Supporting Information

Total Synthesis of Sedum Alkaloids via Catalyst Controlled aza-Cope Rearrangement and Hydroformylation with Formaldehyde

Hong Ren and William D. Wulff*
Department of Chemistry, Michigan State University
East Lansing, MI 48824
E-mail: wulff@chemistry.msu.edu

Table of Contents

I. General information

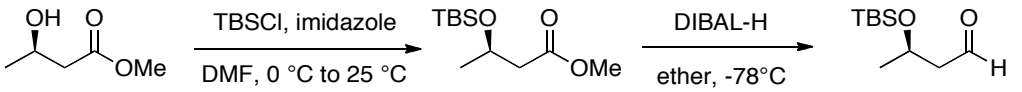
All experiments were performed under a nitrogen atmosphere. Flasks were flame-dried and cooled under nitrogen before use. All solvents were dried appropriately if used in the reaction. VANOL ligand is commercially available from Aldrich as well as Strem Chemicals. If desired, it could be purified using column chromatography on regular silica gel with 2:1 dichloromethane/hexanes. Phenol was sublimed and stored in a dry desiccator. Liquid aldehydes were either used as purchased from Aldrich or distilled before use. (*R*)-methyl 3-hydroxybutanoate was used as purchased from Aldrich with 98% optical purity. (*S*)-methyl 2-hydroxypropanoate was used as purchased from Aldrich with 96% optical purity.

Melting points were measured on a Thomas Hoover capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR were recorded on a Varian 300 MHz, VXR-500 MHz or VXR-600 MHz instrument in $CDCl_3$ unless otherwise noted. $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77.0). The silica gel for column chromatography was purchased from Sorbent Technologies with the following specifications: standard grade, 60 Å porosity, 230 X 400 mesh particle size, 500-600 m^2/g surface area and 0.4 g/mL bulk density. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol.

HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotation was obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (Sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL.

II. Preparation of chiral aldehydes

a) Typical procedure for preparation of 8a and c-d – Illustrated for synthesis of (*R*)-3-((*tert*-butyldimethylsilyl)oxy)butanal 8a.

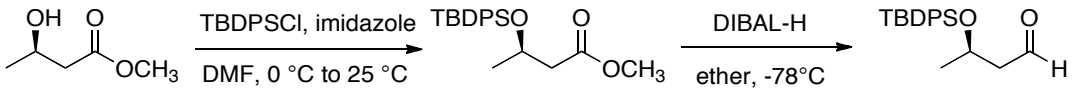


(*R*)-**8a**

To a flame-dried 100 mL round-bottomed flask, fitted with a magnetic stirrer and a nitrogen balloon was added (*R*)-methyl 3-hydroxybutanoate (98% *ee*, 0.96 g, 8.0 mmol) and DMF (20 mL). The mixture was cooled down to 0 °C, then TBSCl (1.44 g, 9.60 mmol) and imidazole (0.680 g, 9.60 mmol) were added. Stirring was continued at room temperature for 24 h. Upon completion, the mixture was charged with brine (60 mL) and stirred for 5 minutes at room temperature. The resulting solution was then extracted with hexanes (60 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:25 EtOAc/hexanes) gave the pure ester (*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)butanoate as a clear oil in 89% isolated yield (1.6 g, 7.1 mmol). R_f = 0.4 (1:25 ethyl acetate /hexanes). *Spectral data*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.013 (s, 3H), 0.035 (s, 3H), 0.84 (s, 9H), 1.16-1.17 (d, 3H, J = 6.0 Hz), 2.35 (dd, 1H, J =

14.5, 5.5 Hz), 2.46 (dd, 1H, *J* = 14.5, 7.5 Hz), 3.64 (s, 3H), 4.24-4.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.08, -4.54, 17.93, 23.93, 25.70, 44.74, 51.37, 65.84, 172.04. The data matches that reported for this compound.[1]

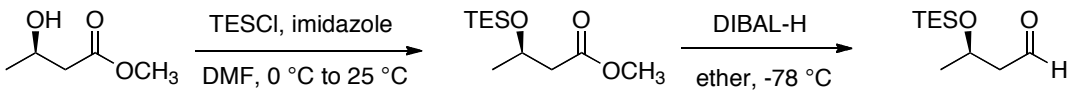
To a flame-dried 250 mL round-bottomed flask, fitted with a magnetic stirrer and a nitrogen balloon was added (*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)butanoate (2.0 g, 8.9 mmol) and ether (30 mL). The mixture was cooled to –78 °C and DIBAL-H (5.40 mL, 13.5 mmol) was added dropwise over a period of 4 minutes. The mixture was then stirred at –78 °C for 2 h. Upon completion, the mixture was quenched with a mixture of methanol and water (3.0 mL, 1:1 V/V), diluted with ether (40 mL) at –78 °C. The flask was then allowed to warm up to room temperature. The mixture was stirred with saturated potassium sodium tartrate solution until it became clear two layers. The organic layer was separated and the aqueous layer washed with ether (30 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:15 EtOAc/hexanes) gave the pure aldehyde (*R*)-**8a** as a clear oil in 71% isolated yield (1.2 g, 6.3 mmol). R_f = 0.2 (1:15 ethyl acetate /hexanes). *Spectral data for* (*R*)-***8a***[2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 1.21 (d, 3H, *J* = 6.0 Hz), 2.41-2.55 (m, 2H), 4.31-4.35 (m, 1H), 9.78 (t, 1H, *J* = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.95, -4.39, 17.94, 24.17, 25.71, 52.99, 64.55, 202.16. The data matches that reported for this compound.[2]



(*R*)-**8c**

*(R)-3-((tert-butyldiphenylsilyl)oxy)butanal **8c**:* (*R*)-methyl 3-hydroxybutanoate (98% *ee*, 0.24 g, 2.0 mmol) was reacted according to the general procedure described above with the exception that TBDPSCl (0.66 g, 2.4 mmol) was added for the preparation of silyl protected ester. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 84% isolated yield (0.66 g, 1.8 mmol). R_f = 0.40 (1:15 ethyl acetate /hexanes). *Spectral data*[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.11 (d, 3H, *J* = 6.0 Hz), 2.38 (dd, 1H, *J* =15, 5.5 Hz), 2.55 (dd, 1H, *J* =15, 7.0 Hz), 3.58 (s, 3H), 4.28-4.32 (m, 1H), 7.34-7.43 (m, 6H), 7.65-7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.16, 23.60, 26.86, 44.42, 51.34, 66.86, 127.46, 127.53, 129.54, 129.60, 133.88, 134.30, 135.84, 171.76.

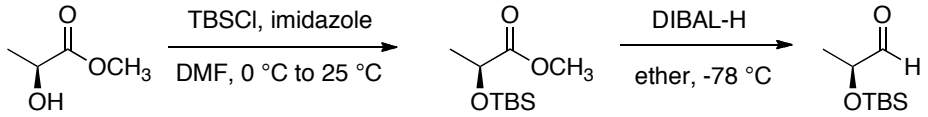
The ester (0.66 g, 1.8 mmol) was reduced according to the procedure described for the preparation of (*R*)-**8a**. Purification of (*R*)-**8c** by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aldehyde (*R*)-**8c** as a clear oil in 84% isolated yield (0.54 g, 1.5 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for* (*R*)-***8c***[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.19 (d, 3H, *J* = 6.0 Hz), 2.42-2.48 (m, 2H), 4.28-4.32 (m, 1H), 7.35-7.43 (m, 6H), 7.62-7.69 (m, 4H), 9.78 (t, 1H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.14, 23.22, 26.92, 43.74, 66.71, 127.59, 127.68, 127.72, 129.75, 129.84, 133.56, 134.80, 135.80, 202.19.



(*R*)-**8d**

(R)-3-((triethylsilyl)oxy)butanal ***8d****:* (*R*)-methyl 3-hydroxybutanoate (98% *ee,* 3.50 g, 30.0 mmol) was reacted according to the general procedure described above with the exception that TESCl (5.4 g, 36 mmol) was added for the preparation of silyl protected ester. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 87% isolated yield (6.08 g, 26.1 mmol). R_f = 0.40 (1:15 ethyl acetate /hexanes). *Spectral data*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57 (t, 6H, *J* = 8.0 Hz), 0.93 (t, 9H, *J* = 7.5 Hz), 1.19 (d, 3H, *J* = 6.5 Hz), 2.34-2.38 (m, 1H), 2.46-2.51 (m, 1H), 3.64 (s, 3H), 4.25-4.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.80, 6.72, 24.00, 44.74, 51.38, 65.06, 172.02.

The ester (6.08 g, 26.1 mmol) was reduced according to the procedure described for the preparation of (*R*)-**8a**. Purification of (*R*)-**8d** by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aldehyde (*R*)-**8d** as a clear oil in 68% isolated yield (3.57 g, 17.7 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data for* (*R*)-***8d***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58 (t, 6H, *J* = 7.5 Hz), 0.93 (t, 9H, *J* = 7.5 Hz), 1.23 (d, 3H, *J* = 6.0 Hz), 2.43-2.57 (m, 2H), 4.32-4.36 (m, 1H), 9.79 (t, 1H, *J* = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.82, 6.76, 24.25, 53.05, 64.29, 202.16; IR (thin film) 2957, 1730, 1458, 1016 cm^{-1}; HRMS (ES+) calcd for $C_{10}H_{22}O_2Si$ *m/z* 203.1463 (M+1), meas 203.1467. $[\alpha]^{23}_D$ = –11.3 (*c* = 1.0, CH_2Cl_2) on **(*R*)-8d**.

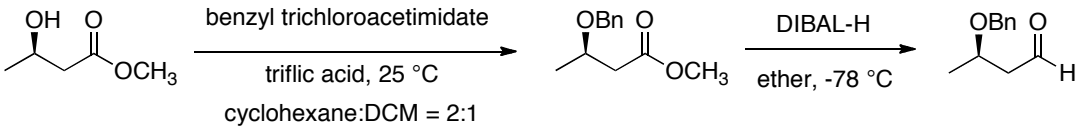


(*S*)-**13**

(S)-2-((tert-butyldimethylsilyl)oxy)propanal ***13***: (*S*)-methyl 2-hydroxypropanoate (96% *ee*, 0.21 g, 2.0 mmol) was reacted according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 75% isolated yield (0.33 g, 1.5 mmol). R_f = 0.30 (1:15 ethyl acetate /hexanes). *Spectral data*[4]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.41 (d, 3H, *J* = 7.0 Hz), 3.70 (s, 3H), 4.31 (dd, 1H, *J* = 13.0, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.32, -5.12, 18.30, 21.35, 25.70, 51.85, 68.38, 174.56.

The ester (0.33 g, 1.5 mmol) was reduced according to the procedure described for the preparation of (*R*)-**8a**. Purification of (*S*)-**13** by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aldehyde (*S*)-**13** as a clear oil in 45% isolated yield (0.13 g, 0.68 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data for* (*S*)-***13***[5]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91(s, 9H), 1.25 (d, 3H, J = 6.5 Hz), 4.07 (dd, 1H, *J* = 6.5, 1.0 Hz), 9.59 (d, 1H, *J* = 1.0 Hz).

b) Procedure for preparation of (*R*)-3-(benzyloxy)butanal 8b.



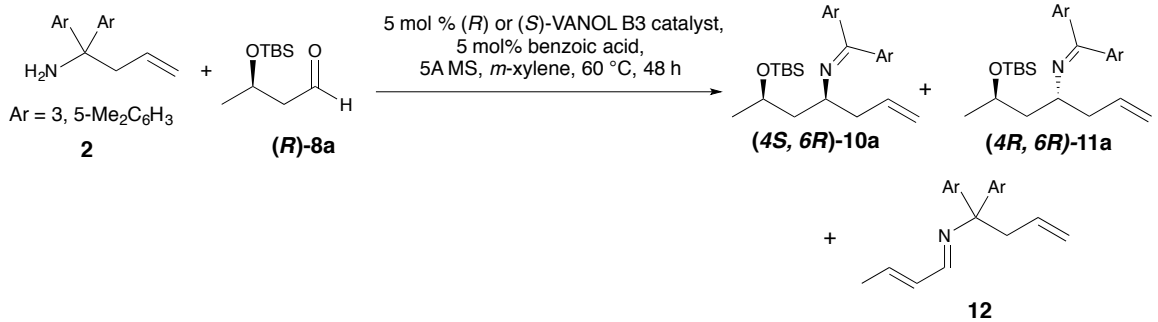
(*R*)-**8b**

To a stirred solution of (*R*)-methyl 3-hydroxybutanoate (98% *ee,* 0.24 g, 2.0 mmol) and benzyl trichloroacetimidate (1.0 g, 4.0 mmol) in co-solvent (20 mL, $V_{cyclohexane}$: V_{DCM} = 2:1) was added triflic acid (30 uL, 0.30 mmol) at room temperature. Stirring was continued for 48 h. The reaction was quenched by addition of sat. $NaHCO_3$ (20 mL), followed by the separation of the organic phase. The aqueous phase was washed with dichloromethane (5 mL x 3), and the combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 60% isolated yield (0.25 g, 1.2 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data*[6]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 6.0), 2.43 (dd, 1H, *J* = 15, 6.0 Hz), 2.65 (dd, 1H, *J* = 15, 7.5 Hz), 3.66 (s, 3H), 3.99-4.03 (m, 1H), 4.50 (d, 1H, *J* = 11.5 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 7.25-7.33 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.65, 41.66, 51.32, 70.64, 71.72, 127.34, 127.44, 128.13, 138.38, 171.64.

The resulting ester (0.25 g, 1.2 mmol) was then subjected to the DIBAL-H reduction as described for the synthesis of (*R*)-**8b**. Purification of **8b** by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure **8b** as a clear oil in 63% isolated yield (0.12 g, 0.76 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data*[7]: ^{1}H NMR (500 MHz, $CDCl_3$) δ1.34 (d, 3H, *J* = 6.0 Hz), 2.53-2.58 (m, 1H), 2.71-2.76 (m, 1H), 4.10-4.12 (m, 1H), 4.51 (d, 1H, *J* = 11.5 Hz), 4.64 (d, 1H, *J* = 11.5 Hz), 7.29-7.39 (m, 5H), 9.83 (t, 1H, *J* = 2.0 Hz).

III. Optimization of the alcohol protecting group

a. Diastereoselective aza-Cope rearrangement with (*R*)-3-((*tert*-butyldimethylsilyl)oxy) butanal 8a.



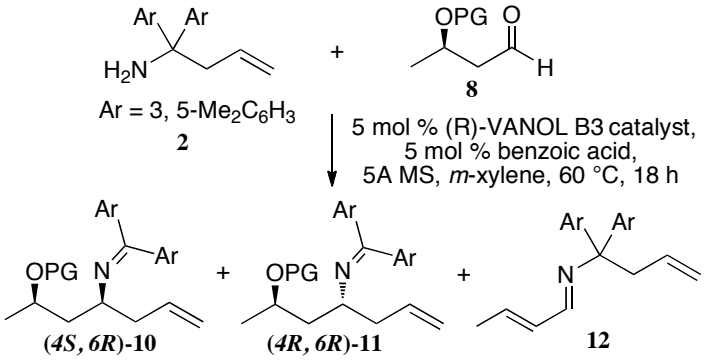
Preparation of catalyst stock solution.[7] A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Nitrogen. To the flask was sequentially added (*R*)-VANOL (44 mg, 0.10 mmol), phenol (19 mg, 0.20 mmol), dry toluene (2.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 150 μL, 0.300 mmol) and water (5.4 μL, 0.30 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenck flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully and slowly opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to cool to room temperature under a low flow of Nitrogen. The residue was then completely dissolved in 2 mL of dry toluene to afford the stock solution of the catalyst.

aza-Cope rearrangement with (R)-VANOL catalyst. A 5 mL Schlenk test tube charged with 5Å powdered molecular sieves (50 mg) and fitted with a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Nitrogen. To the test tube was then added amine **2** (28 mg, 0.10 mmol, 1.0 equiv), 0.10 mL of the catalyst stock solution (5 mol% catalyst) and *m*-xylene (0.35 mL) via a plastic syringe fitted with a metallic needle. The mixture was stirred for 30 min at 60 °C. At the same time, to an oven-dried 5 mL vial was added benzoic acid (12 mg, 0.10 mmol) and *m*-xylene (1 mL). Then (*R*)-**8a** (22 mg, 0.11 mmol) and 50 μL of the benzoic acid stock solution (5 mol%) were transferred to the above catalyst-amine complex under a high flow of Nitrogen via a plastic syringe fitted with a metallic needle. The test tube was closed and the reaction was stirred at 60 °C for 18 h. Purification by flash column chromatography on silica gel (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **10a+11a** as a viscous oil in 48% (22 mg, 0.048 mmol) yield. The diastereoselective ratio of the reaction was determined to be 33:1 by ^{1}H NMR analysis on the crude material and this ratio was unchanged after purification. R_f = 0.20 (1:40 ethyl acetate /hexanes). The ^{1}H NMR analysis of the crude reaction mixture of aza-Cope rearrangement with **8a** suggests the formation of by-product **12**, which was lost on the column when purification of the products was carried out. The ratio of (**10a+11a**):**12** is 3:1. *Spectral data for major diastereomer **10a***: ^{1}H NMR (600 MHz, $CDCl_3$) δ –0.01 (s, 3H), 0.01 (s, 3H), 0.80 (s, 9H), 0.86-0.87 (d, 3H, *J* = 6.0 Hz), 1.62-1.64 (m, 1H), 1.78-1.79 (m, 1H), 2.23-2.33 (m, 2H), 2.26 (s, 6H), 2.30 (s, 6H), 3.34-3.36 (m, 1H), 3.73-3.74 (m, 1H), 4.97-5.02 (m, 2H), 5.70-5.74 (m, 1H), 6.70 (s, 2H), 6.98 (s, 2H), 7.19 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ -4.83, -4.43, 18.14, 21.27, 21.32, 23.30, 25.89, 41.09, 46.19, 58.87, 66.09, 116.34, 125.49, 126.25, 129.61, 131.34, 136.23, 137.40, 137.45, 137.60, 140.43, 167.41; IR (thin film) 2957, 1595, 1474, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3340; $[\alpha]^{23}_D$ = +16.1 (*c* = 1.0, CH_2Cl_2) on **10a**.

aza-Cope rearrangement with (S)-VANOL catalyst. Chiral aldehyde (*R*)-**8a** (22 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived B3 catalyst according to the procedure described for (*R*)-VANOL derived catalyst above. Purification by flash column chromatography on silica gel (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **10a+11a** as a viscous oil in 44% yield (20 mg, 0.044 mmol). The diastereoselective ratio of the reaction with (*S*)-VANOL was determined to be 1:23 by ^{1}H NMR analysis fo the crude reaction

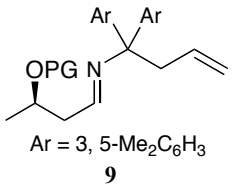
mixture and the ratio is essentially the same after purification (1:20). The ^{1}H NMR analysis of the crude reaction mixture of aza-Cope rearrangement with **8a** suggests the formation of by-product **12**, which was lost on the column when purification of the products was carried out. The ratio of (**10a+11a**):**12** is 4:1. The ^{1}H NMR spectra of the major diastereomer matches that of the minor diastereomer obtained with (*R*)-VANOL derived B3 catalyst. R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for major diastereomer **11a**:* ^{1}H NMR (600 MHz, $CDCl_3$) δ -0.11 (s, 3H), -0.04 (s, 3H), 0.79 (s, 9H), 0.96 (d, 3H, *J* = 6.0 Hz), 1.22-1.26 (m, 1H), 1.58-1.63 (m, 1H), 1.88-1.91 (m, 1H), 2.26-2.32 (m, 1H), 2.26 (s, 6H), 2.31 (s, 6H), 3.38-3.40 (m, 1H), 3.69-3.70 (m, 1H), 4.96-5.01 (m, 2H), 5.67-5.72 (m, 1H), 6.72 (s, 2H), 6.97 (s, 1H), 6.98 (s, 1H), 7.16 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ -4.75, -4.43, 18.06, 21.28, 21.32, 24.14, 25.84, 41.21, 46.54, 59.71, 67.24, 116.21, 125.55, 126.23, 129.61, 131.34, 136.30, 137.40, 137.62, 137.66, 140.57, 167.15; IR (thin film) 2957, 1595, 1474, 1199cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3335; $[\alpha]^{23}_D$ = –29.7 (*c* = 1.0, CH_2Cl_2) on **11a**.

b. Diastereoselective aza-Cope rearrangement with chiral aldehydes 8b and 8c.

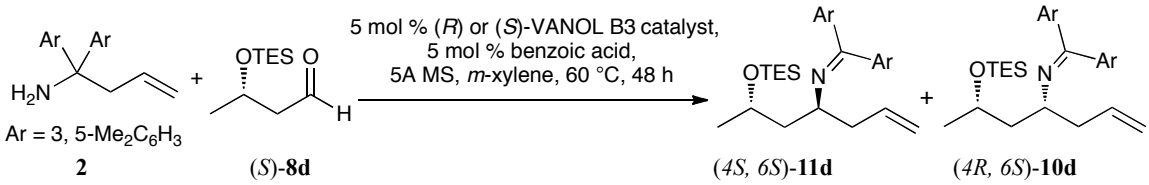


PG		(**10**+**11**):**12**
Bn	**8b**	4:1
TBDPS	**8c**	1:10

Further optimization of the alcohol protecting group were performed with **8b** and **8c** to minimize the formation of by-product **12**. Chiral aldehydes **8b** and **8c** were subjected to the diasteraoselective aza-Cope rearrangement according to the method described for aldehyde **8a**. The ^{1}H NMR analysis of the aza-Cope rearrangement with aldehydes **8b-c** were carried out on crude reaction mixture. As shown in Table 2, when the reactions were incomplete, in most cases, the unreacted material is in the form of amine **2** but in some cases a small amount of imine **9** formed from **8** and **2** is present.



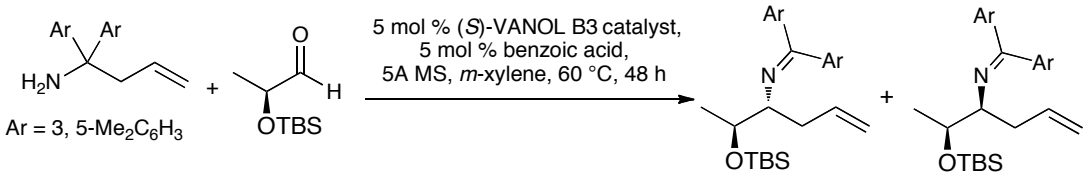
c. Diastereoselective aza-Cope rearrangement with (*S*)-3-((triethylsilyl)oxy) butanal **8d**.



aza-Cope rearrangement with (R)-VANOL catalyst. (*S*)-3-((triethylsilyl)oxy)butanal **8d** (22 mg, 0.11 mmol) was subjected to the diastereoselective aza-Cope rearrangement according to the procedure for **8a**. Purification by column chromatography on silica gel (EtOAc/hexanes 1:30) afforded a mixture of the rearrangement products (*4S, 6S*)-**11d and (*4R, 6S*)-10d** as a viscous oil in 87% yield (40 mg, 0.087 mmol). The diastereoselective ratio of the reaction was determined to be 20:1 (11d:10d) by ^{1}H NMR analysis of the crude reaction mixture and was essentially the same after purification (22:1). R_f = 0.20 (1:30 ethyl acetate /hexanes). *Spectral data for major diastereomer* (*4S, 6S*)-**11d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.51-0.55 (q, 6H, *J* = 8.0 Hz), 0.89-0.92 (t, 9H, *J* = 8.0 Hz), 1.08-1.09 (d, 3H, *J* = 6.0 Hz), 1.67-1.71 (m, 1H), 1.92-1.97 (m, 1H), 2.34-2.42 (m, 2H), 2.32 (s, 6H), 2.36 (s, 6H), 3.45-3.48 (m, 1H), 3.74-3.77 (m, 1H), 5.01-5.07 (m, 2H), 5.73-5.79 (m, 1H), 6.78 (s, 2H), 7.03-7.05 (d, 2H, *J* = 8.0 Hz), 7.22 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.92, 6.83, 21.28, 21.31, 24.23, 41.20, 46.59, 59.66, 66.90, 116.23, 125.56, 126.23, 129.59, 131.33, 136.26, 137.40, 137.57, 137.65, 140.61, 167.20; ; IR (thin film) 2957, 1595, 1458, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3362; $[\alpha]^{23}_D$ = +15.8 (*c* = 1.0, CH_2Cl_2) on (*4S, 6S*)-**11d**.

aza-Cope rearrangement with (S)-VANOL catalyst. Chiral aldehyde (*R*)-**8d** (22 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived B3 catalyst according to the procedure described for (*R*)-VANOL derived catalyst above. Purification by flash column chromatography on silica gel (1:30 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products (*4R, 6S*)-**10d and (*4S, 6S*)-11d** as a viscous oil in 74% yield (34 mg, 0.074 mmol). The diastereoselective ratio of the reaction with (*S*)-VANOL was determined to be 26:1 (10d:11d) by ^{1}H NMR analysis of the crude reaction mixture and the ratio was essentially unchanged after purification (1:23). The ^{1}H NMR spectra of the major diastereomer matches that of the minor diastereomer obtained with (*R*)-VANOL derived B3 catalyst. R_f = 0.20 (1:30 ethyl acetate /hexanes). *Spectral data for major diastereomer* (*4R, 6S*)-**10d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58-0.63 (q, 6H, *J* = 8.0 Hz), 0.89-0.90 (d, 3H, *J* = 6.0 Hz), 0.96-0.99 (t, 9H, *J* = 8.0 Hz), 1.65-1.70 (m, 1H), 1.89-1.95 (m, 1H), 2.34-2.42 (m, 2H), 2.30 (s, 6H), 2.36 (s, 6H), 3.37-3.38 (m, 1H), 3.74-3.78 (m, 1H), 5.02-5.07 (m, 2H), 5.74-5.80 (m, 1H), 6.76 (s, 2H), 7.04 (s, 2H), 7.25 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.88, 6.88, 21.26, 21.31, 23.11, 41.47, 46.42, 58.96, 65.85, 116.41, 125.56, 126.26, 129.59, 131.37, 136.08, 137.38, 137.40, 137.59, 140.40, 167.47; IR (thin film) 2957, 1595, 1458, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3363. $[\alpha]^{23}_D$ = –31.7 (*c* = 1.0, CH_2Cl_2) on (*4R, 6S*)-**10d**.

IV. Diastereoselective aza-Cope rearrangement with (*S*)-2-((*tert*-butyldimethylsilyl) oxy)propanal 13.



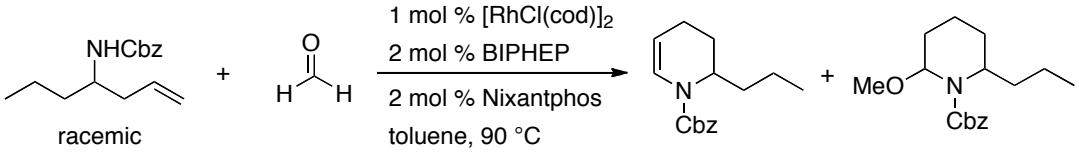
2 **13** **14** **15**

aza-Cope rearrangement with (S)-VANOL catalyst. (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal **13** (21 mg, 0.11 mmol) was subjected to the diastereoselective aza-Cope rearrangement according to the procedure for **8a** except (S)-VANOL was used. Purification by column chromatography on silica gel (EtOAc/hexanes 1:40) afforded a mixture of the rearrangement products **14+15** as a viscous oil in 71% yield (32 mg, 0.071 mmol). The diastereoselective ratio of the reaction was determined to be 12:1 by ^{1}H NMR analysis of the crude reaction mixture and the ratio was unchanged after purification. The following spectral data were collected on a 12:1 ratio of isomers. R_f = 0.20 (1:40 ethyl acetate /hexanes). *Spectral data for diastereomer **14***: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.15 (s, 3H), 0.02 (s, 3H), 0.84 (s, 9H), 1.23-1.25 (d, 3H, *J* = 6.5 Hz), 2.31 (s, 6H), 2.35 (s, 6H), 2.42-2.44 (m, 2H), 3.40-3.42 (m, 1H), 3.77-3.79 (m, 1H), 4.95-5.03 (m, 2H), 5.67-5.72 (m, 1H), 6.80 (s, 2H), 7.02 (s, 2H), 7.24 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (C=N missing) δ -4.99, -4.72, 17.99, 18.15, 19.02, 21.30, 25.83, 35.10, 67.47, 71.29, 115.66, 125.91, 126.27, 127.73, 129.37, 131.24, 133.90, 137.23, 137.39, 137.84, 140.59; IR (thin film) 2958, 1594, 1462, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{29}H_{44}NOSi$ *m/z* 450.3192 (M+1), meas 450.3181. $[\alpha]^{23}_D$ = +14.2 (*c* = 1.0, CH_2Cl_2) on **14**.

aza-Cope rearrangement with (R)-VANOL catalyst. Chiral aldehyde (*S*)-**13** (21 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived B3 catalyst according to the procedure described for (*S*)-VANOL derived catalyst above. Purification by flash column chromatography (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **14+15** as a viscous oil in 71% yield (32 mg, 0.071 mmol). The diastereoselective ratio of the reaction with (*R*)-VANOL was determined to be 2.5:1 by ^{1}H NMR analysis of the crude reaction mixture and was not changed after purification. R_f = 0.20 (1:30 ethyl acetate /hexanes). The following spectral data for **15** was extracted from the spectra data of the 2.5:1 mixture with the aid of the 12:1 mixture described above. *Spectral data for diastereomer **15**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.12-1.13 (d, 3H, *J* = 6.5 Hz), 2.31 (s, 6H), 2.35 (s, 6H), 2.42-2.44 (m, 2H), 3.29-3.32 (m, 1H), 3.96-3.99 (m, 1H), 4.95-5.03 (m, 2H), 5.67-5.72 (m, 1H), 6.78 (s, 2H), 7.00 (s, 2H), 7.23 (s, 2H).

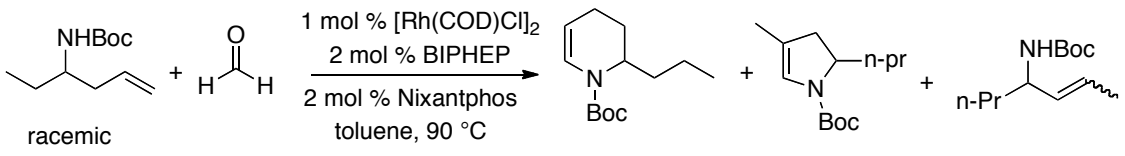
V. Optimization of the intramolecular amidocarbonylation with formaldehyde.

a) Typical procedure for intramolecular amidocarbonylation with formalin.



To a 50 mL Schlenk flask equipped with a T-shaped threaded high vacuum Teflon valve, containing a stirring bar, was added $[RhCl(cod)]_2$ (2.5 mg, 0.0050 mmol), BIPHEP (5.5 mg, 0.010 mmol), Nixantphos (6.0 mg, 0.010 mmol) and 3 mL of toluene under nitrogen. After adding racemic **16a**[11] (0.12 g, 0.50 mmol) and 37% formalin (0.19 mL, 2.5 mmol), the mixture was deoxygenated by the freeze-pump-thaw method (–196 °C to 25 °C, 3 cycles). The Schlenk flask was sealed under vacuum with Teflon valve at –196 °C and then warmed to room temperature. The flask was then heated to 90 °C and stirring continued for 22 h. Upon completion, ^{1}H NMR analysis on the crude reaction mixture showed the formation of the desired product **17a** and the by-product **18** with a ratio of 5:3. The formation of **18** was due to the presence of 15% methanol as a stabilizer in the commercial formalin. The mixture was concentrated and the major product purified by column chromatography on silica gel (1:12 EtOAc/hexanes) to afford compound **17a** as a viscous oil in 46% yield (60 mg, 0.23 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectrum. *Spectral data for **17a**:* ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84-0.94 (m, 3H), 1.24-1.40 (m, 3H), 1.49-1.53 (m, 1H), 1.69-1.83 (m, 1H), 1.91-1.96 (m, 1H), 2.02-2.07 (m, 1H), 4.24 (brs, 0.4H), 4.33 (brs, 0.5H), 4.81 (brs, 0.5H), 4.92 (brs, 0.4H), 5.16 (s, 2H), 6.72-6.74 (d, 0.5H, *J* = 6.5 Hz). 6.82-6.83 (d, 0.4H, *J* = 6.5 Hz), 7.30-7.37 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.92, 13.99, 17.37, 17.54, 19.11, 23.90, 24.03, 32.63, 33.05, 50.16, 50.38, 67.25, 105.84, 106.21, 123.52, 123.99, 127.89, 127.99, 128.29, 128.42, 136.35, 136.43, 152.92, 153.45. IR (thin film) 3020, 2872, 1705, 1415, 1327 cm^{-1}. HRMS (ES+) calcd for $C_{16}H_{22}NO_2$ *m/z* 260.1651 (M+1), meas 260.1659. Compound **18** was observed in the ^{1}H NMR spectrum of the crude reaction mixture but was not isolated, but the following absorptions have been reported for this compound: δ = 3.25 (s, 1.5H), 3.32 (s, 1.5H), 4.19 (s, 0.5H), 4.27 (s, 0.5 H).[9]

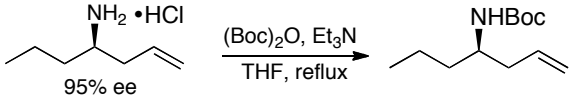
2) Typical procedure for intramolecular amidocarbonylation with paraformaldehyde



To a 50 mL Schlenk flask, containing a stirring bar, was added $[RhCl(cod)]_2$ (10 mg, 0.020 mmol), BIPHEP (22 mg, 0.040 mmol), Nixantphos (24 mg, 0.040 mmol) and 12 mL of toluene under nitrogen.

After adding racemic **16b**[12] (0.42 g, 2.0 mmol) and paraformaldehyde (0.30 g, 10 mmol), the mixture was deoxygenated by the freeze-pump-thaw method (–196 °C to 25 °C, 3 cycles). The Schlenk flask was sealed under vacuum with the Teflon valve at –196 °C and then warmed to room temperature. The flask was then heated to 90 °C and stirring continued for 24 h. Upon completion, the mixture was concentrated and the products purified by column chromatography on silica gel (1:40 EtOAc/hexanes). Compound **17b** was obtained as a viscous oil in 73% yield (0.33 g, 1.5 mmol). R_f = 0.25 (1:40 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectrum. *Spectral data for **17b**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.24-1.42 (m, 4H), 1.46 (s, 9H), 1.63-1.78 (m, 2H), 1.88-2.06 (m, 2H), 4.13 (brs, 0.44H), 4.26 (brs, 0.5H), 4.73 (bs, 0.55H), 4.84 (brs, 0.40H), 6.64 (d, 0.5H, *J* = 7.0 Hz), 6.78 (d, 0.4H, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.06, 19.21, 23.99, 24.27, 28.35, 32.74, 33.22, 49.42, 50.33, 80.21, 104.61, 105.08, 123.96, 124.33; IR (thin film) 2961, 1703, 1653, 1410 cm^{-1}; HRMS (ES+) calcd for $C_{13}H_{24}NO_2$ *m/z* 226.1729 (M+1), meas 226.1723. Compound **19** was isolated as a viscous oil in 13% yield (58 mg, 0.26 mmol). R_f = 0.18 (1:40 ethyl acetate /hexanes) and the ^{1}H NMR spectrum revealed the presence of a 2:3 mixture of rotamers. *Spectral data for **19**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.5 Hz), 0.95-1.78 (m, 4H), 1.45 (s, 9H), 1.65 (s, 3H), 2.08 (brs, 1H), 2.73 (brs, 1H), 4.02 (brs, 0.4H), 4.10 (brs, 0.6H), 6.10 (brs, 0.6H), 6.22 (brs, 0.4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.02, 18.05, 28.49, 36.45, 37.10, 40.45, 41.34, 57.46, 79.45, 117.1, 123.96; IR (thin film) 2965, 1704, 1653, 1418 cm^{-1}; HRMS (ES+) calcd for $C_{13}H_{24}NO_2$ *m/z* 226.1729 (M+1), meas 226.1732. Compound **20** was isolated as a viscous oil in 12% yield (51 mg, 0.24 mmol). *Spectral data for **20**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz), 1.32-1.39 (m, 4H), 1.47 (s, 9H), 1.69 (d, 3H, *J* = 7.0 Hz), 4.03 (brs, 1H), 4.43 (brs, 1H), 5.32-5.36 (m, 1H), 5.56-5.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.87, 17.60, 18.96, 28.41, 37.88, 52.12, 78.99, 125.55, 132.11, 155.34; IR (thin film) 3342, 3005, 2964, 1690, 1522 cm^{-1}; HRMS (ES+) calcd for $C_{12}H_{24}NO_2$ *m/z* 214.1729 (M+1), meas 214.1725.

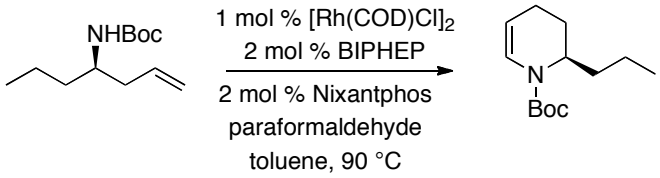
VI. Total synthesis of (-)-Coniine.



(*R*)-21 **(*R*)-16**

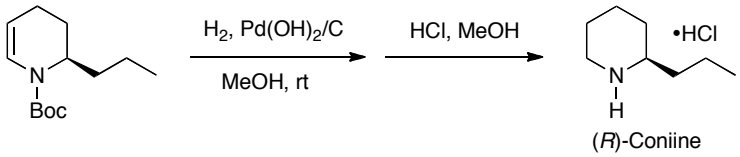
To a 100 mL round-bottomed flask was added amine **21** (0.34 g, 3.0 mmol) and $(Boc)_2O$ (0.75 g, 3.3 mmol). The mixture was dissolved in THF (30 mL), followed by the addition of triethylamine (0.9 mL, 6 mmol). The mixture was stirred at room temperature for 24 hours. Upon completion, the mixture was concentrated and the product was purified by column chromatography on silica gel (1:12 EtOAc/hexanes) to afford (*R*)-*tert*-butyl hept-1-en-4-ylcarbamate ***(R)*-16b** in 76% yield (0.46 g, 2.3 mmol) as a colorless oil. R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for **(R)*-16b**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 8.0 Hz), 1.26-1.40 (m, 13H), 2.11-2.22 (m, 2H), 3.60 (brs, 1H), 4.30 (brs, 1H), 5.01-5.05 (m, 2H), 5.70-5.76 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.92, 19.11, 28.37, 36.84, 39.53, 49.77, 78.84, 117.45, 134.56, 155.54. IR (thin film) 3341, 3005, 2961, 1687, 1525 cm^{-1}. $[\alpha]^{23}_D$ = +15.8 (*c* = 1.0, $CDCl_3$) on

material derived from 95% ee (***R*)-21.**



(*R*)-16b **(*R*)-17b**

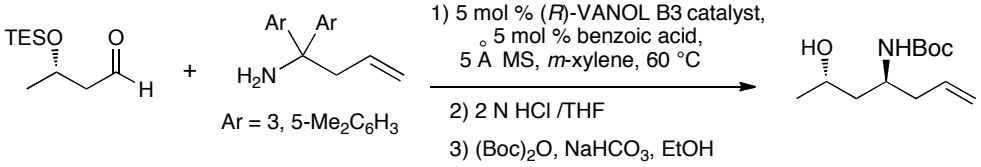
(*R*)-*tert*-butyl hept-1-en-4-ylcarbamate **(*R*)-16b** (0.250 g, 1.25 mmol) was reacted with paraformaldehyde according to the general procedure described in part 2, section IV. The reaction was complete in 40 hours. Upon completion, the reaction mixture was concentrated and the product was purified by column chromatography on silica gel (1:40 EtOAc/hexanes) to afford (*R*)–**17b** in 71% yield (0.20 g, 0.89 mmol) as a colorless oil. R_f = 0.20 (1:40 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H and ^{13}C NMR spectrum. *Spectral data for* (*R*)–**17b***:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.24-1.42 (m, 4H), 1.46 (s, 9H), 1.63-1.78 (m, 2H), 1.88-2.06 (m, 2H), 4.13 (brs, 0.44H), 4.26 (brs, 0.5H), 4.73 (brs, 0.55H), 4.84 (brs, 0.40H), 6.64 (d, 0.5H, *J* = 7.0 Hz), 6.78 (d, 0.4H, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (carbonyl missing) δ 14.06, 17.62, 19.21, 23.99, 24.27, 28.35, 32.74, 33.22, 49.42, 50.33, 80.21, 104.61, 105.08, 123.96, 124.33. IR (thin film) 2961, 1703, 1653, 1410 cm^{-1}. $[\alpha]^{23}_D$ = – 60.3 (*c* = 1.0, $CDCl_3$) on material derived from 95% ee (***R*)-16b**.



(*R*)-17b **22**

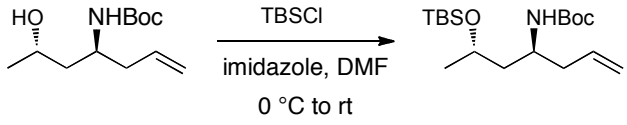
To a 100 mL round bottom flask fitted with a magnetic stir bar was added (*R*)-**17b** (0.2 g, 0.9 mmol), $Pd(OH)_2$ (0.400 g, 0.225 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture) and methanol (27 mL). The flask was then equipped with a 3-way valve connected to vacuum and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 12 h. It was then filtered through a Celite pad and to the methanol solution was then added 2 mL of 2N HCl at room temperature. Stirring was continued for 6 hours and the mixture was concentrated thereafter by rotary evaporation to give (*R*)-Coniine hydrochloride salt **22** which was further dried at 40 °C under vacuum until no weight loss was observed to give a white solid in 91 % yield (0.13 g, 0. 82 mmol, mp 213-215 °C, lit. 215-216 °C[8]). *Spectral data for **23**[8]:* ^{1}H NMR (DMSO, 500 MHz) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.29-1.49 (m, 5H), 1.59-1.82 (m, 5H), 2.81 (dd, 1H, *J* = 22.5, 11.0 Hz), 2.95 (brs, 1H), 3.15 (d, 1H, *J* = 12.5 Hz), 8.46 (d, 2H, *J* =9.3 Hz); ^{13}C NMR (125 MHz, DMSO) δ 13.74, 17.78, 21.71, 21.81, 27.76, 34.94, 43.68, 55.39. $[\alpha]^{23}_D$ = – 6.3 (*c* = 1.0, EtOH) on material derived from 95% ee (***R*)-17b**. These data match that previously reported for this compound. [8]

VII. Total synthesis of (+)-Sedridine.



(*S*)-8d **2** **26**

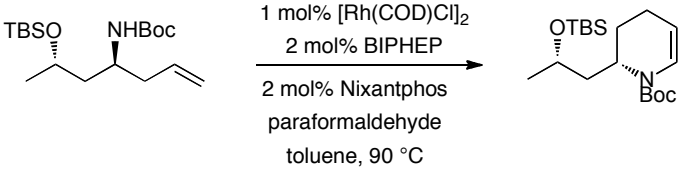
(*S*)-3-((Triethylsilyl)oxy)butanal **8d** (0.70 g, 2.5 mmol) was subjected to the aza-Cope rearrangement according to the general procedure described in section III except that 0.7 g of 5Å MS was used. Upon completion, *m*-xylene was removed by rotary evaporation and the reaction mixture was dissolved in THF (10 mL) and 2N HCl (5.0 mL) was added for hydrolysis. Hydrolysis was finished in 12 h and THF was then removed by rotary evaporation. To the residue was added another 4 mL of H_2O and the aqueous phase was washed with EtOAc (3 mL x 3). The aqueous phase was concentrated to give an off-white solid which was dissolved in EtOH (20 mL). $NaHCO_3$ and $(Boc)_2O$ were added at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then the ice-bath was removed. Stirring was maintained for 24 h at room temperature. Upon completion, EtOH was removed and the residue was dissolved in 20 mL of H_2O. The aqueous phase was extracted with EtOAc (10 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes) to give *tert*-butyl ((4*S*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **26** as a light yellow viscous oil and as a single diastereomer in 72% yield (0.41 g, 1.8 mmol) over three steps. R_f = 0.20 (1:4 ethyl acetate /hexanes). *Spectral data for **26**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 6.0 Hz), 1.29-1.53 (m, 11 H), 2.16-2.23 (m, 2H), 3.76 (brs, 1H), 3.86 (brs, 1H), 4.50 (brs, 1H), 5.05-5.10 (m, 2H), 5.70-5.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.70, 28.31, 39.71, 45.58, 46.88, 63.58, 79.85, 118.06, 134.08, 157.08. IR (thin film) 3339, 3078, 2976, 1684, 1531 cm^{-1}. HRMS (ES+) calcd for $C_{12}H_{24}NO_3$ *m/z* 230.1756 (M+1), meas 230.1752. $[\alpha]^{23}_D$ = +22.9 (*c* = 1.0, CH_2Cl_2) on **26**.



26 **27**

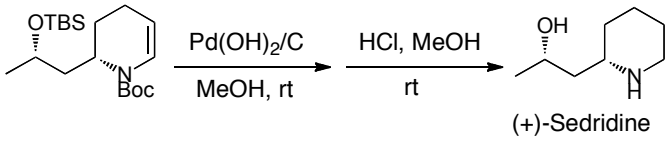
tert-Butyl ((4*S*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **26** (0.62 g, 2.7 mmol) and TBSCl (0.48 g, 3.2 mmol) were dissolved in 7 mL of dry DMF. Imidazole (0.23 g, 3.2 mmol) was added at 0 °C. The ice-bath was then removed and the reaction mixture was stirred at room temperature for 18 h. Upon completion, 40 mL of brine was added to quench the reaction. Stirring was maintained for 5 minutes and the aqueous phase was extracted with hexanes (8 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel (1:8 EtOAc/hexanes) to give *tert*-butyl ((4*S*, 6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **27** in 86% yield (0.80 g, 2.3 mmol) as a white solid (mp 63-64 °C). R_f = 0.50 (1:8 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectra. *Spectral data for **27**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (t, 6H, *J* = 4.5

Hz), 0.87 (s, 9H), 1.12 (d, 3H, *J* = 6.0 Hz), 1.40 (s, 9H), 1.57-1.61 (m, 1H), 2.19-2.23 (m, 1H), 2.30 (brs, 2H), 3.71, (brs, 1H), 3.98 (brs, 1H), 4.97 (brs, 1H), 5.01-5.05 (m, 2H), 5.72-5.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.91, -4.17, 17.93, 23.94, 25.90, 28.41, 39.64, 42.67, 47.80, 66.10, 78.63, 117.22, 134.90, 155.38. IR (thin film) 3316, 2926, 1691, 1531, 1365 cm^{-1}. HRMS (ES+) calcd for $C_{18}H_{38}NO_3Si$ *m/z* 344.2621 (M+1), meas 344.2625. $[\alpha]^{23}_D$ = +49.4 (*c* = 1.0, CH_2Cl_2) on **27**.



27 **28**

tert-Butyl ((4*S*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **27** (0.51 g, 1.5 mmol) was subjected to the intramolecular amidocarbonylation with paraformaldehyde according to the typical procedure in part 2, section IV. Purification by column chromatography on silica gel (1:30 EtOAc/hexanes) afforded (*S*)-*tert*-butyl 2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2*H*)-carboxylate **28** in 78% yield (0.410 g, 1.17 mmol) as a colorless oil. R_f = 0.30 (1:30 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in the ^{1}H NMR spectrum. *Spectral data for **28**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (t, 6H, *J* = 4.5 Hz), 0.87 (s, 9H), 1.14 (d, 3H, *J* = 4.0 Hz), 1.45-1.52 (m, 10H), 1.64-1.68 (m, 2H), 1.77-1.83 (m, 1H), 1.90-1.94 (m, 1H), 2.02-2.09 (m, 1H), 3.87 (t, 1H, *J* = 6.0 Hz), 4.07 (brs, 0.4H, rotamer), 4.28 (brs, 0.5H), 4.73 (brs, 0.5H), 4.84 (brs, 0.4H, rotamer), 6.62 (d, 0.5H, *J* = 8.0 Hz), 6.76 (d, 0.4H, *J* = 8.0 Hz, rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.71, -4.66, -4.48, 17.33, 17.66, 18.04, 23.44, 23.77, 23.87, 24.39, 25.84, 25.87, 28.30, 28.44, 40.73, 40.95, 47.70, 48.85, 66.63, 80.24, 80.38, 104.47, 104.71, 123.97, 124.35, 151.80, 152.26 . IR (thin film) 2927, 1699, 1367, 1169 cm^{-1}. HRMS (ES+) calcd for $C_{19}H_{38}NO_3Si$ *m/z* 356.2621 (M+1), meas 356.2606. $[\alpha]^{23}_D$ = – 7.5 (*c* = 1.0, CH_2Cl_2) on **28**.

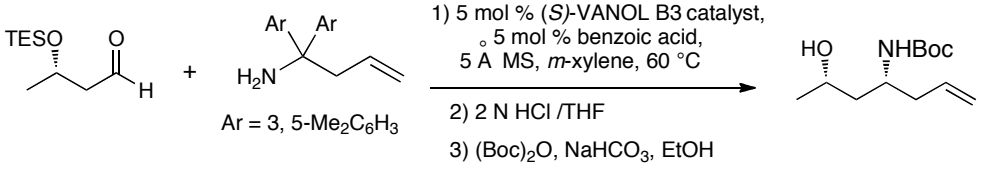


28

To a 100 mL round bottom flask fitted with a magnetic stir bar was added (*S*)-*tert*-butyl 2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2*H*)-carboxylate **28** (0.39 g, 1.1 mmol), $Pd(OH)_2$ (0.49 g, 0.27 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture) and methanol (32 mL). The flask was then equipped with a 3-way valve connected to vacuum and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 12 h. It was then filtered through a Celite pad and to the methanol solution was then added 2 mL of 2N HCl at room temperature. Stirring was continued for 6 hours and the mixture was concentrated thereafter by rotary

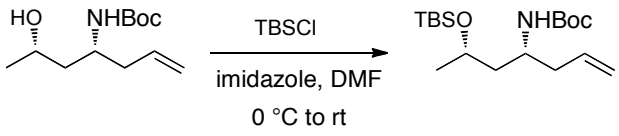
evaporation to give (+)-Sedridine hydrochloride salt as a white solid which was dissolved in 10 mL of 1N NaOH and extracted with EtOAc (3 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give (+)-Sedridine in 83% yield (0.13 g, 0.91 mmol) as a white solid (mp 82-83 °C, lit. 83-84 °C[11]). *Spectral data for* ***(+)-Sedridine****[11]:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.0 Hz), 1.31-1.35 (m, 3H), 1.7-1.43 (m, 1H), 1.50-1.55 (m, 3H), 1.76-1.77 (m, 1H), 2.58 (td, 1H, *J* =12.0, 3.0 Hz), 2.81-2.83 (m, 1H), 3.01 (dd, 1H, *J* = 11.5, 2.5 Hz), 3.05-3.35 (brs, 1H), 4.04-4.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.57, 24.73, 26.10, 31.38, 43.81, 46.90, 54.74, 65.04; $[\alpha]^{23}_D$ = +20.8 (*c* = 1.0, EtOH), Lit.[12] $[\alpha]^{25}_D$ = +28.36, (*c* = 1.13, EtOH). These spectral data match that reported for this compound.[12]

VIII. Total synthesis of (+)-Allosedridine.



(*S*)-8d **2** **23**

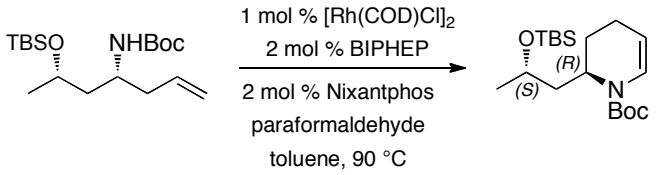
(+)-Allosedridine was obtained in a similar manner to that described for (+)-sedridine utilizing the boroxinate catalyst **6** derived from (*S*)-VANOL. (*S*)-3-((Triethylsilyl)oxy)butanal (0.56 g, 2.0 mmol) was subjected to the aza-Cope rearrangement according to the general procedure described for the synthesis of compound **26** except that (*S*)-VANOL B3 catalyst was used. Purification by column chromatography on silica gel (1:2 EtOAc/hexanes) afforded *tert*-butyl ((4*R*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **23** in 60% yield (0.28 g, 1.2 mmol) and as a single diastereomer as a light yellow viscous oil. R_f = 0.20 (1:2 ethyl acetate /hexanes). *Spectral data for* ***23****:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 6.0 Hz), 1.45 (s, 9H), 1.53-1.65 (m, 2H), 2.24-2.31 (m, 2H), 2.48 (brs, 1H), 3.76 (brs, 1H), 3.94 (t, 1H, *J* =5.0 Hz), 4.61 (brs, 1H), 5.09-5.13 (m, 2H), 5.74-5.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.81, 28.38, 40.21, 44.31, 48.69, 66.48, 79.50, 118.10, 134.11, 156.2. IR (thin film) 3339, 2978, 1686, 1527 cm^{-1}. HRMS (ES+) calcd for $C_{12}H_{24}NO_3$ *m/z* 230.1756 (M+1), meas 230.1765. $[\alpha]^{23}_D$ = – 7.4 (*c* = 0.5, CH_2Cl_2) on **23**.



23 **24**

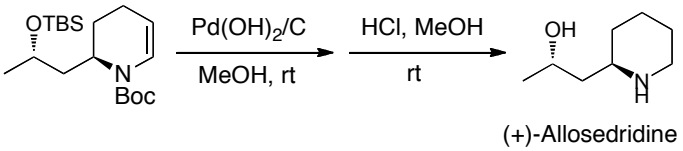
tert-Butyl ((4*R*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **23** (0.25 g, 1.1 mmol) was reacted with TBSCl as described for the synthesis of compound **27**. Purification of the product by column chromatography on silica gel (1:8 EtOAc/hexanes) afforded *tert*-butyl ((4*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **24** in 74% yield (0.28 g, 0.82 mmol) as a clear viscous oil. R_f = 0.40 (1:8 ethyl acetate /hexanes). *Spectral data for* ***24****:* ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.02 (s, 6H), 0.81 (s, 9H), 1.10 (d, 3H, *J* = 6.0 Hz), 1.35 (s, 9H), 1.48 (brs, 2H), 2.18 (brs, 2H), 3.56-3.58 (m, 1H), 3.82 (q, 1H, *J* = 6.0 Hz), 4.55 (brs, 1H), 4.99 (d, 2H, *J* = 12.5 Hz), 5.66-5.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.82, -4.38, 17.93,

23.81, 25.83, 28.31, 39.79, 44.37, 48.27, 66.82, 78.67, 117.51, 134.38, 155.29. IR (thin film) 2959, 1705, 1498, 1174 cm^{-1}. HRMS (ES+) calcd for $C_{18}H_{38}NO_3Si$ *m/z* 344.2621 (M+1), meas 344.2631. $[\alpha]^{23}_D$ = –10.2 (*c* = 1.0, CH_2Cl_2) on **24**.



24 **25**

tert-Butyl ((4*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **24** (0.26 g, 0.75 mmol) was subjected to intramolecular amidocarbonylation with paraformaldehyde according to the typical procedure in part 2, section IV. Purification of the product by column chromatography on silica gel (1:30 EtOAc/hexanes) afforded *(R)-tert-butyl 2-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2H)-carboxylate* **25** in 72% yield (0.19 g, 0.54 mmol) as a clear viscous oil. R_f = 0.30 (1:30 ethyl acetate /hexanes). A 1:1 mixture of rotamers was observed in the ^{1}H NMR spectrum. *Spectral data for **25**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.007 (s, 6H), 0.85 (s, 9H), 1.18-1.23 (m, 3H), 1.36-1.42 (m, 1H), 1.46 (s, 9H), 1.65-2.35 (m, 5H), 3.86 (d, 1H, *J* = 5.5 Hz), 4.23 (brs, 0.6H), 4.33 (brs, 0.4H), 4.77 (brs, 0.5H), 4.85 (brs, 0.5H), 6.62 (d, 0.4H, *J* = 7.0 Hz), 6.77 (d, 0.5H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.85, -4.55, -4.29, 17.61, 17.84, 18.10, 23.49, 24.07, 24.19, 25.34, 25.88, 28.38, 28.51, 29.68, 40.30, 41.14, 46.69, 47.84, 65.50, 66.26, 80.23, 80.36, 104.87, 105.15, 124.08, 152.11, 152.46. IR (thin film) 2957, 1705, 1653, 1410 cm^{-1}. HRMS (ES+) calcd for $C_{19}H_{38}NO_3Si$ *m/z* 356.2621 (M+1), meas 356.2629 $[\alpha]^{23}_D$ = +25.1 (*c* = 0.5, CH_2Cl_2) on **25**.



25

(R)-tert-Butyl-2-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2H)-carboxylate ***25*** (0.17 g, 0.50 mmol) was subjected to the reduction conditions followed by hydrolysis to remove the protecting groups as described for the synthesis of (+)-Sedridine. The product was obtained in 74% yield (52 mg, 0.37 mmol) as white crystals (mp 65-66 °C, lit. 62 °C[12]). *Spectral data for **(+)-Allosedridine**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01-1.06 (m, 1H), 1.08 (d, 3H, *J* = 6.0 Hz), 1.11-1.26 (m, 2H), 1.41-1.49 (m, 2H), 1.53-1.59 (m, 2H), 1.74-1.78 (m, 1H), 2.50-2.56 (m, 1H), 2.63-2.68 (m, 1H), 2.98 (dd, 1H, *J* = 10, 4.5 Hz), 3.93-3.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.80, 24.48, 27.36, 34.37, 44.40, 45.99, 58.14, 69.03. $[\alpha]^{23}_D$ = +15.0 (*c* = 1.0, MeOH), Lit.[12] $[\alpha]^{25}_D$ = +17.10, (*c* = 1.55, MeOH).

References:

1) Schwehm, C.; Wohland, M.; Maier, M. E. *Synlett* **2010**, *12*, 1789-1792.

2) Leclair, C. A.; Boxer, M. B.; Thomas, C. J.; Maloney, D. J. *Tetrahedron Lett.* **2010**, *51*, 6852-6855.

3) Jogireddy, R.; Barluenga, S.; Winssinger, N.; *Chemmedchem* **2010**, *5*, 670-673.

4) Hiroki, F.; Isamu, S. *Org. Lett.* **2008**, *10*, 3153-3156.

5) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem*. **2004**, *69*, 4626-4647.

6) Seebach. D.; Braendli, U.; Schurrenberger, P.; Przybylski, M. *Helv. Chim Acta* **1988**, *71*, 155-167.

7) a). Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **121**, 2035-2044; b). Borg, T.; Tuzina, P.; Somfai, P. *J. Org. Chem*. **2011**, *76*, 8070-8075.

8) Ren, H.; Wulff, W. D. *J. Am. Chem. Soc*. **2011**, *133*, 5656-5659.

9) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J.Org. Chem*. **2010**, *75*, 8670-8673.

10) Vilaivan, T. *J. Org. Chem.* **2005**, *70*, 3464-3471.

11) Murahashi, S.; Imada, Y.; Kohno, M.; Kawakami, T. S*ynlett*, **1993**, 395.

12) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594-8601.