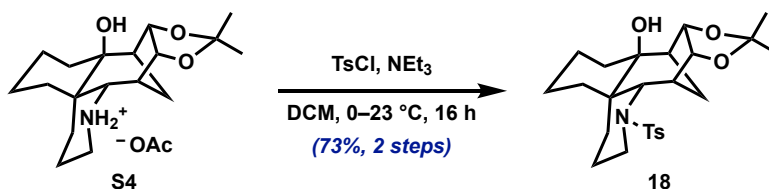
**MS** (ESI): Calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_3$   $[\text{M} + \text{H}]^+$  397.2612; Found 397.2558;

**$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (d,  $J$  = 6.8 Hz, 2H), 7.30 (t,  $J$  = 7.6 Hz, 2H), 7.25–7.20 (m, 1H), 5.80–5.74 (m, 1H), 5.64–5.58 (m, 1H), 5.17 (dd,  $J$  = 5.4, 1.6 Hz, 1H), 4.13 (dd,  $J$  = 5.4, 1.7 Hz, 1H), 3.66 (AB q,  $J$  = 35.0, 13.8 Hz, 2H), 2.71 (dd,  $J$  = 18.7, 4.9 Hz, 1H), 2.52–2.45 (m, 2H), 2.42–2.35 (m, 2H), 2.33 (br s, 1H), 2.26 (d,  $J$  = 13.0 Hz, 1H), 2.11 (br s, 1H), 2.02 (s, 1H), 1.96 (dd,  $J$  = 18.4, 4.5 Hz, 1H), 1.91 (ddd,  $J$  = 13.9, 6.2, 2.3 Hz, 1H), 1.87–1.77 (m, 3H), 1.56–1.48 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H);

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1, 129.4, 128.6, 128.3, 126.9, 126.1, 109.9, 86.7, 80.8, 72.0, 62.6, 59.1, 48.4, 44.9, 40.3, 39.0, 38.3, 35.3, 26.6, 26.5, 26.0, 24.5, 22.5.



**Hydrogenated product S4.** RCM product **17** (356 mg, 0.902 mmol, 1.0 equiv) was dissolved in MeOH/AcOH (3:1, 40 mL) and sparged with argon for 5 min. Palladium on carbon (10% w/w, 190 mg, 0.180 mmol Pd, 0.20 equiv) was added to the solution, which was then sparged with H<sub>2</sub> gas for 5 min and left under H<sub>2</sub> atmosphere (balloon) to stir overnight (16 h). Upon completion, the reaction is flushed briefly with argon to remove the remaining H<sub>2</sub> and the reaction mixture is filtered through a Celite pad and concentrated *in vacuo*; excess AcOH was removed by azeotrope with toluene (2 × 10 mL). The resulting crude product was used directly in the next reaction.



**N-Tosyl protected 18.** Crude ammonium salt **S4** (~0.902 mmol, 1.0 equiv) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and cooled to 0 °C. Triethylamine (0.75 mL, 5.4 mmol, 6.0 equiv) was added dropwise, stirred for 15 min, followed by addition of TsCl (344 mg, 1.804 mmol, 2.0 equiv). The reaction is allowed to warm to room temperature overnight (16 h). The reaction is quenched with saturated NaHCO<sub>3</sub> solution (20 mL), diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (20 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the combined organics dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–30%) to give *N*-tosyl protected **18** (305 mg, 73%, 2 steps) as a colorless oil, solid. X-ray quality crystals could be obtained by recrystallization from EtOAc/hexanes.

**Physical properties:** colorless solid;

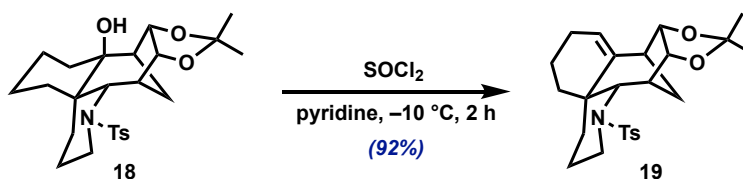
**R<sub>f</sub>** = 0.25 (silica gel, 40% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>25</sub>H<sub>35</sub>NO<sub>5</sub>S<sup>+</sup> [M + H]<sup>+</sup> 462.2309; Found 462.2319;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.46 (dd, *J* = 5.2, 1.8 Hz, 1H), 3.66 (s, 1H), 3.49 (dt, *J* = 12.8, 4.3 Hz, 1H), 2.96 (ddd, *J* = 12.4, 11.2, 3.2 Hz, 1H), 2.41 (s, 3H), 2.23 (d, *J* = 12.8 Hz, 1H), 2.03 (s, 1H), 1.96–1.85 (m, 1H), 1.84–1.71 (m, 5H), 1.71–1.59 (m, 2H), 1.59–1.49 (m, 3H), 1.48 (s, 1H), 1.44–1.32 (m, 3H), 1.37 (s, 3H), 1.31 (s, 3H);

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 142.9, 138.1, 129.8, 127.2, 110.1, 86.6, 80.4, 73.1, 58.0, 48.9, 47.4, 40.2, 39.8, 34.0, 28.4, 26.8, 26.0, 24.7, 24.6, 21.7, 21.6, 19.4, 18.6.





**Alkene 19.** Alcohol **18** (274 mg, 0.594 mmol, 1.0 equiv) was dissolved in dry pyridine (7.5 mL) under inert atmosphere and cooled to  $-10\text{ }^{\circ}\text{C}$ . Thionyl chloride (86  $\mu\text{L}$ , 1.188 mmol, 2 equiv) was added dropwise and the reaction stirred for 2 h at this temperature. Upon completion, determined by TLC, the reaction is quenched with 0.33 M HCl solution (5 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL) and  $\text{H}_2\text{O}$  (10 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was then extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 15\text{ mL}$ ). The combined organic extracts were then dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–30%) to give alkene **19** (243 mg, 92%) as a colorless oil.

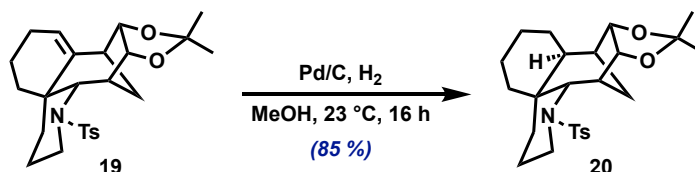
**Physical properties:** Colorless oil/foam;

$R_f = 0.27$  (silica gel, 15% EtOAc/hexanes);

**MS** (ESI): calculated for  $\text{C}_{25}\text{H}_{33}\text{NO}_4\text{S}$   $[\text{M} + \text{H}]^+$  444.2209; Found 444.2214;

**$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.3\text{ Hz}$ , 2H), 7.28 (d,  $J = 8.0\text{ Hz}$ , 2H), 5.59 (br t,  $J = 3.1\text{ Hz}$ , 1H), 4.46 (d,  $J = 5.3\text{ Hz}$ , 1H), 4.17 (d,  $J = 5.3\text{ Hz}$ , 1H), 3.62 (d,  $J = 13.4\text{ Hz}$ , 1H), 3.38 (s, 1H), 2.85 (td,  $J = 13.0, 2.8\text{ Hz}$ , 1H), 2.64 (s, 1H), 2.42 (s, 3H), 2.18 (d,  $J = 12.7\text{ Hz}$ , 1H), 2.09–1.94 (m, 4H), 1.85 (td,  $J = 14.6, 4.9\text{ Hz}$ , 1H), 1.72 (dt,  $J = 12.8, 3.9\text{ Hz}$ , 1H), 1.69–1.60 (m, 2H), 1.60–1.54 (m, 2H), 1.54–1.48 (m, 1H), 1.40 (s, 3H), 1.29 (s, 3H), 1.07–0.98 (m, 1H);

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 139.9, 138.4, 129.8, 127.2, 127.1, 110.6, 88.5, 85.8, 61.3, 46.5, 46.3, 40.9, 35.3, 33.1, 30.3, 25.8, 25.4, 25.0, 24.3, 21.7, 21.6, 18.0.



**Hydrogenation product 20.** Alkene **19** (10 mg, 0.0225 mmol, 1.0 equiv) was dissolved in MeOH (1.5 mL) and sparged with argon for 5 min. Palladium on carbon (10% w/w, 5.0 mg, 0.00470 mmol Pd, 0.21 equiv) was added to the solution, which was then sparged with  $\text{H}_2$  gas for 5 min and left under  $\text{H}_2$  atmosphere (balloon) to stir overnight (16 h). Upon completion, the reaction is flushed briefly with argon to remove the remaining  $\text{H}_2$  and the reaction mixture is filtered through a Celite pad and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, EtOAc/hexanes, 20%) to give reduced product **20** (8.5 mg, 85%) as a colorless solid. **20** can be crystallized from EtOAc/hexanes.

**Physical properties:** Colorless solid;

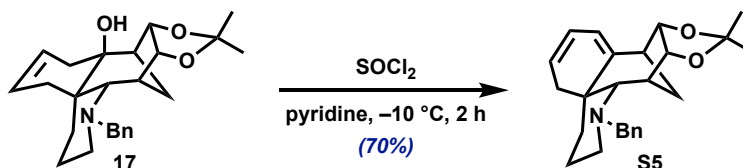
$R_f = 0.23$  (silica gel, 20% EtOAc/hexanes);

**MS** (ESI): Calcd for  $\text{C}_{25}\text{H}_{35}\text{NO}_4\text{S}$   $[\text{M} + \text{H}]^+$  446.2360 Found 446.2343;

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 8.3\text{ Hz}$ , 2H), 7.28 (d,  $J = 8.1\text{ Hz}$ , 2H), 4.90 (d,  $J = 5.3\text{ Hz}$ , 1H), 4.62 (dd,  $J = 5.3, 1.7\text{ Hz}$ , 1H), 3.88 (dd,  $J = 15.3, 9.6\text{ Hz}$ , 1H), 3.41 (s, 1H), 3.35 (ddd,  $J$



= 15.1, 10.2, 7.5 Hz, 1H), 2.48 (t,  $J$  = 2.3 Hz, 1H), 2.42 (s, 3H), 2.11 (t,  $J$  = 3.6 Hz, 1H), 1.96–1.80 (m, 3H), 1.64 (d,  $J$  = 12.1 Hz, 1H), 1.61–1.45 (m, 6H), 1.45–1.34 (m, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.00 (d,  $J$  = 9.8 Hz, 1H), 0.46 (ddd,  $J$  = 14.3, 10.5, 7.5 Hz, 1H);  
 $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 138.3, 129.8, 127.1, 109.7, 82.6, 81.2, 61.4, 49.5, 48.0, 39.8, 37.8, 35.1, 34.5, 29.5, 28.2, 27.8, 25.8, 24.1, 21.8, 21.7, 20.5, 18.3.



**Diene S5.** RCM product **17** (20.2 mg, 0.0438 mmol, 1.0 equiv) was dissolved in dry pyridine (2 mL) under argon and cooled to  $-10\text{ }^{\circ}\text{C}$ . Thionyl chloride (6  $\mu\text{L}$ , 0.0876 mmol, 2 equiv) was added and the reaction stirred for 2 h at this temperature. Upon completion, determined by TLC, the reaction is quenched with 0.33 M HCl solution (2 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (5 mL) and  $\text{H}_2\text{O}$  (5 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous solution was then extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, EtOAc/hexanes, 10%) to give diene **S5** (11.6 mg, 70%) as a colorless oil.

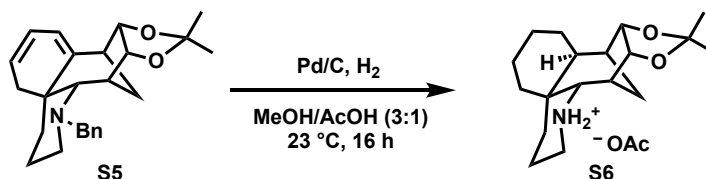
**Physical properties:** Colorless oil;

$R_f$  = 0.46 (silica gel, 10% EtOAc/hexanes);

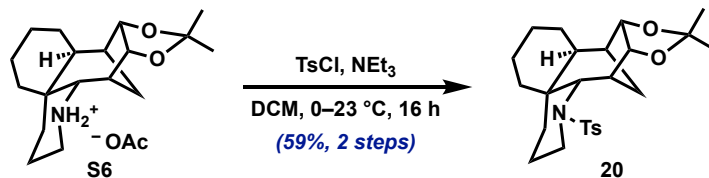
**MS** (ESI): Calcd for  $\text{C}_{25}\text{H}_{31}\text{NO}_2$   $[\text{M} + \text{H}]^+$  378.2428; Found 378.2435;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.34 (m, 2H), 7.34–7.28 (m, 2H), 7.25–7.20 (m, 1H), 5.86 (ddd,  $J$  = 9.4, 5.2, 3.3 Hz, 1H), 5.73 (d,  $J$  = 5.2 Hz, 1H), 5.69–5.62 (m, 1H), 4.18 (dd,  $J$  = 5.4, 1.4 Hz, 1H), 4.07 (d,  $J$  = 5.4 Hz, 1H), 3.67 (app t,  $J$  = 14.6 Hz, 2H), 3.02 (dd,  $J$  = 17.8, 6.3 Hz, 1H), 2.71 (d,  $J$  = 3.8 Hz, 1H), 2.56 (dd,  $J$  = 4.1 Hz, 1H), 2.53–2.39 (m, 2H), 2.22 (s, 1H), 2.12 (d,  $J$  = 12.4 Hz, 1H), 2.09–2.01 (m, 1H), 1.92–1.83 (m, 2H), 1.77–1.61 (m, 1H), 1.51–1.44 (m, 1H), 1.46 (s, 3H), 1.44–1.36 (m, 1H), 1.25 (s, 3H);

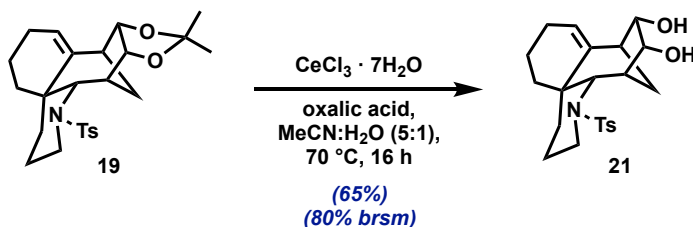
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.7, 139.8, 128.6, 128.3, 127.0, 125.1, 124.3, 120.8, 110.2, 87.4, 86.6, 67.0, 58.9, 47.7, 46.2, 37.6, 36.0, 35.9, 25.9, 25.0, 24.4, 24.2, 22.0.



**Hydrogenated product S6.** Diene product **S5** (9.7 mg, 0.0257 mmol, 1.0 equiv.) was dissolved in MeOH/AcOH (3:1, 6 mL) and sparged with argon for 5 min. Palladium on carbon (10% w/w, 2.7 mg, 0.0253 mmol Pd, 0.1 equiv) was added directly to the solution and then sparged with  $\text{H}_2$  gas for 5 min and left under  $\text{H}_2$  atmosphere (balloon) to stir overnight. Upon completion, the reaction is flushed briefly with argon to remove the remaining  $\text{H}_2$  and the reaction mixture is filtered through a Celite pad and concentrated *in vacuo*; excess AcOH was removed by azeotrope with toluene ( $2 \times 2$  mL). The resulting crude product was used directly in the next reaction.



***N*-Tosyl protected 20.** Crude ammonium salt **S6** (~0.0257 mmol, 1.0 equiv) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (1.2 mL) and cooled to 0 °C. Triethylamine (14  $\mu\text{L}$ , 0.103 mmol, 4.0 equiv) was added dropwise, stirred for 15 min, followed by addition of TsCl (10 mg, 0.0514 mmol, 2.0 equiv). The reaction is allowed to warm to room temperature overnight (16 h). Upon completion, the reaction is quenched with saturated  $\text{NaHCO}_3$  solution (1.5 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (4 mL) and  $\text{H}_2\text{O}$  (4 mL) and transferred to a separatory funnel. The aqueous layer was then extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  5 mL), and the combined organics dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, EtOAc/hexanes, 20%) to give *N*-tosyl protected **20** (6.7 mg, 59% yield, 2 steps) as a colorless solid. NMR data matched those obtained previously.



**Diol 21.** Acetonide **19** (233 mg, 0.526 mmol, 1.0 equiv) was dissolved in MeCN (20 mL) and  $\text{H}_2\text{O}$  (4 mL) under argon. Crushed  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (391 mg, 1.05 mmol, 2.0 equiv) and oxalic acid (189 mg, 2.10 mmol, 4.0 equiv) were added to solution. The reaction mixture was then capped, heated to 70 °C and stirred for 16 h. The reaction is quenched with saturated aqueous  $\text{NaHCO}_3$  solution (10 mL), diluted with EtOAc (20 mL) and  $\text{H}_2\text{O}$  (10 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (2  $\times$  25 mL). The combined organic extracts were then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–60%) to give diol **21** (138 mg, 65%, 80% brsm) as a colorless oil, along with recovered starting material (42 mg, 18%).

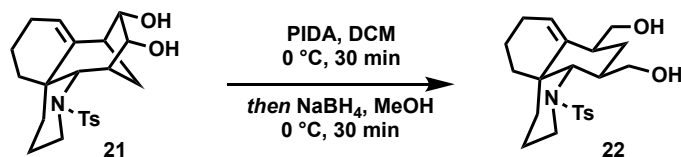
**Physical properties:** Colorless oil;

$R_f$  = 0.28 (silica gel, 60% EtOAc/hexanes);

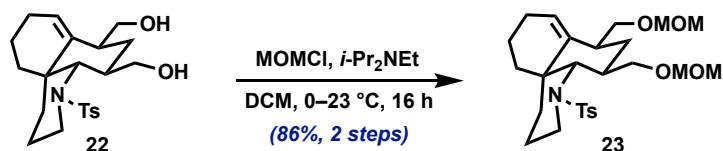
**MS** (ESI): for  $\text{C}_{22}\text{H}_{29}\text{NO}_4\text{S}$   $[\text{M} + \text{H}]^+$  404.1890; Found 404.1888;

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.3 Hz, 2H), 7.30 (d,  $J$  = 8.0 Hz, 2H), 5.60 (ddd,  $J$  = 4.4, 3.2, 1.3 Hz, 1H), 4.07 (d,  $J$  = 5.8 Hz, 1H), 3.83 (br s, 1H), 3.70 (d,  $J$  = 14.4 Hz, 1H), 3.35 (s, 1H), 2.95–2.84 (m, 2H), 2.64 (s, 1H), 2.52 (s, 1H), 2.42 (s, 3H), 2.13 (d,  $J$  = 12.7 Hz, 1H), 2.09–1.92 (m, 3H), 1.89 (br s, 1H), 1.85–1.74 (m, 1H), 1.70 (dt,  $J$  = 12.9, 4.2 Hz, 1H), 1.66–1.47 (m, 5H), 1.05–0.92 (m, 1H);

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.3, 141.1, 138.4, 129.8, 127.2, 126.2, 80.2, 62.8, 49.8, 49.7, 41.0, 34.6, 33.2, 30.3, 25.8, 24.9, 21.69, 21.66, 18.0. [**Note:** 1 carbon signal missing due to overlap]



**Cleaved diol 22.** Bridged diol **21** (56.4 mg, 0.140 mmol, 1.0 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to 0 °C. (Diacetoxyiodo)benzene (PIDA, 54 mg, 0.168 mmol, 1.2 equiv) was added to the solution. Upon complete consumption of starting material (monitored by TLC), the reaction was diluted with MeOH (5 mL) and NaBH<sub>4</sub> (26 mg, 0.700 mmol, 5.0 equiv) was added at 0 °C. Upon completion (TLC), the reaction mixture is quenched with H<sub>2</sub>O (10 mL), diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL). The combined organic extracts were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product was used directly in the next reaction.



**Bis-MOM ether 23.** Crude diol **22** (~0.140 mmol, 1.0 equiv) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under inert atmosphere and cooled to 0 °C. Diisopropylethylamine (487 μL, 2.796 mmol, 20.0 equiv) was added dropwise, stirred for 2 min, and then MOMCl (127 μL, 1.678 mmol, 12.0 equiv) was added dropwise to the solution. Upon completion by TLC (typically 16 h), the reaction mixture is quenched with H<sub>2</sub>O (8 mL), diluted with CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 8 mL). The organic extracts were then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–30%) to give bis-MOM ether product **23** (59 mg, 86%, 2 steps).

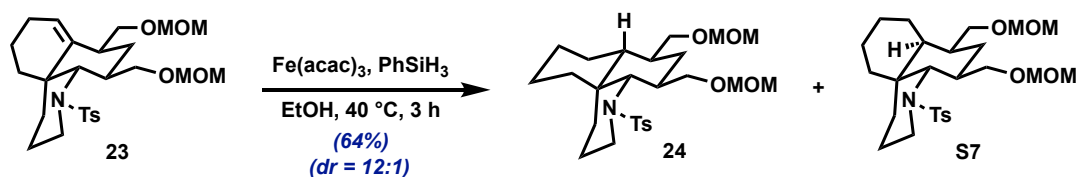
**Physical properties:** Colorless oil;

**R<sub>f</sub>** = 0.39 (silica gel, 60% EtOAc/hexanes);

**MS** (ESI): calcd for C<sub>26</sub>H<sub>39</sub>NO<sub>6</sub>S [M + H]<sup>+</sup> 494.2571; Found 494.2557;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.40 (s, 1H), 4.62 (AB q, *J* = 9.4, 6.6 Hz, 2H), 4.45 (AB q, *J* = 15.2, 6.4 Hz, 2H), 3.75–3.58 (m, 3H), 3.44 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.41–3.29 (m, 1H), 3.34 (s, 3H), 3.27 (s, 3H), 3.15 (dd, *J* = 9.6, 7.8 Hz, 1H), 2.95 (td, *J* = 13.7, 3.3 Hz, 1H), 2.48–2.31 (m, 2H), 2.39 (s, 3H), 2.18 (dt, *J* = 12.7, 3.7 Hz, 1H), 2.04–1.93 (m, 2H), 1.90 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.86–1.76 (m, 1H), 1.76–1.59 (m, 1H), 1.55–1.46 (m, 1H), 1.46–1.31 (m, 4H), 0.94 (q, *J* = 12.6 Hz, 1H);

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 142.8, 141.8, 138.8, 129.5, 127.1, 121.0, 96.9, 96.7, 70.1, 69.9, 63.2, 55.4, 55.3, 39.8, 38.6, 37.2, 35.0, 33.6, 32.4, 27.8, 26.1, 21.6, 20.2, 18.3.



**Reduced bis-MOM ether 24.** Following a modified procedure,<sup>5</sup> alkene **23** (37.2 mg, 0.0755 mmol, 1.0 equiv) was dissolved in absolute EtOH (3 mL) under argon. Fe(acac)<sub>3</sub> (5 mg, 0.0151 mmol, 0.2 equiv) was added and the solution was sparged for 10 min with argon. PhSiH<sub>3</sub> (47  $\mu$ L, 0.378 mmol, 5.0 equiv) was then added dropwise, the solution sparged for additional 30 s, the reaction vessel sealed and heated at 40  $^\circ$ C. After 3 h, the reaction mixture is concentrated *in vacuo*. The resulting crude product, containing a mixture of diastereomers (dr = 12:1), was directly purified by pTLC (silica gel, 20% EtOAc/hexanes, for 4 runs) to give reduced diMOM ether product **24** (23.7 mg, 64%) as a colorless oil, with the major desired isomer matching previous literature data.

**Physical properties for 24 (desired diastereomer):** Colorless oil;

**R<sub>f</sub>** = 0.43 (silica gel, 60% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>26</sub>H<sub>41</sub>NO<sub>6</sub>S [M + H]<sup>+</sup> 496.2727; Found 496.2716;

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.68 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 2H), 4.58 (AB q, *J* = 11.4, 6.6 Hz, 2H), 4.44 (AB q, *J* = 24.3, 6.3 Hz, 2H), 3.65 (dd, *J* = 14.1, 5.2 Hz, 1H), 3.50–3.42 (m, 2H), 3.39 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.33 (s, 3H), 3.31–3.25 (m, 1H), 3.27 (s, 3H), 3.12 (t, *J* = 8.8 Hz, 1H), 2.94 (td, *J* = 13.5, 3.4 Hz, 1H), 2.40 (s, 3H), 2.37–2.28 (m, 1H), 2.12 (dt, *J* = 13.3, 4.1 Hz, 1H), 2.04 (d, *J* = 13.9 Hz, 1H), 1.71 (d, *J* = 13.9 Hz, 2H), 1.66–1.56 (m, 1H), 1.56–1.48 (m, 2H), 1.46–1.41 (m, 1H), 1.38 (d, *J* = 13.4 Hz, 1H), 1.38 (d, *J* = 13.4 Hz, 1H), 1.31–1.16 (m, 5H), 1.12 (td, *J* = 12.6, 3.7 Hz, 1H), 0.92 (td, *J* = 13.4, 3.9 Hz, 1H);

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  142.7, 138.9, 129.5, 127.1, 96.8, 96.7, 70.4, 70.2, 63.6, 55.34, 55.25, 47.6, 40.3, 37.4, 35.4, 34.3, 34.1, 33.8, 26.4, 23.3, 21.6, 20.9, 20.0, 19.8.

**Table S1:** Comparison of <sup>1</sup>H NMR shifts ( $\delta$ ) of Weinreb's<sup>1</sup> and our own **24** in CDCl<sub>3</sub>.

Weinreb* (300 MHz)	Smith (600 MHz)
7.73 (d, <i>J</i> = 8.3 Hz, 2H)	7.68 (d, <i>J</i> = 8.0, 2H)
7.28 (d, <i>J</i> = 6.9 Hz, 2H)	7.25 (d, <i>J</i> = 9.2 Hz, 2H)
4.60 (q, <i>J</i> = 6.6 Hz, 2H)	4.58 (AB q, <i>J</i> = 11.4, 6.6 Hz, 2H)
4.47 (q, <i>J</i> = 6.4 Hz, 2H)	4.44 (AB q, <i>J</i> = 24.3, 6.3 Hz, 2H)
3.69 (dd, <i>J</i> = 13.5, 3.6 Hz, 1H)	3.65 (dd, <i>J</i> = 14.1, 5.2 Hz, 1H)
3.38–3.53 (m, 3H)	3.50–3.42 (m, 2H)
	3.39 (dd, <i>J</i> = 9.6, 5.7 Hz, 1H)
3.37 (s, 3H)	3.33 (s, 3H)
3.30 (s, 3H)	3.31–3.25 (m, 1H)
	3.27 (s, 3H)
3.15 (t, <i>J</i> = 9.4 Hz, 1H)	3.12 (t, <i>J</i> = 8.8 Hz, 1H)
2.97 (td, <i>J</i> = 11.9, 3.5 Hz, 1H)	2.94 (td, <i>J</i> = 13.5, 3.4 Hz, 1H)
2.30–2.43 (m, 4H)	2.40 (s, 3H)
	2.37–2.28 (m, 1H)

2.05–2.18 (m, 2H)	2.12 (dt, $J = 13.3, 4.1$ Hz, 1H)
	2.04 (d, $J = 13.9$ Hz, 1H)
0.86–1.76 (m, 15H)	1.71 (d, $J = 13.9$ Hz, 2H)
	1.66–1.56 (m, 1H)
	1.56–1.48 (m, 2H)
	1.46–1.41 (m, 1H)
	1.38 (d, $J = 13.4$ Hz, 1H)
	1.31–1.16 (m, 5H)
	1.12 (td, $J = 12.6, 3.7$ Hz, 1H)
	0.92 (td, $J = 13.4, 3.9$ Hz, 1H)

\*Weinreb's  $^1\text{H}$  NMR data referenced to  $\text{CDCl}_3$  at  $\delta$  7.29.

**Table S2:** Comparison of  $^{13}\text{C}$  NMR shifts ( $\delta$ ) of Weinreb's<sup>1</sup> and our own **24** in  $\text{CDCl}_3$ .

<i>Weinreb*</i> (75 MHz)	<i>Smith</i> (151 MHz)
142.9	142.7
139.2	138.9
129.7	129.5
127.3	127.1
97.0	96.8
97.0	96.7
70.7	70.4
70.5	70.2
63.9	63.6
55.6	55.34
55.5	55.25
47.9	47.6
40.6	40.3
37.6	37.4
35.6	35.4
34.6	34.3
34.3	34.1
34.1	33.8
30.7 <sup>a</sup>	—
30.1 <sup>a</sup>	—
26.7	26.4
23.6	23.3
21.8	21.6
21.1	20.9
20.3	20.0
20.1	19.8

\*Weinreb's  $^{13}\text{C}$  NMR data referenced to  $\text{CDCl}_3$  at  $\delta$  77.46.

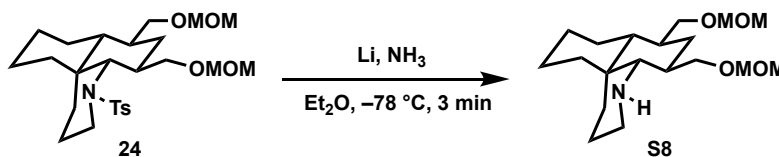
<sup>a</sup>Unknown impurity signal.

**Physical properties for S7 (undesired diastereomer):** Colorless oil;

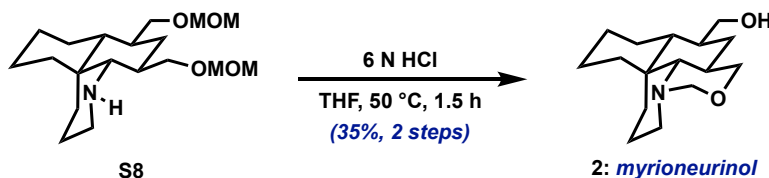
**R<sub>f</sub>** = 0.40 (silica gel, 60% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>26</sub>H<sub>41</sub>NO<sub>6</sub>S [M + Na]<sup>+</sup> 518.2547; Found 518.2549.

[**Note:** Attempted isolation of **S7** by standard purification techniques gave only small amounts of material of insufficient purity for NMR characterization]



**Tricyclic Amine S8.** Following a modified literature procedure,<sup>1</sup> anhydrous ammonia (ca. 5 mL) was condensed in a flame dried flask at  $-78\text{ }^{\circ}\text{C}$  and Li metal (ca. 20 mg, excess) was added until a blue color persisted. A solution of bis-MOM ether **24** (25 mg, 0.0503 mmol, 1.0 equiv) dissolved in dry Et<sub>2</sub>O (4 mL) was added dropwise and the reaction mixture was stirred for 3 min at  $-78\text{ }^{\circ}\text{C}$ , then quenched with NH<sub>4</sub>Cl(s) at that temperature. The reaction mixture was warmed to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub>, filtered through a Celite pad, and concentrated. The crude product was redissolved in Et<sub>2</sub>O (10 mL) then diluted with 0.33 M HCl aqueous solution (10 mL) to pH of 1–2 and the layers were transferred to a separatory funnel. The layers were separated and the organic layer was reextracted with 0.33 M HCl aqueous solution (10 mL). The combined aqueous extracts were basified with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution until the pH measured  $>10$ . The basified aqueous layer was extracted with CHCl<sub>3</sub>:*i*-PrOH (4:1, 8  $\times$  10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting crude product after the acid/base extraction matched that of previously reported purified amine **S8** and was carried forward without further purification.



**(±)-Myrioneurinol (2).** Following a known procedure,<sup>1</sup> to a stirred solution of crude amine **S8** (~0.0503 mmol, 1.0 equiv) in THF (6 mL) was added 6 N HCl<sub>(aq)</sub> (4 mL). The reaction mixture was heated at  $50\text{ }^{\circ}\text{C}$  for 1.5 h and then cooled to room temperature. The mixture was basified with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> until pH measured  $>10$ . The mixture was transferred to a separatory funnel and the layers were separated. The mixture was then extracted with CHCl<sub>3</sub>:*i*-PrOH (4:1, 4  $\times$  10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, 100% Et<sub>2</sub>O) to give (±)-myrioneurinol (**2**, 4.6 mg, 35%, 2 steps) as a colorless oil.

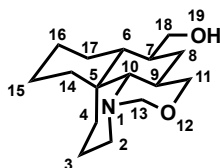
**Physical properties:** Colorless oil;

**R<sub>f</sub>** = 0.20 (silica gel, 100% Et<sub>2</sub>O);

**MS** (ESI): Calcd for C<sub>16</sub>H<sub>27</sub>NO<sub>2</sub> [M + H]<sup>+</sup> 266.2115; Found 266.2119;

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  4.46 (dd,  $J$  = 10.3, 1.1 Hz, 1H), 4.41 (d,  $J$  = 10.4 Hz, 1H), 3.90 (ddd,  $J$  = 10.8, 4.2, 1.1 Hz, 1H), 3.64 (dd,  $J$  = 10.6, 3.4 Hz, 1H), 3.49 (dd,  $J$  = 10.6, 6.0 Hz, 1H),

3.26 (ddd,  $J = 13.2, 11.5, 3.8$  Hz, 1H), 3.20 (t,  $J = 10.7$  Hz, 1H), 2.66 (dd,  $J = 11.8, 4.9$  Hz, 1H), 2.51–2.41 (m, 2H), 2.27 (d,  $J = 10.9$  Hz, 1H), 1.81–1.71 (m, 2H), 1.67 (dt,  $J = 13.8, 3.4$  Hz, 1H), 1.61–1.52 (m, 3H), 1.52–1.46 (m, 2H), 1.44–1.33 (m, 2H), 1.32–1.24 (m, 1H), 1.20 (qd,  $J = 12.1, 3.4$  Hz, 1H), 1.16–1.08 (m, 1H), 0.85 (tdd,  $J = 13.5, 4.5, 1.6$  Hz, 1H), 0.79 (q,  $J = 12.2$  Hz, 1H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  87.0, 73.7, 69.7, 65.6, 47.8, 45.2, 37.2, 36.4, 34.5, 31.2, 27.4, 26.8, 23.2, 20.64, 20.58, 19.9.

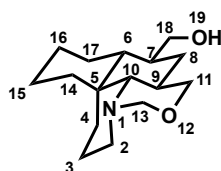


**2: myrioneurinol**

**Table S3:** Comparison of  $^1\text{H}$  NMR shifts ( $\delta$ ) of natural,<sup>6</sup> our and Weinreb's<sup>1</sup> synthetic myrioneurinol **2** in  $\text{CDCl}_3$ .

Position	Natural <b>2</b> (400 MHz)	Synthetic <b>2</b> (Smith) (600 MHz)	Synthetic <b>2</b> (Weinreb) (850 MHz)
2	3.22 (ddd, $J = 12.2, 11.0, 4.0$ Hz, 1H)	3.26 (ddd, $J = 13.2, 11.5, 3.8$ Hz, 1H)	3.28 (td, $J = 13.6, 4.3$ Hz, 1H)
2'	2.61 (ddd, $J = 11.0, 4.8, 0.5$ Hz, 1H)	2.66 (dd, $J = 11.8, 4.9$ Hz, 1H)	2.67 (dd, $J = 11.9, 5.1$ Hz, 1H)
3	1.72 (m, 1H)	1.81–1.71 (m, 1 of 2H)	1.80–1.74 (m, 2H)
3'	1.50 (m, 1H)	1.61–1.52 (m, 1 of 3H)	1.56 (dt, $J = 12.8, 3.4$ Hz, 1 of 2H)
4	1.63 (br d, $J = 13.3, 13.3, 3.0$ Hz, 1H)	1.67 (dt, $J = 13.8, 3.4$ Hz, 1H)	1.68 (br d, $J = 13.6$ Hz, 1H)
4'	1.32 (br d, $J = 13.3$ Hz, 1H)	1.44–1.33 (m, 1 of 2H)	1.45–1.35 (m, 2H)
5	—	—	—
6	1.11 (ddd, $J = 10.5, 10.5, 3.0$ Hz, 1H)	1.16–1.08 (m, 1H)	1.14 (td, $J = 11.1, 2.6$ Hz, 1H)
7	1.45 (dddd, $J = 12.1, 10.5, 6.0, 3.5, 3.5$ Hz, 1H)	1.52–1.46 (m, 1 of 2H)	1.53–1.48 (m, 2H)
8	1.50 (ddd, $J = 12.1, 4.0, 3.5$ Hz, 1H)	1.61–1.52 (m, 1 of 3H)	1.59 (dd, $J = 12.8, 2.6$ Hz, 1H)
8'	0.74 (ddd, $J = 12.1, 12.0, 12.0$ Hz, 1H)	0.79 (q, $J = 12.2$ Hz, 1H)	0.80 (q, $J = 11.9$ Hz, 1H)
9	2.40 (dddd, $J = 12.0, 11.0, 10.6, 4.2, 4.0$ Hz, 1H)	2.51–2.41 (m, 1 of 2H)	2.46 (qt, $J = 12.8, 4.3$ Hz, 1H)
10	2.22 (d, $J = 11.0$ Hz, 1H)	2.27 (d, $J = 10.9$ Hz, 1H),	2.28 (d, $J = 11.1$ Hz, 1H)
11	3.86 (ddd, $J = 10.8, 4.2, 1.0$ Hz, 1H)	3.90 (ddd, $J = 10.8, 4.2, 1.1$ Hz, 1H)	3.91 (dd, $J = 11.1, 4.3$ Hz, 1H)
11'	3.15 (dd, $J = 10.8, 10.6$ Hz, 1H)	3.20 (t, $J = 10.7$ Hz, 1H)	3.21 (t, $J = 11.1$ Hz, 1H)
13	4.41 (dd, $J = 10.3, 1.0$ Hz, 1H)	4.46 (dd, $J = 10.3, 1.1$ Hz, 1H)	4.47 (d, $J = 10.2$ Hz, 1H)
13'	4.36 (d, $J = 10.3$ Hz, 1H)	4.41 (d, $J = 10.4$ Hz, 1H)	4.42 (d, $J = 10.2$ Hz, 1H)
14	2.44 (br d, $J = 13.2$ Hz, 1H)	2.51–2.41 (m, 1 of 2H)	2.49 (br d, $J = 12.8$ Hz, 1H)

14'	0.80 (br d, $J = 13.2, 13.2, 4.1, 1.0$ Hz, 1H)	0.85 (tdd, $J = 13.5, 4.5, 1.6$ Hz, 1H)	0.87 (td, $J = 14.5, 3.4$ Hz, 1H)
15	1.45 (m)	1.52–1.46 (m, 1 of 2H)	1.53–1.48 (m, 2H)
15'	1.32 (m)	1.44–1.33 (m, 1 of 2H)	1.45–1.35 (m, 2H)
16	1.72 (m)	1.81–1.71 (m, 1 of 2H)	1.80–1.74 (m, 2H)
16'	1.20 (m)	1.32–1.24 (m, 1H)	1.30–1.24 (m, 2H)
17	1.55 (m)	1.61–1.52 (m, 1 of 3H)	1.56 (dt, $J = 12.8, 3.4$ Hz, 1 of 2H)
17'	1.12 (dddd, $J = 10.5, 10.4, 9.8, 3.5$ Hz, 1H)	1.20 (qd, $J = 12.1, 3.4$ Hz, 1H)	1.20 (qd, $J = 12.8, 3.4$ Hz, 1H)
18	3.59 (dd, $J = 10.6, 3.5$ Hz, 1H)	3.64 (dd, $J = 10.6, 3.4$ Hz, 1H)	3.64 (dd, $J = 11.1, 4.3$ Hz, 1H)
18'	3.42 (dd, $J = 10.6, 6.0$ Hz, 1H)	3.49 (dd, $J = 10.6, 6.0$ Hz, 1H)	3.48 (dd, $J = 10.2, 6.0$ Hz, 1H)



**2: myrioneurinol**

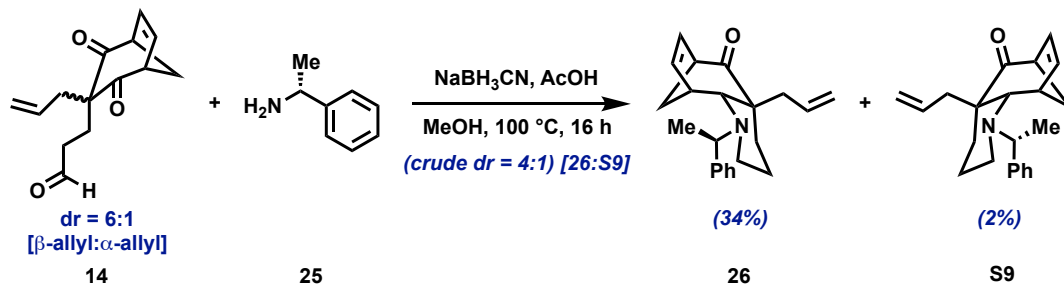
**Table S4:** Comparison of  $^{13}\text{C}$  NMR shifts ( $\delta$ ) of natural,<sup>6</sup> our and Weinreb's<sup>1</sup> synthetic myrioneurinol **2** in  $\text{CDCl}_3$ .

Position	Natural <sup>a</sup> <b>2</b> (75 MHz)	Synthetic <b>2</b> ( <i>Smith</i> ) (151 MHz)	Synthetic <b>2</b> ( <i>Weinreb</i> <sup>b</sup> ) (150 MHz)
2	44.9	45.2	45.0
3	20.4	20.58	20.5
4	19.7	19.9	19.8
5	36.2	36.4	36.3
6	47.6	47.8	47.7
7	37.0	37.2	37.1
8	31.0	31.2	31.1
9	27.1	27.4	27.2
10	69.5	69.7	69.6
11	73.4	73.7	73.6
13	86.7	87.0	86.8
14	34.2	34.5	34.4
15	20.4	20.64	20.5
16	26.6	26.8	26.7
17	23.0	23.2	23.1
18	65.1	65.6	65.4

<sup>a</sup>Natural **2** referenced to  $\text{CDCl}_3$  at  $\delta$  77.0. <sup>b</sup>Weinreb's  $\text{CDCl}_3$  referenced to  $\delta$  77.08



**Formal asymmetric route:**



**α-Methylbenzylamine reductive amination products 26 and S9.** A solution of aldehyde **14** (dr = 6.0:1.0, obtained via careful chromatography; 72 mg, 0.303 mmol, 1.0 equiv) in dry MeOH (5 mL) under argon in a microwave vial was treated with (R)-α-methylbenzylamine (**25**, 46 μL, 0.364 mmol, 1.2 equiv), glacial acetic acid (17 μL, 0.303 mmol, 1.0 equiv), and NaBH<sub>3</sub>CN (57 mg, 0.910 mmol, 3.0 equiv). The reaction vial was sealed and heated at 100 °C overnight (16 h). After cooling to room temperature, the reaction was quenched with NaHCO<sub>3</sub> (5 mL), diluted with EtOAc (15 mL) and H<sub>2</sub>O (10 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude product (dr ~ 4:1) was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–10%) to give desired double reductive amination product **26** (28 mg, 34% based on β-allyl **14**) and minor diastereomer **S9** (1.6 mg, 2% based on β-allyl **14**) both as colorless oils.

**Physical properties for major diastereomer 26.** Colorless oil;

**R<sub>f</sub>** = 0.29 (silica gel, 10% EtOAc/hexanes);

**MS** (ESI): Calcd for C<sub>22</sub>H<sub>27</sub>NO [M + H]<sup>+</sup> 322.2165; Found 322.2162;

**Optical rotation:** [α]<sub>D</sub><sup>25</sup> = –258.3 (c = 1.04, CHCl<sub>3</sub>);

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.37–7.28 (m, 4H), 7.25–7.20 (m, 1H), 6.38 (dd, *J* = 5.4, 3.1 Hz, 1H), 5.82 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.59 (dtd, *J* = 17.1, 9.8, 4.7 Hz, 1H), 5.09 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.03 (dt, *J* = 10.0, 1.9 Hz, 1H), 3.73 (q, *J* = 6.7 Hz, 1H), 3.19 (t, *J* = 3.7 Hz, 1H), 3.17 (s, 1H), 3.03 (dd, *J* = 4.9, 3.1 Hz, 1H), 2.73–2.63 (m, 2H), 2.58 (ddt, *J* = 13.5, 4.8, 1.7 Hz, 1H), 2.46 (td, *J* = 11.7, 3.0 Hz, 1H), 2.40–2.32 (m, 1H), 2.13–2.05 (m, 1H), 2.05–1.99 (m, 1H), 1.68–1.53 (m, 1H), 1.51–1.37 (m, 2H), 1.19 (d, *J* = 6.6 Hz, 3H);

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 206.7, 147.5, 141.6, 136.1, 129.7, 128.6, 127.0, 126.9, 117.4, 61.2, 54.2, 54.0, 52.9, 43.5, 40.2, 36.6, 36.4, 33.6, 22.4, 21.8.

**Physical properties for minor diastereomer S9.** Colorless oil;

**R<sub>f</sub>** = 0.22 (silica gel, 10% EtOAc/hexanes);

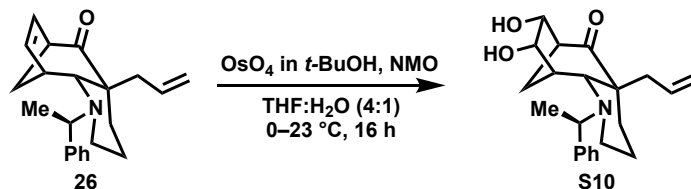
**MS** (ESI): Calcd for C<sub>22</sub>H<sub>27</sub>NO [M + H]<sup>+</sup> 322.2165; Found 322.2165;

**Optical rotation:** [α]<sub>D</sub><sup>25</sup> = 276.4 (c = 0.27, CHCl<sub>3</sub>);

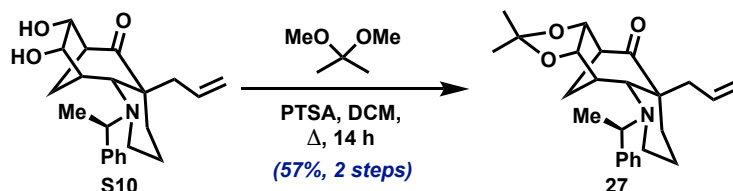
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.28 (d, *J* = 4.3 Hz, 4H), 7.25–7.18 (m, 1H), 5.73 (dd, *J* = 5.4, 3.1 Hz, 1H), 5.56 (dd, *J* = 5.5, 3.3 Hz, 1H), 5.25–5.13 (m, 1H), 4.75 (br s, 1H), 4.74–4.70 (m, 1H), 3.80 (q, *J* = 6.5 Hz, 1H), 3.06 (q, *J* = 3.6 Hz, 2H), 3.00–2.93 (m, 1H), 2.63 (td, *J* = 11.2, 3.4 Hz, 1H), 2.60 (d, *J* = 11.6 Hz, 1H), 2.53 (s, 1H), 2.47–2.34 (m, 2H), 2.05–1.94 (m, 2H), 1.85–1.72 (m,

1H), 1.72–1.64 (m, 1H), 1.44 (dt,  $J = 14.2, 4.5$  Hz, 1H), 1.39 (d,  $J = 6.5$  Hz, 2H), 1.33–1.23 (m, 1H);

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  207.1, 145.2, 141.8, 135.4, 128.7, 128.4, 127.7, 127.0, 117.5, 60.4, 56.0, 54.0, 53.2, 41.5, 40.1, 37.0, 35.8, 34.1, 22.8, 22.4.



**Diol S10.** *N*- $\alpha$ -methylbenzyl amine **26** (267 mg, 0.8253 mmol, 1.0 equiv) was dissolved in THF (24 mL) and water (6 mL) and cooled to 0 °C under argon. NMO (102 mg, 0.8666 mmol, 1.05 equiv) was added to the solution followed by dropwise addition of  $\text{OsO}_4$  in *t*-BuOH solution (2.5 wt.%, 517  $\mu\text{L}$ , 0.04126 mmol, 0.05 equiv). The reaction was allowed to warm to room temperature and stirred overnight (16 h). Upon completion, determined by TLC, the reaction mixture was quenched with saturated  $\text{Na}_2\text{SO}_3$  solution (15 mL), allowed to stir for 30 min and transferred to a separatory funnel, diluted with water (15 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer extracted with EtOAc ( $2 \times 30$  mL). The organic layer was then dried ( $\text{NaSO}_4$ ), filtered, and concentrated *in vacuo*. The resulting crude diol **S10** was used directly in the next reaction.



**Acetonide 27.** Crude diol **S10** (~0.825 mmol, 1.0 equiv) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (50 mL) under argon. 2,2-Dimethoxypropane (0.51 mL, 4.162 mmol, 5.0 equiv) and *p*-TsOH $\cdot\text{H}_2\text{O}$  (171 mg, 0.899 mmol, 1.1 equiv) were added and the solution was heated at reflux overnight (14 h). Upon completion, determined by TLC, the reaction mixture was quenched with  $\text{NaHCO}_3$  (30 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and  $\text{H}_2\text{O}$  (30 mL), transferred to a separatory funnel. The layers were separated, and the aqueous layer was then extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL), and the combined organics dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0–10%) to give acetonide **27** (186 mg, 57%, 2 steps) as a colorless oil.

**Physical properties:** Colorless oil;

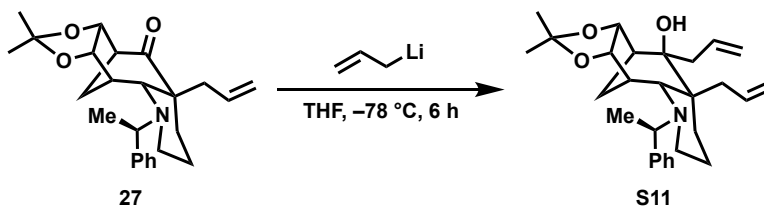
$R_f = 0.20$  (silica gel, 10% EtOAc/hexanes);

**MS** (ESI): calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_3$   $[\text{M} + \text{H}]^+$  396.2533, found 396.2528;

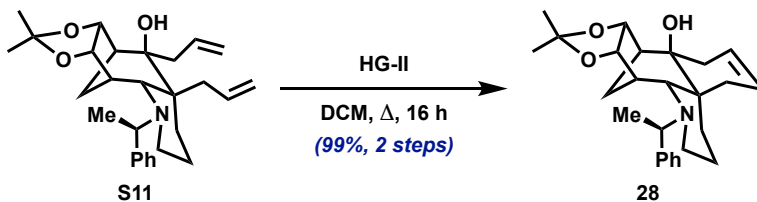
**Optical rotation:**  $[\alpha]^{25}_{\text{D}} = -17.2$  ( $c = 0.107$ ,  $\text{CHCl}_3$ );

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.29 (m, 4H), 7.25–7.21 (m, 1H), 5.62 (dtd,  $J = 17.1, 9.9, 4.8$  Hz, 1H), 5.17 (dt,  $J = 17.1, 2.0$  Hz, 1H), 5.11 (ddd,  $J = 10.0, 2.4, 1.2$  Hz, 1H), 4.30 (dd,  $J = 5.4, 1.6$  Hz, 1H), 4.27 (dd,  $J = 5.4, 1.5$  Hz, 1H), 3.72 (q,  $J = 6.6$  Hz, 1H), 3.14 (s, 1H), 2.85 (dd,  $J = 3.5, 2.0$  Hz, 1H), 2.75 (dd,  $J = 13.3, 9.8$  Hz, 1H), 2.67 (d,  $J = 2.5$  Hz, 1H), 2.55 (ddt,  $J = 13.4, 5.0,$

1.6 Hz, 1H), 2.40–2.30 (m, 3H), 2.14 (dt,  $J = 13.1, 3.5$  Hz, 1H), 1.96 (td,  $J = 13.6, 5.9$  Hz, 1H), 1.67–1.57 (m, 1H), 1.48 (s, 3H), 1.47–1.41 (m, 1H), 1.34 (dd,  $J = 14.6, 4.4$  Hz, 1H), 1.31 (s, 3H), 1.25 (d,  $J = 6.6$  Hz, 3H);  
 $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  213.3, 147.3, 135.7, 128.6, 127.0, 118.7, 110.9, 85.8, 82.1, 61.2, 56.0, 53.0, 51.0, 43.8, 39.3, 37.5, 31.9, 27.5, 25.8, 24.2, 22.4, 22.3. [Note: 1 Ar carbon signal missing due to overlap]



**Diallyl product S11.** Acetonide product **27** (11.3 mg, 0.0286 mmol, 1.0 equiv) was dissolved in dry THF (1.5 mL) under argon and cooled to  $-78^\circ\text{C}$ . Freshly prepared allyllithium solution (0.33 M, 867  $\mu\text{L}$ , 0.286 mmol, 10.0 equiv) was added dropwise and the reaction mixture was allowed to stir for 6–8 h at  $-78^\circ\text{C}$ . The reaction mixture was acidified to pH 1–2 with 0.33 M HCl solution (5 mL), diluted with ether (4 mL) and  $\text{H}_2\text{O}$  (2 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with ether (5 mL). The combined ether layers are extracted with additional 0.33 M HCl (5 mL). The combined acidic aqueous layers were then basified using aqueous  $\text{Na}_2\text{CO}_3$  solution until pH >10 and then extracted with EtOAc ( $3 \times 6$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentrated *in vacuo* and the resulting crude diallyl product was used directly in the next reaction.



**RCM product 28.** Crude diallylated product **S11** ( $\sim 0.0286$  mmol, 1.0 equiv) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) and sparged with argon for 20 minutes. Hoveyda–Grubbs II catalyst (1.0 mg, 0.00160 mmol, 6 mol%) was added and the solution was refluxed overnight. Upon completion, determined by TLC, the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, 20% EtOAc/hexanes) to give RCM product **28** (11.9 mg, 99%, 2 steps) as a colorless oil.

**Physical properties:** Colorless oil;

$R_f = 0.20$  (silica gel, 10% EtOAc/hexanes);

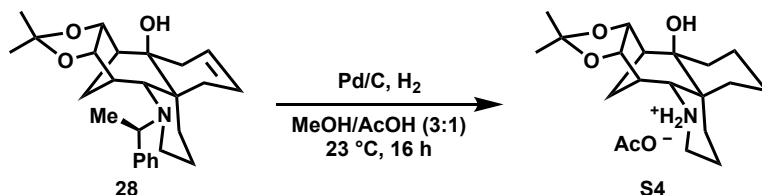
**MS** (ESI): calcd for  $\text{C}_{26}\text{H}_{35}\text{NO}_3$   $[\text{M} + \text{H}]^+$  410.2690, found 410.2688;

**Optical rotation:**  $[\alpha]_D^{25} = -24.2$  ( $c = 0.447$ ,  $\text{CHCl}_3$ );

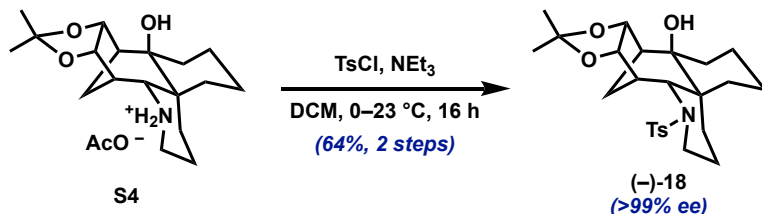
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.32 (m, 2H), 7.28 (t,  $J = 7.7$  Hz, 2H), 7.22–7.18 (m, 1H), 5.83–5.78 (m, 1H), 5.67–5.61 (m, 1H), 5.25 (d,  $J = 4.7$  Hz, 1H), 4.40 (dd,  $J = 5.3, 1.7$  Hz, 1H), 3.65 (q,  $J = 6.6$  Hz, 1H), 2.99 (s, 1H), 2.76 (dd,  $J = 18.6, 4.8$  Hz, 1H), 2.41 (ddd,  $J = 17.7, 4.4, 2.2$

Hz, 1H), 2.35–2.25 (m, 3H), 2.20 (d,  $J = 12.2$  Hz, 1H), 2.16 (s, 1H), 2.09 (s, 1H), 2.01 (dd,  $J = 17.8, 4.7$  Hz, 1H), 1.95 (d,  $J = 19.6$  Hz, 1H), 1.92–1.85 (m, 2H), 1.62 (dtd,  $J = 17.8, 12.9, 6.8$  Hz, 1H), 1.48 (s, 3H), 1.46 (d,  $J = 6.2$  Hz, 1H), 1.43–1.38 (m, 1H), 1.35 (s, 3H), 1.27 (d,  $J = 6.6$  Hz, 3H);

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  148.0, 129.4, 128.4, 127.1, 126.7, 126.0, 110.0, 86.9, 80.8, 72.2, 61.0, 58.4, 48.1, 43.8, 40.1, 39.1, 38.4, 35.9, 26.8, 26.7, 26.1, 24.6, 23.1, 22.4.



**Hydrogenated product S4.** RCM product **28** (6.7 mg, 0.0164 mmol, 1.0 equiv) was dissolved in MeOH/AcOH (3:1, 1.2 mL) and sparged with argon for 5 min. Palladium on carbon (10% w/w, 3.0 mg, 0.00328 mmol Pd, 0.20 equiv) was added to the solution, which was then sparged with  $\text{H}_2$  gas for 5 min and left under  $\text{H}_2$  atmosphere (balloon) to stir overnight (16 h). Upon completion, the reaction is flushed briefly with argon to remove the remaining  $\text{H}_2$  and the reaction mixture is filtered through a Celite pad and concentrated *in vacuo*; excess AcOH was removed by azeotrope with toluene (2 x 2 mL). The resulting crude product was used directly in the next reaction.



**N-Tosyl protected (–)-18.** Crude ammonium salt **S4** (~0.0164 mmol, 1.0 equiv) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (1.2 mL) and cooled to 0  $^\circ\text{C}$ . Triethylamine (14  $\mu\text{L}$ , 0.0984 mmol, 6.0 equiv) was added dropwise, stirred for 15 min, followed by addition of TsCl (6 mg, 0.0328 mmol, 2.0 equiv). The reaction is allowed to warm to room temperature overnight (16 h). Upon completion, the reaction is quenched with saturated  $\text{NaHCO}_3$  solution (3 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (4 mL) and  $\text{H}_2\text{O}$  (3 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was then extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 5 mL), and the combined organics dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The resulting crude product was purified by pTLC (silica gel, 20% EtOAc/hexanes) to give N-tosyl protected (–)-**18** (4.8 mg, 64%, 2 steps) as a pale white solid. The enantiopurity was determined to be >99% ee by HPLC (OJ-H, hexane/*i*-PrOH = 85/15, 0.8 mL/min,  $t_R$  (major) = 15.31 min,  $t_R$  (minor) = 22.61 min).  $^1\text{H}$  and  $^{13}\text{C}$  NMR data matched that of our racemic sample. X-ray quality crystals could be obtained by recrystallization from EtOAc/hexanes.

**Physical properties:** Pale white solid;

**MS** (ESI): calcd for  $\text{C}_{25}\text{H}_{35}\text{NO}_5\text{S}$   $[\text{M} + \text{H}]^+$  462.2309, found 462.2306;

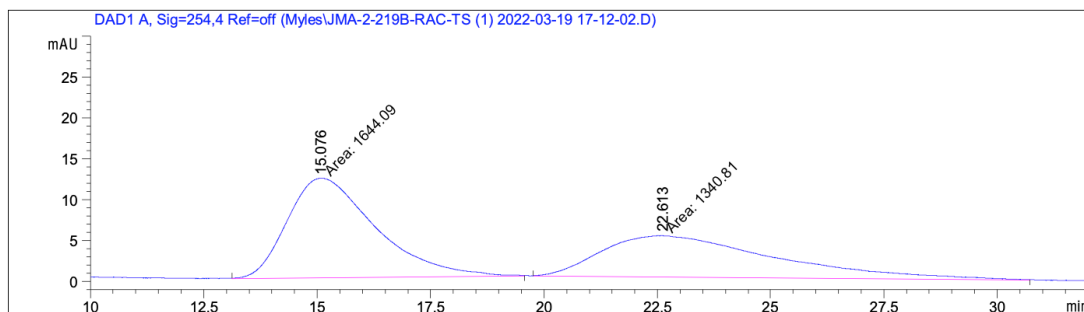
**Optical rotation:**  $[\alpha]^{26}_\text{D} = -11.2$  ( $c = 0.267$ ,  $\text{CHCl}_3$ , >99% ee);

## HPLC Traces for (±)-18 and (–)-18:

(±)-18 (OJ-H, hexane/*i*-PrOH = 85/15, 0.8 mL/min):

Sample Info : OJ-H Hex;IPA 85:15\_0.8 mL/min\_asym

Additional Info : Peak(s) manually integrated



Signal 1: DAD1 A, Sig=254,4 Ref=off

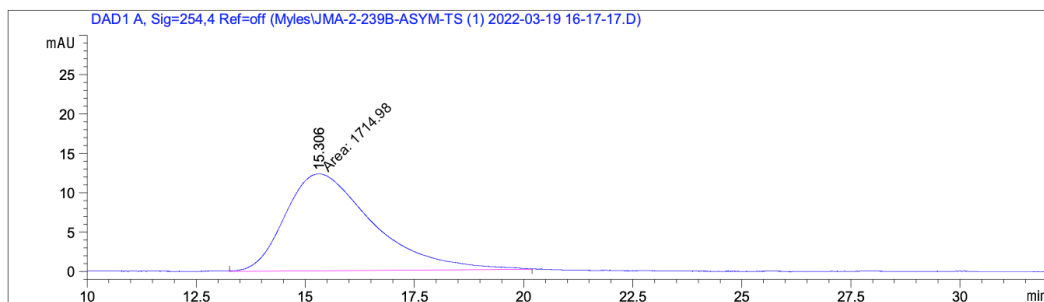
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.076	MM	2.2498	1644.09302	12.17956	55.0804
2	22.613	MM	4.4182	1340.80518	5.05792	44.9196

Totals : 2984.89819 17.23748

(–)-18 (OJ-H, hexane/*i*-PrOH = 85/15, 0.8 mL/min):

Sample Info : OJ-H Hex;IPA 85:15\_0.8 mL/min\_asym

Additional Info : Peak(s) manually integrated

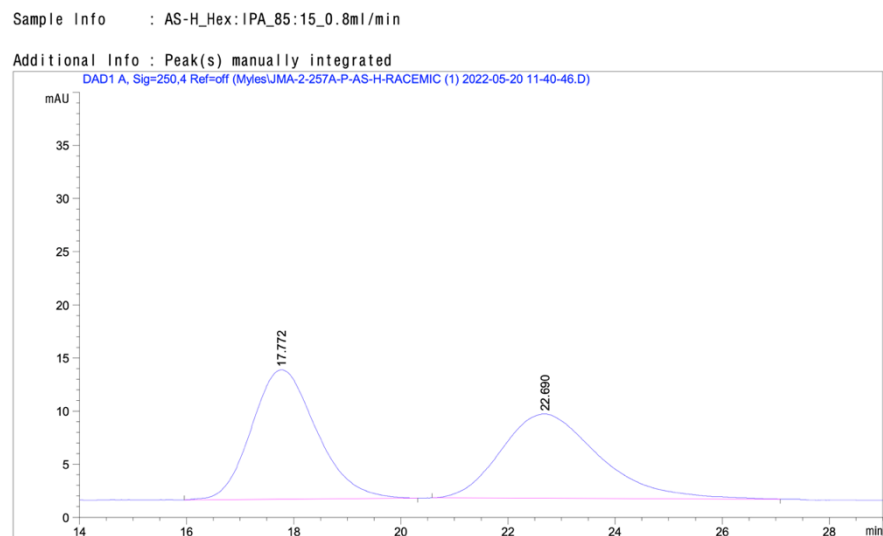


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.306	MM	2.3225	1714.97815	12.30678	100.0000

Totals : 1714.97815 12.30678

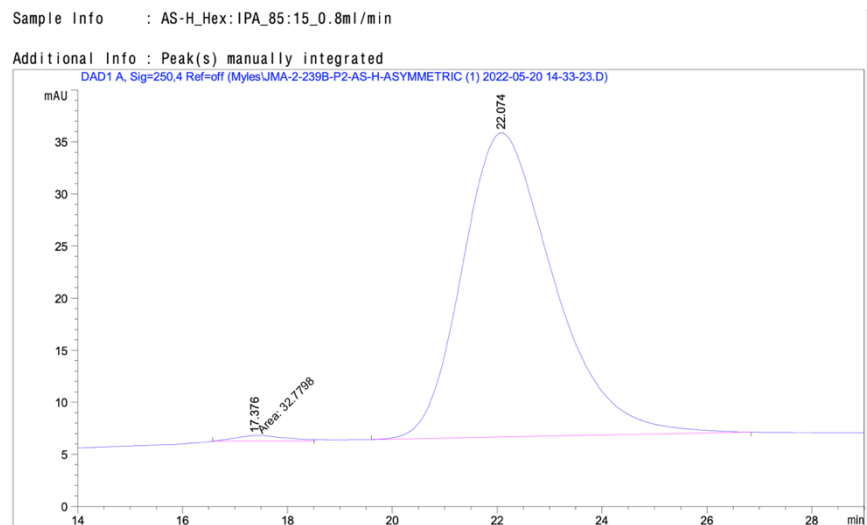
(±)-18 (AS-H, hexane/*i*-PrOH = 85/15, 0.8 mL/min):



Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.772	BB	1.0692	1022.61987	12.18366	50.4437
2	22.690	BB	1.4894	1004.62854	7.94416	49.5563
Totals :				2027.24841	20.12782	

(-)-18 (AS-H, hexane/*i*-PrOH = 85/15, 0.8 mL/min):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.376	MM	1.0819	32.77981	5.04991e-1	0.9180
2	22.074	BB	1.6513	3537.96094	29.20577	99.0820
Totals :				3570.74075	29.71076	

## 5. Details for Single Crystal X-ray Analyses of 18, 20 and (–)-18

**X-ray Experimental for C<sub>25</sub>H<sub>35</sub>NO<sub>5</sub>S (18):** Crystals grew as colorless plates by slow evaporation from ethyl acetate hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.26 x 0.23 x 0.065 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a  $\mu$ -focus Cu K $\alpha$  radiation source ( $\lambda$  = 1.5418 Å) with collimating mirror monochromators. A total of 1300 frames of data were collected using  $\omega$ -scans with a scan range of 1° and a counting time of 3 seconds per frame for frames collected with a detector offset of +/- 41.6° and 11 seconds per frame with frames collected with a detector offset of 107.1°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.40.71a.<sup>7</sup> The structure was solved by direct methods using SHELXT<sup>8</sup> and refined by full-matrix least-squares on F<sup>2</sup> with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/8.<sup>9</sup> Structure analysis was aided by use of the programs PLATON<sup>10</sup> and OLEX2<sup>11</sup>. The hydrogen atoms on the carbon atoms were in ideal geometry with Uiso set to 1.2xUeq of the attached carbon atom (1.5xUeq for methyl groups). The hydrogen atom on O1 was located in a  $\Delta F$  map and refined with an isotropic displacement parameter. Initially, the hydrogen atoms bound to C3 and C10 were calculated in ideal geometry. This model resulted in a close H...H contact. Subsequently, the hydrogen atoms on these two carbon atoms were refined without constraints.

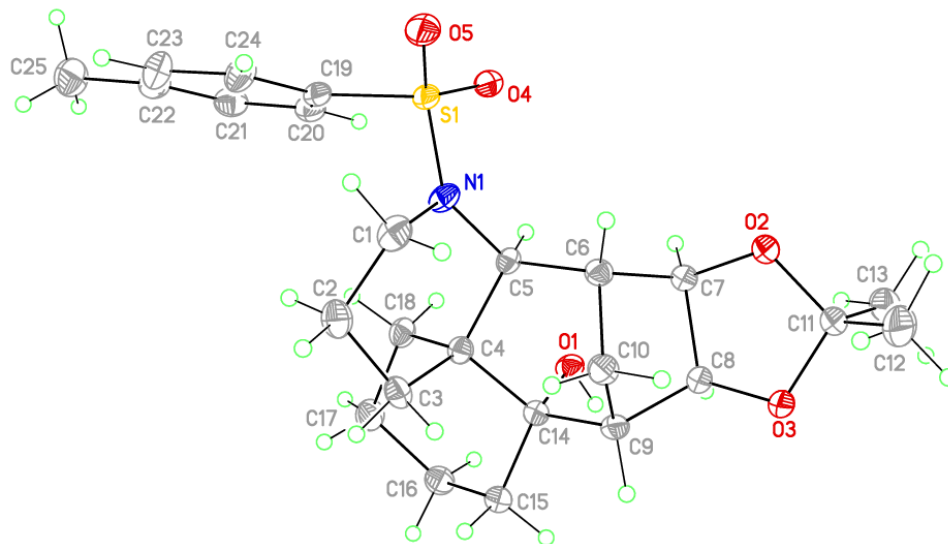
The function,  $\Sigma w(|F_o|^2 - |F_c|^2)^2$ , was minimized, where  $w = 1/[(\sigma(F_o))^2 + (0.0423 \cdot P)^2 + (1.0733 \cdot P)]$  and  $P = (|F_o|^2 + 2|F_c|^2)/3$ .  $R_w(F^2)$  refined to 0.0624, with  $R(F)$  equal to 0.0245 and a goodness of fit,  $S$ , = 1.04. Definitions used for calculating  $R(F)$ ,  $R_w(F^2)$  and the goodness of fit,  $S$ , are given below.<sup>12</sup> The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).<sup>13</sup> All figures were generated using SHELXTL/PC.<sup>14</sup> Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

**Table 1. Crystal data and structure refinement for 1.**

Empirical formula	C <sub>25</sub> H <sub>35</sub> N O <sub>5</sub> S	
Formula weight	461.60	
Temperature	100.04(11) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 17.0148(3) Å	$\alpha = 90^\circ$ .
	b = 11.5648(2) Å	$\beta = 90^\circ$ .
	c = 11.7645(2) Å	$\gamma = 90^\circ$ .
Volume	2314.93(7) Å <sup>3</sup>	

Z	4
Density (calculated)	1.324 Mg/m <sup>3</sup>
Absorption coefficient	1.544 mm <sup>-1</sup>
F(000)	992
Crystal size	0.264 x 0.231 x 0.065 mm <sup>3</sup>
Theta range for data collection	3.822 to 73.231°.
Index ranges	-20<=h<=20, -13<=k<=14, -14<=l<=13
Reflections collected	16751
Independent reflections	4294 [R(int) = 0.0226]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian and multi-scan
Max. and min. transmission	1.000 and 0.563
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4294 / 1 / 312
Goodness-of-fit on F <sup>2</sup>	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0624
R indices (all data)	R1 = 0.0250, wR2 = 0.0630
Absolute structure parameter	-0.005(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.245 and -0.202 e.Å <sup>-3</sup>

**Figure S2.** View of **18** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.





**X-ray Experimental for C<sub>25</sub>H<sub>35</sub>NO<sub>4</sub>S (20):** Crystals grew as clusters of large, colorless prisms by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.25 x 0.19 x 0.17 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a  $\mu$ -focus Cu K $\alpha$  radiation source ( $\lambda$  = 1.5418 Å) with collimating mirror monochromators. A total of 1851 frames of data were collected using  $\omega$ -scans with a scan range of 1° and a counting time of 2 seconds per frame for frames collected with a detector offset of +/- 41.7° and 5 seconds per frame with frames collected with a detector offset of 107.1°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.40.71a.<sup>7</sup> The structure was solved by direct methods using SHELXT<sup>8</sup> and refined by full-matrix least-squares on F<sup>2</sup> with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/8.<sup>9</sup> Structure analysis was aided by use of the programs PLATON<sup>10</sup> and OLEX2.<sup>11</sup> The hydrogen atoms on the carbon atoms were initially calculated in an ideal geometry but were eventually refined with isotropic displacement parameters.

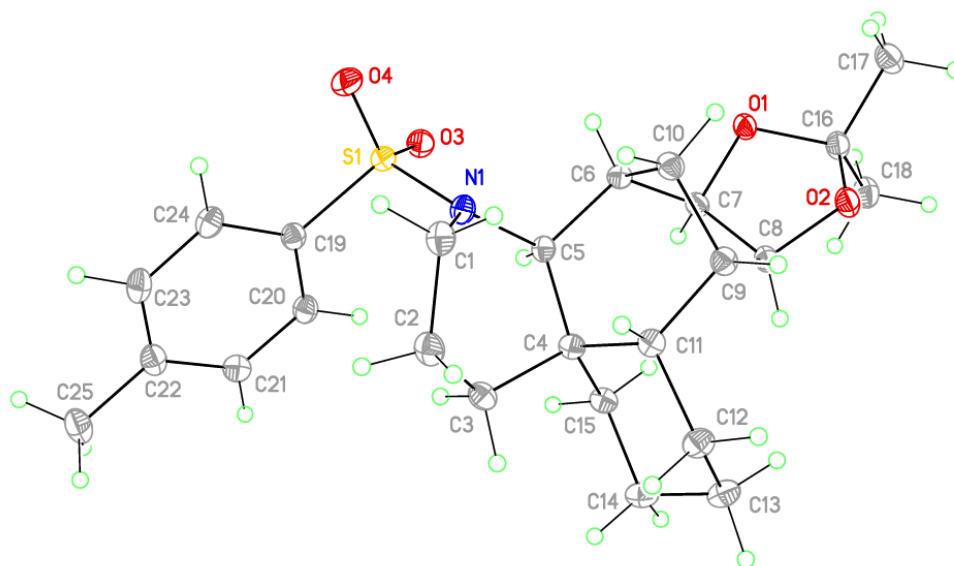
The function,  $\Sigma w(|F_o|^2 - |F_c|^2)^2$ , was minimized, where  $w = 1/[(\sigma(F_o))^2 + (0.0423 \cdot P)^2 + (1.0733 \cdot P)]$  and  $P = (|F_o|^2 + 2|F_c|^2)/3$ .  $R_w(F^2)$  refined to 0.0793, with  $R(F)$  equal to 0.0306 and a goodness of fit,  $S$ , = 1.03. Definitions used for calculating  $R(F)$ ,  $R_w(F^2)$  and the goodness of fit,  $S$ , are given below.<sup>12</sup> The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).<sup>13</sup> All figures were generated using SHELXTL/PC.<sup>14</sup> Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

**Table 1. Crystal data and structure refinement for 20.**

Empirical formula	C <sub>25</sub> H <sub>35</sub> N O <sub>4</sub> S	
Formula weight	445.60	
Temperature	100.03(10) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	$a = 11.58796(8)$ Å	$\alpha = 90^\circ$ .
	$b = 8.83389(6)$ Å	$\beta = 101.5364(8)^\circ$ .
	$c = 21.9905(2)$ Å	$\gamma = 90^\circ$ .
Volume	2205.62(3) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.342 Mg/m <sup>3</sup>	
Absorption coefficient	1.565 mm <sup>-1</sup>	
F(000)	960	

Crystal size	0.249 x 0.192 x 0.173 mm <sup>3</sup>
Theta range for data collection	3.893 to 73.469°.
Index ranges	-14<= <i>h</i> <=14, -10<= <i>k</i> <=10, -25<= <i>l</i> <=27
Reflections collected	24386
Independent reflections	4377 [R(int) = 0.0205]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian and multi-scan
Max. and min. transmission	1.000 and 0.702
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4377 / 0 / 420
Goodness-of-fit on F <sup>2</sup>	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0306, wR2 = 0.0786
R indices (all data)	R1 = 0.0315, wR2 = 0.0793
Extinction coefficient	n/a
Largest diff. peak and hole	0.315 and -0.488 e.Å <sup>-3</sup>

**Figure S3.** View of **20** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



**X-ray Experimental for C<sub>25</sub>H<sub>35</sub>NO<sub>5</sub>S [(-)-18]:** Crystals grew as large, colorless prisms by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.33 x 0.25 x 0.17 mm. The data were collected on a Rigaku Oxford Diffraction HyPix6000E Dual Source diffractometer using a  $\mu$ -focus Cu K $\alpha$  radiation source ( $\lambda$  = 1.5418Å) with collimating mirror monochromators. A total of 3876 frames of data were collected using  $\omega$ -scans with a scan range of 0.5° and a counting time of 6 seconds per frame for frames

collected with a detector offset of  $\pm 48.6^\circ$  and 21 seconds per frame with frames collected with a detector offset of  $107.8^\circ$ . The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.41.120a.<sup>7</sup> The structure was solved by direct methods using SHELXT<sup>8</sup> and refined by full-matrix least-squares on  $F^2$  with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/3.<sup>9</sup> Structure analysis was aided by use of the programs PLATON<sup>10</sup> and OLEX2.<sup>11</sup> The hydrogen atoms on the carbon atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

The absolute configuration was determined using the method of Flack<sup>15</sup> and confirmed using the Hooft y-parameter method, which resulted in a Hooft y-parameter of -0.008(9).<sup>16</sup>

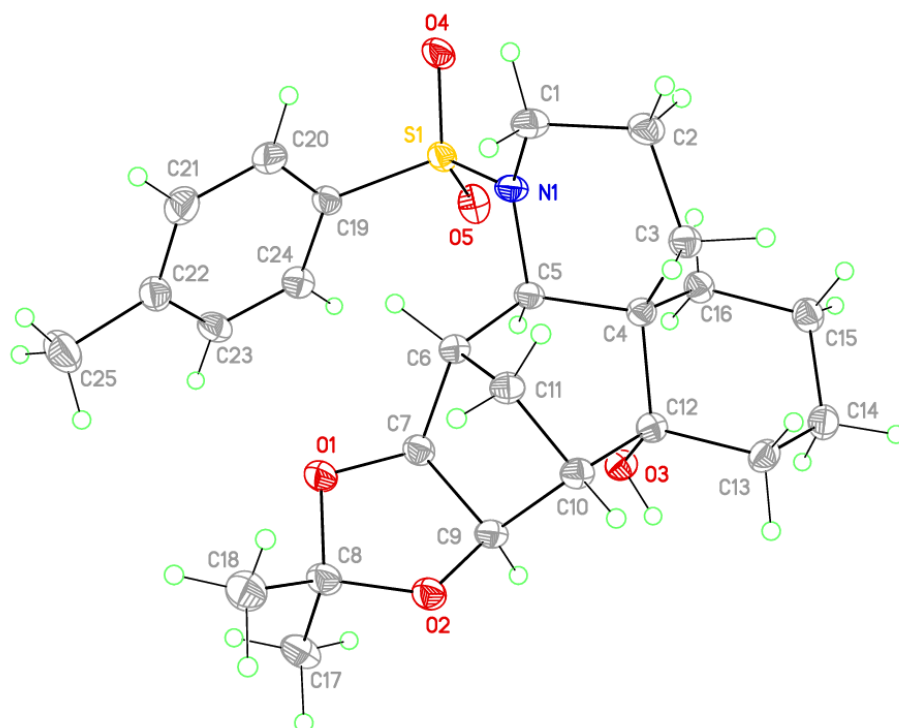
The function,  $\sum w(|F_o|^2 - |F_c|^2)^2$ , was minimized, where  $w = 1/[(\sigma(F_o))^2 + (0.0423 \cdot P)^2 + (1.0733 \cdot P)]$  and  $P = (|F_o|^2 + 2|F_c|^2)/3$ .  $R_w(F^2)$  refined to 0.0974, with  $R(F)$  equal to 0.0375 and a goodness of fit,  $S$ , = 1.08. Definitions used for calculating  $R(F)$ ,  $R_w(F^2)$  and the goodness of fit,  $S$ , are given below.<sup>12</sup> The data were checked for secondary extinction but no correction was needed. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).<sup>13</sup> All figures were generated using SHELXTL/PC.<sup>14</sup> Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

**Table 1. Crystal data and structure refinement for (–)-18.**

Empirical formula	C <sub>25</sub> H <sub>35</sub> N O <sub>5</sub> S	
Formula weight	461.60	
Temperature	100.0(9) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	$a = 8.31399(5)$ Å	$\alpha = 90^\circ$ .
	$b = 12.10612(9)$ Å	$\beta = 90^\circ$ .
	$c = 22.80445(15)$ Å	$\gamma = 90^\circ$ .
Volume	2295.27(3) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.336 Mg/m <sup>3</sup>	
Absorption coefficient	1.557 mm <sup>-1</sup>	
F(000)	992	
Crystal size	0.334 x 0.248 x 0.167 mm <sup>3</sup>	
Theta range for data collection	5.329 to 76.898°.	
Index ranges	-10 ≤ h ≤ 10, -14 ≤ k ≤ 14, -28 ≤ l ≤ 27	

Reflections collected	26218
Independent reflections	4754 [R(int) = 0.0888]
Completeness to theta = 67.684°	99.7 %
Absorption correction	Gaussian and multi-scan
Max. and min. transmission	1.000 and 0.422
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4754 / 192 / 308
Goodness-of-fit on F <sup>2</sup>	1.105
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.0974
R indices (all data)	R1 = 0.0375, wR2 = 0.0974
Absolute structure parameter	-0.005(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.354 and -0.269 e.Å <sup>-3</sup>

**Figure S4.** View of (–)-**18** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



## 6. References

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12.  $R_w(F^2) = \{\sum w(|F_o|^2 - |F_c|^2)^2 / \sum w(|F_o|^4)\}^{1/2}$  where  $w$  is the weight given each reflection.  $R(F) = \sum (|F_o| - |F_c|) / \sum |F_o|$  for reflections with  $F_o > 4(\sigma(F_o))$ .  $S = [\sum w(|F_o|^2 - |F_c|^2)^2 / (n - p)]^{1/2}$ , where  $n$  is the number of reflections and  $p$  is the number of refined parameters.
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## 7. NMR Spectra

