Published in final edited form as:

Tetrahedron. 2010 June 26; 66(26): 4701–4709. doi:10.1016/j.tet.2010.03.015.

An Enantioselective Approach to the *Securinega* Alkaloids: The Total Synthesis of (+)-Norsecurinine and (+)-Allonorsecurinine†

Matthew R. Medeiros^a and John L. Wood^b

^aDepartment of Chemistry, Yale University, New Haven, CT 06520, USA

^bDepartment of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

Keywords

Securinga Alkaloids; Norsecurinine; Allonorsecurinine; Total Synthesis; Rhodium Carbenoid; Claisen Rearrangement

1. Introduction

The *Securinega* alkaloids¹ are a small family of natural products isolated from the Euphorbiaceae family of plants (Figure 1). Structurally, they typically consist of either an indolizidine (securinine-type, **1**) or pyrrolizidine (norsecurinine-type, **2**) framework with an α , β , γ , δ -unsaturated bicyclic lactone moiety. Additionally, skeletally rearranged (i.e., secu'amamine, **5**),² A-ring methoxylated (i.e., phyllanthine, **4**)³, oxidized (i.e., phyllantidine, **6** and nirurine, **7**),⁴ and dimeric (i.e., flueggenines, **8** and **9**)⁵ congeners have been reported. The enantiomers of some *Securinega* alkaloids, virosecurinine (**3**),⁶ viroallosecurinine,⁷ and (–)-norsecurinine,⁸ have also been isolated from natural sources.

A broad spectrum of biological activities coupled with synthetically challenging morphologies has prompted many synthetic efforts towards this family of metabolites.^{9–15} We became interested in this family of alkaloids upon recognizing the presence of a masked tertiary alcohol flanked by two carbonyls embedded in their structures (grayed bonds in **2**). Conceivably, a flexible route to this functional group would provide a gateway to access any member of the *Securinega* alkaloids. Accordingly, we reckoned the enantioselective rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration domino process developed in our laboratory¹⁶ would provide an interesting stereo-controlled approach to the desired tertiary alcohol functionality. Herein, we report the application of this domino sequence to the synthesis of (+)-norsecurinine¹⁷ and (+)-allonorsecurinine.⁹

†This manuscript is dedicated to Professor Brian M. Stoltz on the occasion of his receiving the Tetrahedron Young Investigator Award.

© 2010 Elsevier Ltd. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary material Copies of ¹H and ¹³C NMR spectra and experimental procedures for the synthesis of (+)-allonorsecurinine are available online at——.

2. Results and Discussion

2.1 Retrosynthetic analysis for (+)-norsecurinine

Retrosynthetically, we envisioned completing the synthesis of (+)-norsecurinine with annulation of the butenolide from α -hydroxy enone **10** (Scheme 1).^{14,18} Tricyclic enone **10** was imagined to arise from a halogenation-initiated cyclization of ketone **11** followed by β -elimination.¹⁵ Cyclohexene **11** would be prepared by ring-closing metathesis of allyl ketone **12**, while the A-ring would be generated from **13** via a reductive amination. Tertiary alcohol **13** would result from the key domino process using (*S*)-(+)-3-buten-2-ol ((+)-**14**).¹⁹ Finally, α -diazo- β -ketoester **15** could easily be accessed from commercially available materials.

2.2 Synthesis of (+)-norsecurinine

Our synthesis commenced with the opening of *N*-Boc-2-pyrrolidinone (**16**) with ethyl lithiodiazoacetate²⁰ followed by Boc protection under standard conditions to yield diazoester **15** (Scheme 2). The optimal conditions determined in our original studies of the O–H insertion/Claisen rearrangement involved heating a solution of the diazoester, allylic alcohol and 0.1–1.0 mol% $\text{Rh}_2(\text{OAc})_4$ in benzene at reflux.²¹ In our current preliminary studies, we found that heating the reaction to reflux in toluene provided more consistent results (data not shown). Conducting the O–H insertion/Claisen rearrangement using ($\pm$)-**14** in the presence of 1 mol% $\text{Rh}_2(\text{OAc})_4$ in toluene at reflux resulted in 37% yield (unoptimized) of desired tertiary alcohol **19**. Encouraged by this result we attempted to effect the 1,2-allyl migration by treatment of **19** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temperature. Unfortunately, these conditions yielded an intractable mixture of compounds. A screen of alternative Lewis and protic acids primarily resulted in recovered starting material or decomposition (see chart in Scheme 2). The problems encountered with our attempt to incorporate the requisite amine early in the synthesis prompted us to investigate an alternative route.

Reviewing the retrosynthesis, it seemed feasible to begin the synthesis with a functional group that could be converted to an amine subsequent to the domino sequence. To this end, butyrolactone (**20**) was opened with ethyl lithiodiazoacetate and the resulting primary alcohol was tosylated to provide **21** in 62% yield over the two steps (Scheme 3). After some experimentation, we found that conducting the key domino process in one pot²² with ($\pm$)-**14** in the presence of 0.1 mol% $\text{Rh}_2(\text{OAc})_4$ in toluene at reflux followed by addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temperature provided tertiary alcohol **22** in 69% yield. Treatment of **22** with NaN_3 in DMF cleanly provided azide **23**, which was subjected to PPh_3 in wet THF to initiate a Staudinger reduction/aza-Wittig sequence²³ providing imine **24**. A minor byproduct observed under these conditions was cyclopropane **25**. Attempts to prevent the formation of **25** by changing temperature, equivalents of water or phosphine proved fruitless.

Although an effective route to imine **24** had been developed, some difficulties encountered with scale-up and variable yields for the opening of butyrolactone with ethyl lithiodiazoacetate led us to seek an alternative strategy. We found that adapting a procedure reported by Staudinger²⁴ and Bestmann²⁵ for the coupling of acid chlorides with diazoesters cleanly provided chloride **27** in high yield after removal of the byproduct (ethyl chloroacetate) by distillation at low pressure (Scheme 4). Chloride **27** was subjected to the optimized domino process conditions, 1.05 eq (+)-**14** (98:2 er)²⁶ and 0.1 mol% $\text{Rh}_2(\text{OAc})_4$, to give tertiary alcohol **28** in 63% yield and 95:5 er.²⁷ Substitution of the primary chloride with azide proceeded cleanly allowing the Staudinger reduction/aza-Wittig sequence to be carried out without purification of intermediate azide (+)-**23**, providing imine **24** in 76% yield over the two steps.

Proceeding forward, imine **24** was reduced with NaBH₄ in MeOH to yield an inseparable mixture of diastereomeric amino esters **29**, which were directly converted to *t*-butyl carbamates **30** with Boc₂O and DMAP (Scheme 5). The derived carbamates proved separable by simple column chromatography and the major isomer (**30a**) was reduced to aldehyde **31a** by treatment with DIBALH at low temperature, albeit in moderate yield. Warming the reaction above 0 °C resulted in a complex mixture of products.

To circumvent this problem we found that reduction of imine **24** with NaBH₄ in EtOH followed by oxidation of the inseparable mixture of diols **32** with IBX provided a separable mixture of aldehydes **31** in a more convenient manner (Scheme 6).²⁸

Prior to continuing with the synthesis, the stereochemical outcome of the NaBH₄ reduction was delineated (Scheme 7). To this end, carbamate esters **30a** and **30b** were individually subjected to DIBALH at room temperature and the resulting crude diols were treated with NaH in THF. Nuclear Overhauser effect (nOe) analysis of cyclic carbamates **5S**, **4S-33a** and **5R-4S-33b** revealed the illustrated stereochemical relationships (relevant nOes indicated with double headed arrows).

Having assigned the stereochemistry, the synthesis continued with alkylation of aldehyde **31a** using allylmagnesium bromide to furnish **34** followed by ring-closing metathesis using Grubbs's second generation catalyst to provide cyclohexene **35** as a mixture of diastereomers (Scheme 8). Given that the newly produced hydroxyl stereocenter would eventually undergo oxidation, the mixture of diastereomers was advanced without separation. Adopting a strategy used by Liras and coworkers for their synthesis of (±)-securinine,¹⁵ cyclohexene **35** was treated with Br₂ at 0 °C to yield dibromide **36** as a single diastereomer based on ¹H NMR analysis. We found that dropwise addition of Br₂ at 0 °C was essential to avoid the formation of **37** obtained from attack of the carbamate carbonyl on the secondary bromide.²⁹ After some experimentation, we found that Swern oxidation of alcohol **36** supplied enone **38** in good yield. During their syntheses of (–)-securinine, Honda¹³ and Figueredo¹¹ had demonstrated that the stereochemistry of the bromide was inconsequential for cyclization, and it was presumed that this would apply to norsecurinine as well.

With enone **38** in hand, we were ready to construct the tricyclic core of norsecurinine (Scheme 9a). After some experimentation, we found that removal of the Boc group with excess TFA followed by addition of Et₃N furnished unstable tricycle **10**. Some attempts were made to convert hydroxy enone **10** to norsecurinine directly using the Bestmann ketene ylide (**39**),³⁰ however, these attempts failed. Weinreb and coworkers also noted the recalcitrance of a similar substrate towards acylation with the Bestmann reagent.¹² Consequently, we turned to a two step procedure involving DCC mediated acylation of the tertiary alcohol with diethylphosphonoacetic acid followed by intramolecular Horner-Wadsworth-Emmons reaction to complete the synthesis of (+)-norsecurinine (**2**). Spectral data for (+)-**2** were in accord with that reported in the literature. The synthesis of (+)-allonorsecurinine (**40**) was realized utilizing a similar route from aldehyde **31b** (Scheme 9b).

3. Conclusion

We have presented the total synthesis of (+)-norsecurinine and (+)-allonorsecurinine highlighting an enantioselective rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration domino process. Targeting the tertiary alcohol moiety in these molecules provides a flexible strategy that will allow access to other members of the *Securinega* family of alkaloids. The synthesis of these compounds is underway.

4. Experimental

4.1 General Methods

Unless otherwise stated, reactions were stirred in flame-dried glassware under an atmosphere of nitrogen. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous *N,N*-dimethylformamide was purchased from Sigma-Aldrich and stored under nitrogen atmosphere. Commercially available reagents were obtained from Sigma-Aldrich, Strem, or Alfa Aesar and were used as received. (*S*)-(+)-3-buten-2-ol ((+)-**14**) was synthesized according to a procedure by Klingler and Psiorz.¹⁹ (Triphenylphosphoranylidene)-ketene (**39**) was synthesized according to the procedure described by Schobert.³¹ All known compounds were identified by comparison of NMR spectra to those reported in the literature.

Thin layer chromatography was performed using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 µm). Developed plates were visualized using a 254 nm UV lamp and/or with the appropriate dip solution (ethanolic anisaldehyde or potassium permanganate) followed by heating. Flash chromatography was generally performed according to the protocol described by Still *et al.*,³² with Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected.

Chiral high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR and samples were analyzed as thin films on NaCl plates (sample dissolved in CH₂Cl₂) and are reported as wavenumber (cm⁻¹). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (¹H) and carbon (¹³C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 °C in CDCl₃ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (*ppm*) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

4.2 Experimental Procedures

4.2.1 Mono-*t*-butylcarbamate 18—Freshly prepared LDA (7.0 mL, 3.6 mmol) was added dropwise to a solution of ethyl diazoacetate (373 µL, 3.6 mmol) and Boc-2-pyrrolidinone (**16**) (517 mg, 2.8 mmol) in dry THF (19 mL) at -78 °C. After 1.5 hours the reaction was quenched at -78 °C by the dropwise addition of acetic acid (5 mL). The mixture was concentrated to about 10% of its original volume *in vacuo* and diluted with EtOAc (10 mL). The organic layer was washed with NaHCO₃ (sat. 2 × 5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution, 90:10 to 70:30 hexanes/EtOAc) then recrystallized from hot hexanes to yield **18** (649 mg, 77% yield) as yellow needles. *R*_f = 0.34, 70:30 hexanes:EtOAc; mp 61–62 °C; ¹H NMR (CDCl₃, 400 MHz) δ 4.66 (brs, 1H), 4.29 (q, *J*=7.1 Hz, 2H), 3.18–3.14 (m, 2H), 2.88 (t, *J*=7.2 Hz, 2H), 1.83 (quint, *J*=7.0 Hz, 2H), 1.43 (s, 9H), 1.32 (t, *J*=7.1 Hz, 3H) 192.5, 161.5, 156.1, 79.3, 61.6, 40.1, 37.5, 28.5, 24.7, 14.5; ¹³C NMR (CDCl₃, 100 MHz) δ; IR (thin film, NaCl) 3382(w), 2135(m), 1717(s), 1654(m), 1522(m), 1368(m), 1304(m), 1250(m), 1172(m), 1135(w), 1089(w), 1022(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₃H₂₂N₃NaO₅ [M+Na]⁺: 322.1373, found: 322.1375.

4.2.2 Bis-*t*-butylcarbamate 15—To a solution of **18** (300 mg, 1.00 mmol) and DMAP (12 mg, 0.010 mmol) in CH₃CN (1 mL) was added Boc₂O (240 mg, 1.10 mmol) as a solution in CH₃CN (1 mL). The reaction was refluxed for 10 hours. Upon completion the mixture was diluted with EtOAc (5 mL) and H₂O (3 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (1 × 3 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution, 90:10 to 85:15 hexanes/EtOAc) to yield **15** (265 mg, 66% yield) as a yellow oil. *R*_f = 0.43, 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 4.27 (q, *J*=7.1 Hz, 2H), 3.62 (t, *J*=7.1 Hz, 2H), 2.85 (t, *J*=7.3 Hz, 2H), 1.90 (quint, *J*=7.2 Hz, 2H), 1.49 (s, 18H), 1.31 (t, *J*=7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 192.1, 161.4, 152.7, 82.4, 61.5, 45.8, 37.5, 28.2, 23.6, 14.5; IR (thin film, NaCl) 2980(m), 2935(m), 2134(s), 1789(w), 1719(s), 1659(m), 1456(w), 1368(s), 1303(s), 1174(m), 1136(s), 1109(m), 1020(w), 854(w), 746(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₈H₂₉N₃NaO₇ [M+Na]⁺: 422.1914, found: 422.1896.

4.2.3 α-Keto-ester (±)-19—To a solution of **15** (55.6 mg, 0.140 mmol) in toluene (700 μL) was added (±)-3-buten-2-ol (12.0 μL, 0.140 mmol) and Rh₂(OAc)₄ (0.6 mg, 0.0014 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 minutes the reaction was cooled to room temperature, concentrated and purified by flash chromatography (gradient elution, 90:10 to 85:15 hexanes/EtOAc) to give (±)-**19** (23.2 mg, 37% yield) as a clear, pale yellow oil. *R*_f = 0.54, 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.54 (dddd, *J*=12.9, 6.4, 6.4, 6.4 Hz, 1H), 5.35–5.27 (m, 1H), 4.32 (q, *J*=7.1 Hz, 2H), 3.55 (t, *J*=7.1 Hz, 2H), 3.28 (s, 1H), 2.65 (dd, *J*=14.0, 7.3 Hz, 1H), 2.41 (dd, *J*=14.0, 7.3 Hz, 1H), 1.94 (ddd, *J*=13.6, 11.1, 4.9 Hz, 1H), 1.79–1.61 (m, 2H), 1.64 (dd, *J*=6.3, 1.1 Hz, 3H), 1.48 (s, 18H), 1.48–1.44 (m, 1H), 1.35 (t, *J*=7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 199.5, 162.4, 152.7, 131.2, 123.8, 82.4, 81.4, 62.5, 46.3, 41.9, 35.0, 28.2, 23.3, 18.2, 14.1; IR (thin film, NaCl) 3486(m), 2980(m), 2936(m), 1733(s), 1698(s), 1456(m), 1368(s), 1300(m), 1131(s), 1045(m), 969(m), 856(w), 782(w), 667(w); HRMS (ESI-APCI) *m/z* calcd. for C₂₂H₃₇NNaO₈ [M+Na]⁺: 466.2411, found: 466.241.

4.2.4 Diazo tosylate 21—*p*-Toluenesulfonic acid (4.70 g, 24.8 mmol) was added to a solution of ethyl 2-diazo-6-hydroxy-3-oxohexanoate³³ (3.30 g, 16.5 mmol) and Et₃N (4.00 mL, 28.9 mmol) in CH₂Cl₂ (37 mL). The reaction was stirred at room temperature for 9 hours before adding NaHCO₃ (sat. 20 mL) and extracting the aqueous layer with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting orange oil was purified by flash chromatography (gradient elution, 90:10 to 80:20 hexanes/EtOAc) to yield **21** (4.35 g, 75% yield) as a yellow oil. *R*_f = 0.59, 50:50 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 7.76 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 4.28 (q, *J*=7.1 Hz, 2H), 4.07 (t, *J*=6.2 Hz, 2H), 2.88 (t, *J*=7.0 Hz, 2H), 2.43 (s, 3H), 1.97 (quint, *J*=6.5 Hz, 2H), 1.32 (t, *J*=7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 191.4, 161.3, 144.9, 133.1, 130.0, 128.1, 69.7, 61.7, 35.9, 23.4, 21.8, 14.5; IR (thin film, NaCl) 2137(s), 1715(s), 1652(s), 1362(s), 1303(s), 1213(m), 1176(s), 1096(m), 927(m), 554(m); HRMS (APCI) *m/z* calcd. for C₁₅H₁₉N₂O₆S [M+H]⁺: 355.0956, found: 355.0955.

4.2.5 Tosylate (±)-22—To a solution of **21** (994 mg, 2.80 mmol) in toluene (14 mL) was added (±)-3-buten-2-ol (242 μL, 2.80 mmol) and Rh₂(OAc)₄ (12.4 mg, 0.028 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 minutes the reaction was cooled to room temperature before adding BF₃•Et₂O (443 μL, 3.50 mmol). After two hours, the reaction was concentrated and purified by flash chromatography (gradient elution 98:2 to 90:10 benzene/EtOAc) to give (±)-**22** (772 mg, 69% yield) as a clear, pale yellow oil. *R*_f = 0.52, 90:10 benzene:EtOAc (2x); ¹H NMR (CDCl₃, 400 MHz) δ 7.75 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 5.55 (dddd, *J*=15.1, 6.5, 6.5, 6.5 Hz, 1H),

5.31–5.23 (m, 1H), 4.22 (dddd, $J=17.9, 10.8, 7.1, 3.6$ Hz, 2H), 4.01 (ddd, $J=6.4, 5.9, 1.3$ Hz, 2H), 3.91 (s, 1H), 2.79 (ddd, $J=18.8, 7.0, 7.0$ Hz, 1H), 2.71 (dddd, $J=14.3, 7.0, 1.2, 1.2$ Hz, 1H), 2.59–2.49 (m, 2H), 2.43 (s, 3H), 1.90 (app quint, $J=6.5$ Hz, 2H), 1.62 (dd, $J=6.5, 1.5$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 205.7, 170.7, 145.0, 133.0, 131.0, 130.0, 128.0, 123.1, 83.7, 69.4, 63.0, 38.8, 33.2, 23.0, 21.8, 18.2, 14.2; IR (thin film, NaCl) 3483(m), 2981(m), 1721(s), 1598(m), 1447(m), 1361(s), 1189(m), 1177(s), 1098(m), 971(m), 925(m), 816(m), 664(m), 555(m); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{19}\text{H}_{26}\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$: 421.1308, found: 421.1294.

4.2.6 Diazo chloride 27—A 3-necked 100 mL flask charged with 4-chlorobutyryl chloride (**26**) was fitted with a glass stopper, a cold water condenser topped with a drying tube containing solid KOH open to the atmosphere, and an addition funnel charged with ethyl diazoacetate (18.0 mL, 174 mmol). The flask was placed in a room temperature water bath before dropwise addition of ethyl diazoacetate. Once addition was complete, the reaction was heated to 60 °C for six hours. Removal of byproducts by distillation (1.5 torr, 50 °C bath temperature) provided pure **27** (17.2 g, 91% yield) as a clear, yellow oil. $R_f = 0.5$, 85:15 hexanes:EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 4.30 (q, $J=7.1$ Hz, 2H), 3.61 (t, $J=6.4$ Hz, 2H), 3.03 (t, $J=7.1$ Hz, 2H), 2.12 (quint., $J=6.8$ Hz, 2H), 1.33 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) 191.7, 161.4, 61.7, 44.4, 37.4, 27.0, 14.5; IR (thin film, NaCl) 2983(m), 2137(s), 1716(s), 1657(s), 1445(w), 1373(s), 1305(s), 1223(s), 1174(w), 1126(m), 1020(m), 745(w); HRMS (APCI) m/z calcd. for $\text{C}_8\text{H}_{12}\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 219.0531, found: 219.0531.

4.2.7 Chloride (–)-28—To a solution of **27** (5.00 g, 22.8 mmol) in toluene (114 mL) was added (*S*)-(+)-3-buten-2-ol (2.07 mL, 23.9 mmol) and $\text{Rh}_2(\text{OAc})_4$ (10.2 mg, 0.023 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 minutes the reaction was cooled to room temperature before adding $\text{BF}_3 \cdot \text{Et}_2\text{O}$. After two hours, the reaction was concentrated and purified by flash chromatography (90:10 hexanes:EtOAc) to give (–)-**28** (5.90 g, 63% yield) as a clear, colorless oil. $R_f = 0.43$, 85:15 hexanes:EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 5.63–5.45 (m, 1H), 5.34–5.26 (m, 1H), 4.29–4.19 (m, 1H), 4.05 (s, 1H), 3.53 (t, $J=6.22$ Hz, 2H), 2.86 (dt, $J=18.7, 6.8$ Hz, 1H), 2.75–2.58 (m, 3H), 2.07–2.01 (m, 2H), 1.63 (d, $J=6.43$ Hz, 3H), 1.28 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 205.8, 170.7, 130.9, 123.1, 83.7, 62.9, 44.1, 38.6, 34.2, 26.2, 18.2, 14.2; IR (thin film, NaCl) 3482(m), 2975(m), 2934(m), 1721(s), 1449(m), 1367(m), 1260(s), 1214(s), 1142(m), 1096(m); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{12}\text{H}_{19}\text{ClO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 285.0864, found 285.0864. $[\alpha]_D^{22} = +3.96$ ($c = 2.20$, CHCl_3)

4.2.8 Imine (–)-24—To a solution of (–)-**28** (5.70 g, 21.7 mmol) in anhydrous *N,N*-dimethylformamide (50.0 mL) was added sodium azide (7.1 g, 108 mmol). The mixture was heated to 80 °C for three hours. Upon completion, the reaction was passed through filter paper and the filtrate diluted with diethyl ether (50 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (4 $\times$ 50 mL). The organic layers were then washed with water (5 $\times$ 50 mL), and brine (1 $\times$ 50 mL). The combined organic layers were dried over MgSO_4 . Concentration *in vacuo* yielded a crude orange oil, which was dissolved in wet THF (80 mL). To this solution was added PPh_3 and the mixture was heated to 50 °C for 1.5 hours. Upon completion, the reaction was concentrated to about 20% of the initial volume. The resulting viscous oil was triturated with hexanes:EtOAc (90:10, 30 mL) and purified by flash chromatography (90:10 to 70:30 hexanes:EtOAc). The first fraction, eluting at 90:10 hexanes:EtOAc, consisted of cyclopropyl ketone (–)-**25** (393 mg, 8% yield) as a clear, pale yellow oil. The second fraction, eluting at 70:30 hexanes:EtOAc, consisted of desired imine (–)-**24** (3.71 g, 76% yield, 2 steps) as a clear, pale yellow oil. $R_f = 0.24$, 70:30 hexanes:EtOAc; ^1H NMR (CDCl_3 ,

300 MHz) δ 5.62–5.50 (m, 1H), 5.48–5.33 (m, 1H), 4.42 (br s, 1H), 4.27–4.18 (m, 2H), 3.87–3.82 (m, 2H), 2.75–2.52 (m, 4H), 2.00–1.90 (m, 2H), 1.63 (d, $J=6.28$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 177.4, 172.3, 130.1, 124.1, 78.5, 62.2, 60.3, 40.1, 34.0, 23.6, 18.3, 14.4; IR (thin film, NaCl) 3422(w), 2976(m), 2938(m), 2870(w), 1731(s), 1448(w), 1431(w), 1367(w), 1258(m), 1212(s), 1135(m), 1096(m), 1057(w), 1029(w), 972(m), 861(w); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{12}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 226.1437, found: 226.1441. $[\alpha]_D^{22} = -25.9$ ($c = 1.48$, CHCl_3)

(–)-**25**: $R_f = 0.43$ 85:15 hexanes:EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 5.77–5.72 (m, 1H), 5.52–5.44 (m, 1H), 4.44–4.37 (m, 3H), 2.98 (dd, $J=14.2$, 6.90 Hz, 1H), 2.88 (dd, $J=14.3$, 7.38 Hz, 1H), 2.51–2.47 (m, 1H), 1.79 (d, $J=6.24$ Hz, 3H), 1.43 (t, $J=7.1$ Hz, 3H), 1.29–1.14 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 206.3, 170.4, 130.3, 123.2, 83.8, 62.1, 38.5, 17.9, 16.1, 14.0, 12.8, 12.2; IR (thin film, NaCl) 3465(s), 2983(m), 2919(w), 1738(s), 1705(s), 1447(m), 1379(m), 1262(s), 1221(s), 1156(w), 1070(m), 1032(m), 971(m), 860(w), 668(w); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 227.1278, found 227.1274. $[\alpha]_D^{22} = -30.0$ ($c = 1.80$, CHCl_3)

4.2.9 Diol 32—To a solution of (–)-**24** (3.35 g, 14.8 mmol) in absolute EtOH (50 mL) was added NaBH_4 (1.6 g, 44.4 mmol). After stirring the reaction at room temperature for 4 hours, DMAP (170 mg, 1.39 mmol) was added and the reaction was cooled to 0 °C before adding Boc_2O (3.5 g, 16.3 mmol) portionwise. After addition, the ice bath was removed and the reaction stirred for one hour at room temperature. Upon completion, the EtOH was removed *in vacuo* and the residue diluted with water (50 mL) and CH_2Cl_2 (50 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO_4 and concentrated. The residue was purified by flash chromatography (90:10 to 80:20 hexanes:EtOAc). The first fraction, eluting at 90:10 hexanes:EtOAc, consisted of a separable diastereomeric mixture of the *N*-Boc amino esters (–)-**30a** and (+)-**30b** (756 mg, 16% yield, dr 1.4:1). The second fraction, eluting at 80:20 hexanes:EtOAc, consisted of an inseparable diastereomeric mixture of *N*-Boc amino diols **32** (2.31 g, 55% yield, 2 steps) as a clear, colorless oil. $R_f = 0.31$ 70:30 hexanes:EtOAc; (partially characterized) ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.8, 128.7, 128.1, 126.0, 125.8, 80.8, 80.7, 66.0, 65.5, 62.4, 62.0, 61.9, 48.2, 48.2, 37.2, 36.8, 28.5, 27.1, 26.6, 24.6, 24.3, 18.2; HRMS (ESI-APCI) m/z calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 286.2013, found 286.2016.

(–)-**30a**: clear, colorless oil; $R_f = 0.52$ 70:30 hexanes:EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 5.54–5.42 (m, 2H), 5.24 (br s, 1H), 4.22–4.16 (m, 3H), 3.57 (br s, 1H), 3.16 (br s, 1H), 2.55 (br s, 1H), 2.38 (br s, 1H), 1.93 (br s, 1H), 1.62 (br s, 4H), 1.46 (br s, 9H), 1.26 (br s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.6, 156.9, 129.0, 124.9, 81.5, 80.1, 63.8, 61.3, 47.9, 39.9, 28.3, 27.4, 24.2, 18.0, 14.2; IR (thin film, NaCl) 3511(m), 3320(m), 2977(s), 2934(s), 1724(s), 1696(s), 1394(s), 1367(s), 1168(s), 1109(s), 1055(m), 972(m), 772(m); HRMS (ESI-APCI) m/z calcd for $\text{C}_{17}\text{H}_{30}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 328.2118, found 328.2122. $[\alpha]_D^{22} = -43.0$ ($c = 0.82$, CHCl_3)

(+)-**30b**: white solid; $R_f = 0.61$ 70:30 hexanes:EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 5.57–5.48 (m, 1H), 5.40–5.33 (m, 1H), 4.29 (dq, $J=10.7$, 7.1 Hz), 4.18–4.15 (m, 1H), 4.11 (par dq, $J=10.6$, 7.1 Hz, 1H), 3.71 (br s, 1H), 3.53 (br s, 1H), 3.26–3.19 (m 1H), 2.48 (app dd, $J=8.0$, 6.9, 5.7 Hz, 1H), 2.31 (app dd, $J=8.02$, 5.9, 5.8 Hz, 1H), 2.05–1.83 (m, 3H), 1.74–1.67 (m, 1H), 1.63 (d, $J=6.3$ Hz, 3H), 1.42 (s, 9H), 1.30 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 175.1, 155.7, 129.4, 124.9, 79.9, 79.8, 63.0, 62.1, 48.1, 38.4, 26.6, 24.6, 18.2, 14.2; IR (thin film, NaCl) 3434(s), 2978(w), 1725(m), 1698(s), 1654(m), 1390(s), 1258(w), 1213(w), 1171(m), 1096(w), 969(w); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{17}\text{H}_{30}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 328.2118, found 328.2108. $[\alpha]_D^{22} = +55.4$ ($c = 2.42$, CHCl_3)

4.2.10 Cyclic carbamates (±)-33a and (±)-38b—DIBALH (619 μ L, 0.619 mmol) was added to a solution of (±)-30a (169 mg, 0.516 mmol) in dry CH_2Cl_2 (2.6 mL) at 0 °C. The solution was then warmed to room temperature and stirred for two hours. Upon completion, the reaction was quenched with MeOH/ H_2O (1:1, 5 mL) at 0 °C. The mixture was filtered through Celite with CH_2Cl_2 to yield crude (±)-32a. (±)-30b (138 mg, 0.422 mmol) was subjected to similar conditions to yield crude (±)-32b. (±)-32a (82.4 mg, 0.290 mmol) and (±)-32b (51.9 mg, 0.180 mmol) were independently treated with excess NaH in dry THF (1.5 mL) at room temperature to provide (±)-33a (34.8 mg, 32% yield, two steps) and (±)-33b (14.8 mg, 17% yield, 2 steps) respectively after purification by flash chromatography (gradient elution, 90:10 to 70:30 hexanes/EtOAc).

(±)-33a: ^1H NMR (C_6D_6 , 400 MHz) δ 5.45–5.37 (m, 1H), 5.28–5.19 (m, 1H), 5.13 (s, 1H), 4.10 (d, $J=11.2$ Hz, 1H), 3.65 (d, $J=11.1$ Hz, 1H), 3.61 (par dd, $J=7.5, 3.0$ Hz, 1H), 3.34–3.29 (m, 1H), 2.77 (dd, $J=10.5, 5.7$ Hz, 1H), 2.14 (app dd, $J=14.1, 6.6$ Hz, 1H), 2.02–1.92 (m, 1H), 1.87 (dd, $J=14.2, 7.9$ Hz, 1H), 1.58–1.49 (m, 1H), 1.50 (d, $J=6.3$ Hz, 1H), 1.43–1.37 (m, 1H), 1.25–1.12 (m, 1H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 152.9, 128.6, 125.2, 74.5, 66.1, 63.0, 47.3, 39.4, 25.8, 22.6, 17.8; HRMS (ESI-APCI) calcd. for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1281, found: 212.1284.

(±)-33b: ^1H NMR (CDCl_3 , 400 MHz) δ 5.66 (dddd, $J=15.2, 6.4, 6.4, 6.3$ Hz, 1H), 5.53–5.45 (m, 1H), 4.02 (d, $J=10.7$ Hz, 1H), 3.84 (d, $J=10.6$ Hz, 1H), 3.61 (dd, $J=10.5, 5.5$ Hz, 1H), 3.49–3.44 (m, 2H), 2.77 (d, $J=4.1$ Hz, 1H), 2.19 (d, $J=7.4$ Hz, 2H), 2.07–1.93 (m, 2H), 1.85–1.74 (m, 1H), 1.74 (d, $J=6.4$ Hz, 3H), 1.69–1.61 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.4, 132.5, 123.3, 71.5, 66.9, 65.1, 47.2, 33.7, 26.8, 22.9, 18.3; HRMS (ESI-APCI) calcd. for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1281, found: 212.1284.

4.2.11 Aldehydes (+)-31a and (–)-31b—To a solution of 32 (2.10 g, 7.40 mmol) in wet EtOAc (50 mL) was added IBX²⁸ (6.20 g, 22.2 mmol). The mixture was refluxed open to the atmosphere for 6 hours. The reaction was filtered through a pad of Celite, concentrated and directly purified by flash chromatography (90:10 hexanes:EtOAc) to provide the desired *N*-Boc amino aldehyde (1.85 g, 89% yield) as a mixture of diastereomers. The diastereomers were separated by flash chromatography (98:2 to 95:5 EtOAc: CH_2Cl_2) to provide (+)-31a as a clear, colorless oil and (–)-31b as a clear, colorless oil.

(+)-31a: $R_f = 0.35$ 95:5 CH_2Cl_2 :EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 9.62 (s, 1H), 5.55–5.47 (m, 1H), 5.30–5.22 (m, 1H), 4.12 (br s, 1H), 3.71 (s, 1H), 3.40 (br s, 1H), 3.21–3.17 (m, 1H), 2.42 (dd, $J=14.3, 7.8$ Hz, 1H), 2.34–2.29 (m, 1H), 2.09–1.89 (m, 3H), 1.73–1.68 (m, 1H) 1.59 (d, $J=6.2$ Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 201.8, 155.4, 129.9, 123.4, 82.8, 79.9, 60.6, 47.4, 37.3, 28.2, 25.7, 24.7, 17.9; IR (thin film, NaCl) 3479(m), 2976(s), 1723(s), 1682(s), 1479(m), 1393(s), 1255(m), 1169(s), 1118(m), 971(m), 915(m), 856(w), 817(w), 772(w); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 306.1676, found 306.1672. $[\alpha]_D^{22} = +39.3$ ($c = 2.68$, CHCl_3)

(–)-31b: $R_f = 0.48$ 95:5 CH_2Cl_2 :EtOAc; ^1H NMR (CDCl_3 , 400 MHz) δ 9.64 (s, 1H), 6.39 (br s, 1H), 5.57–5.48 (m, 2H), 3.98 (t, $J=7.1$ Hz, 1H), 3.57 (br s, 1H), 3.09 (br s, 1H), 2.4–2.26 (m, 2H), 2.05–1.91 (m, 2H), 1.80 (br s, 1H), 1.63 (d, $J=5.2$, 3H), 1.45 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 206.7, 157.8, 129.5, 124.5, 82.1, 81.3, 64.0, 48.2, 37.3, 27.4, 24.3, 18.2; IR (thin film, NaCl) 3297(s), 2977(s), 2888(m), 1730(s), 1693(s), 1658(s), 1402(s), 1250(m), 1166(s), 1112(m), 974(m), 855(m), 776(m); HRMS (ESI-APCI) m/z calcd. for $\text{C}_{15}\text{H}_{25}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 306.1676, found 306.1673. $[\alpha]_D^{22} = -40.3$ ($c = 2.63$, CHCl_3)

4.2.12 Allyl alcohol 34—To a solution of (+)-**31a** (1.00 g, 3.55 mmol) in THF (18 mL) was added freshly prepared allylmagnesium bromide (1.0 M in Et₂O, 10.6 mL, 10.6 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 mins before warming to room temperature and stirring for 1 hour more. The reaction was quenched with sat. NH₄Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (gradient elution, 90:10 to 85:15 hexanes:EtOAc) to yield (–)-**34a** and (–)-**34b** (824 mg, 72% yield, combined) as pale yellow oils. The diastereomers were characterized separately.

(–)-**34a** (β-OH): *R*_f = 0.44 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.98–5.88 (m, 1H), 5.50–5.47 (m, 2H), 5.10–5.03 (m, 2H), 4.65 (br s, 1H), 4.10–4.07 (m, 1H), 3.57–3.49 (m, 3H), 3.24–3.17 (m, 1H), 2.36–2.22 (m, 3H), 2.08–1.85 (m, 4H), 1.78–1.71 (m, 1H), 1.66 (d, *J* = 3.3 Hz, 3H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.8, 136.8, 128.3, 126.0, 116.4, 80.8, 78.0, 72.7, 62.8, 48.2, 37.6, 35.7, 28.5, 27.15, 24.3, 18.3; IR (thin film, NaCl) 3416(s), 3074(w), 2977(m), 2933(m), 1662(s), 1395(m), 1255(w), 1168(m), 976(w), 907(w), 774(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₈H₃₂NO₄ [M+H]⁺: 326.2326, found: 326.2327. [α]_D²² = –48.9 (c = 2.02, CHCl₃)

(–)-**34b** (α-OH): *R*_f = 0.53 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.87–5.78 (m, 1H), 5.69 (br s, 1H), 5.55–5.48 (m, 1H), 5.13–5.09 (m, 2H), 4.02 (dd, *J* = 8.5, 6.7 Hz), 3.68–3.63 (m, 1H), 3.55–3.53 (m, 1H), 3.26–3.20 (m, 1H), 2.66–2.62 (m, 1H), 2.27–2.18 (m, 3H), 2.07–1.98 (m, 3H), 1.88–1.83 (m, 1H), 1.68–1.59 (m, 4H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.2, 136.8, 127.9, 126.9, 118.1, 80.8, 77.5, 74.1, 65.2, 48.6, 36.9, 36.2, 28.5, 27.8, 24.3, 18.4; IR (thin film, NaCl) 3420(s), 2977(w), 2932(w), 1650(s), 1408(m), 1367(m), 1251(w), 1167(m), 977(w), 907(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₈H₃₂NO₄ [M+H]⁺: 326.2326, found: 326.2327. [α]_D²² = –51.9 (c = 1.73, CHCl₃)

4.2.13 Cyclohexene 35—To a solution of (–)-**34a** and (–)-**34b** (794 mg, 2.44 mmol) in CH₂Cl₂ (24 mL) was added Grubbs's 2nd generation catalyst, and the reaction was refluxed for 1.5 hours. The mixture was concentrated and purified by flash chromatography (gradient elution, 85:15 to 75:25 hexanes:EtOAc) to yield (–)-**35a** and (+)-**35b** (598 mg, 87% yield, combined) as beige foams. The diastereomers were characterized separately.

(–)-**35a** (β-OH): *R*_f = 0.11 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.67–5.60 (m, 1H), 4.11 (br s, 1H), 3.82 (br s, 1H), 3.66 (br s, 1H), 3.20 (dt, *J* = 10.96, 7.1, 7.0 Hz, 1H), 2.64 (d, *J* = 18.5 Hz, 1H), 2.54 (d, *J* = 18.7 Hz, 1H), 2.28–2.23 (m, 1H), 2.07 (d, *J* = 17.9 Hz, 1H), 2.01–1.87 (d, *J* = 19.0 Hz, 1H and m, 2H), 1.75–1.67 (m, 1H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.6, 124.4, 123.6, 80.5, 74.3, 69.8, 64.6, 48.2, 32.2, 32.0, 28.6, 27.7, 24.7; IR (thin film, NaCl) 3426(m), 2970(m), 2904(m), 1664(s), 1398(s), 1362(m), 1168(s), 1106(w), 1024(w), 906(m), 878(w), 727(m), 650(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₅H₂₆NO₄ [M+H]⁺: 284.1856, found: 284.1855. [α]_D²² = –80.9 (c = 1.12, CHCl₃)

(+)-**35b** (α-OH): *R*_f = 0.21 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.61 (br s, 1H), 5.52 (br s, 2H), 4.13 (app d, *J* = 8.8 Hz, 1H), 3.70–3.67 (m, 1H), 3.55–3.52 (m, 1H), 3.31–3.26 (m, 1H), 2.37–2.20 (m, 5H), 2.10–1.99 (m, 4H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.5, 124.7, 123.1, 80.6, 74.9, 67.3, 60.5, 48.2, 30.7, 29.4, 28.3, 25.5, 24.2; IR (thin film, NaCl) 3392(m), 3027(w), 2976(m), 2902(m), 1667(s), 1395(s), 1345(w), 1255(w), 1168(m), 1119(m), 1078(m), 890(m), 774(w), 732(w), 668(w); HRMS (ESI-APCI) *m/z* calcd. for C₁₅H₂₆NO₄ [M+H]⁺: 284.1856, found: 284.1860. [α]_D²² = +15.7 (c = 0.74, CHCl₃)

4.2.14 Dibromide 36—To a solution of (–)-**35a** and (+)-**35b** (602 mg, 2.12 mmol) in CH₂Cl₂ (42 mL) was added a solution of Br₂ (53.3 μ L, 3.18 mmol) in CH₂Cl₂ (5 mL) dropwise at 0 °C. The reaction was stirred for 5 mins before pouring into a 10% solution of Na₂S₂O₃. The aqueous layer was extracted with CH₂Cl₂ (4 $\times$ 20 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated to yield (–)-**36a** and (+)-**36b** (893 mg, 95% yield, combined) as a mixture, which was carried forward without further purification. An aliquot of the mixture was purified for characterization purposes.

(–)-**36a** (β -OH): white powder; R_f = 0.21 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 5.34 (br s, 1H), 4.14–4.06 (m, 3H), 3.55 (br s, 2H), 3.32–3.31 (m, 1H), 3.05 (br s, 1H), 2.67–2.63 (m, 2H), 2.21–2.18 (m, 1H), 2.10–1.87 (m, 5H), 1.47 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.7, 81.6, 76.1, 74.9, 52.9, 52.4, 48.8, 42.1, 40.7, 28.4, 26.8, 24.4; IR (thin film, NaCl) 3376(m), 2975(m), 2894(w), 1662(s), 1477(w), 1448(w), 1392(s), 1367(s), 1257(w), 1166(s), 1066(w), 1032(w), 898(w), 871(w), 680(w); HRMS (ESI-APCI) m/z calcd. for C₁₅H₂₆Br₂NO₄ [M+H]⁺: 442.0223, found: 442.0216. $[\alpha]_D^{22}$ = –1.53 (c = 1.76, CHCl₃)

(+)-**36b** (α -OH): white foam; R_f = 0.48 70:30 hexanes:EtOAc ¹H NMR (CDCl₃, 400 MHz) δ 4.91 (br s, 1H), 4.70 (br s, 1H), 4.54 (br s, 1H), 4.02–3.95 (m, 2H), 3.51–3.48 (m, 1H), 3.30–3.24 (m, 1H), 2.81 (s, 1H), 2.62 (ddd, J =14.2, 10.9, 2.9 Hz, 1H), 2.27 (dd, J = 15.3, 4.1 Hz, 1H), 2.14–2.10 (m, 1H), 2.04–1.80 (m, 1H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.5, 80.7, 75.7, 65.9, 61.2, 53.2, 47.9, 47.49, 31.6, 31.1, 28.2, 25.3, 24.2; IR (thin film, NaCl) 3407(m), 2976(m), 2932(w), 1667(s), 1478(w), 1393(s), 1367(s), 1247(w), 1166(s), 1121(m), 1074(w), 1042(w), 986(w), 938(w), 890(w), 738(m); HRMS (ESI-APCI) m/z calcd. for C₁₅H₂₆Br₂NO₄ [M+H]⁺: 442.0223, found: 442.0210. $[\alpha]_D^{22}$ = +7.10 (c = 1.62, CHCl₃)

4.2.15 Enone (–)-38—Anhydrous DMSO (900 μ L, 22.7 mmol) in CH₂Cl₂ (1 mL) was added to a solution of oxalyl chloride (805 μ L, 5.27 mmol) in CH₂Cl₂ (12 mL) at –78 °C. The mixture was stirred for 10 mins before adding a solution of (–)-**36a** and (+)-**36b** (940 mg, 2.11 mmol) in CH₂Cl₂ (7 mL) dropwise. This mixture was stirred for 10 mins before adding Et₃N (2.90 mL, 21.1 mmol) and allowing the reaction to warm to room temperature. After 1 hour the reaction was diluted with CH₂Cl₂ and washed with commercial bleach solution (12% NaClO₄, 2 $\times$ 15 mL). The combined aqueous layers were back extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (90:10 hexanes:EtOAc) to yield (–)-**38** (760 mg, 75% yield) as a viscous orange oil. R_f = 0.53, 70:30 hexanes:EtOAc; ¹H NMR (CDCl₃, 400 MHz) δ 7.02 (d, J =10.0 Hz, 1H), 6.01 (d, J =9.86 Hz, 1H), 5.88 (br s, 1H), 4.09 (br s, 1H), 3.78 (s, 1H), 3.54 (br s, 1H), 3.39–3.27 (m, 1H), 2.92–2.89 (m, 1H), 2.26 (app t, J =12.0, 11.0 Hz, 1H), 2.00–1.92 (m, 1H), 1.72–1.62 (m, 3H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 200.5, 156.2, 151.8, 125.7, 80.5, 79.9, 59.3, 47.7, 44.3, 42.2, 28.3, 25.1, 24.6; IR (thin film, NaCl) 3477(w), 2975(m), 1685(s), 1398(s), 1229(w), 1163(s), 1106(m), 1065(w), 917(w), 819(w), 768(w); HRMS (ESI-APCI) C₁₅H₂₂BrNNaO₄ [M+Na]⁺: 382.0624, found: 382.0624. $[\alpha]_D^{22}$ = –132.3 (c = 3.12, CHCl₃)

4.2.16 (+)-Norsecurinine, 2—To a solution of (–)-**38** (250mg, 0.69 mmol) in dry CH₂Cl₂ (7 mL) was added trifluoroacetic acid (550 μ L, 6.9 mmol). The solution was refluxed until TLC showed complete consumption of starting material. The reaction was concentrated *in vacuo* and then rediluted with dry CH₂Cl₂ (5 mL). Triethylamine (142 μ L, 1.04 mmol) was added and the reaction was stirred at room temperature for 15 mins. The brown solution was concentrated *in vacuo* and triturated with EtOAc. The mixture was filtered through a fritted funnel and the filter cake washed with EtOAc (2 $\times$ 5 mL). The

brownish liquid was concentrated and redissolved in dry CH_2Cl_2 (6 mL). To this solution was added diethylphosphonoacetic acid (255 mg, 1.3 mmol) and DCC (268 mg, 1.3 mmol) as a solution in dry CH_2Cl_2 (3 mL). The mixture was refluxed for 1 hour before being filtered through a fritted funnel. The crude filtrate was concentrated *in vacuo* and redissolved in dry THF (6 mL). The solution was cooled to 0 °C before adding NaH (31.2 mg, 1.3 mmol, washed with hexanes). The mixture was stirred at 0 °C for 15 mins then at room temperature for 10 mins. After quenching with H_2O (5 mL) the aqueous layer was extracted with EtOAc (6 × 5 mL). The combined organic layers were dried over MgSO_4 and concentrated. The resulting residue was purified by flash chromatography using gradient elution (95:5 to 90:10 CH_2Cl_2 /MeOH) to yield (+)-**2** (54 mg, 38% yield, 3 steps) as a yellow oil. $R_f = 0.10$ 90:10 CH_2Cl_2 :MeOH; ^1H NMR (CDCl_3 , 400 MHz) δ 6.73 (dd, $J=8.9$, 6.5 Hz, 1H), 6.47 (d, $J=8.9$ Hz, 1H), 5.65 (s, 1H), 3.61 (app t, $J=5.6$ Hz, 1H), 3.27 (app dd, $J=8.0$, 6.0 Hz, 1H), 3.19–3.16 (m, 1H), 2.57 (dd, $J=10.5$, 4.7 Hz, 1H), 2.54–2.50 (m, 1H), 2.00–1.94 (m, 2H), 1.81–1.74 (m, 2H), 1.71 (d, $J=10.5$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.9, 168.5, 143.9, 120.6, 108.0, 92.0, 65.3, 59.9, 55.4, 35.9, 29.5, 26.9; $[\alpha]_D^{22} = +183$ ($c = 1.36$, EtOH)

4.2.17 (+)-Allonorsecurinine 40—yellow oil; $R_f = 0.24$, 90:10 CH_2Cl_2 :MeOH; ^1H NMR (CDCl_3 , 400 MHz) δ 6.86 (dd, $J=9.1$, 5.4 Hz, 1H), 6.71 (dd, $J=9.1$, 0.7 Hz, 1H), 5.79 (s, 1H), 4.16 (t, $J=7.4$ Hz, 1H), 3.98 (app t, $J=4.9$ Hz, 1H), 2.95–2.89 (m, 2H), 2.87–2.81 (m, 1H), 2.04 (d, $J=10.0$ Hz, 1H), 1.91–1.62 (m, 3H), 1.30–1.21 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.4, 167.1, 149.2, 124.0, 110.1, 90.8, 69.2, 57.8, 49.4, 47.0, 27.9, 25.5; $[\alpha]_D^{22} = +738$ ($c=1.30$, EtOH).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding from the NIH (Grant No. 1 RO1 CA/GA 93591-O1A) is gratefully acknowledged. Dr. Chris Rithner, Don Heyse and Don Dick are acknowledged for their assistance with instrumentation.

References and Notes

- (a). Snieckus, V. The Securinega Alkaloids. In: Manske, RHF., editor. The Alkaloids. Vol. Vol. 14. 1975. p. 425-506. (b) Weinreb SM. Nat. Prod. Rep 2009;26:758–775. [PubMed: 19471684]
- Ohsaki A, Ishiyama H, Yoneda K, Kobayashi J. Tetrahedron Lett 2003;44:3097–3099.
- Parello J. Bull. Chim. Soc. Fr 1968:1117.
- (a). Horii Z, Imanishi T, Yamauchi M, Hanaoka M, Parello J, Munavalli S. Tetrahedron Lett 1972;13:1877. (b) Parello J, Munavalli S. C. R. Acad. Sci. Paris 1965;260:337. [PubMed: 14305444] (c) Petchnaree P, Bunyapraphatsara N, Cordell GA, Cowe HJ, Cox PJ, Howie RA, L. PS. J. Chem. Soc., Perkin Trans. 1 1986:1551–1556.
- Gan LS, Fan CQ, Yang SP, Wu Y, Lin LP, Ding J, Yue JM. Org. Lett 2006;8:2285–2288. [PubMed: 16706507]
- Nakano T, Yang TH, Terao S. Chem. Ind 1962:1651.
- Saito S, Iwamoto T, Tanaka T, Matsumura C, Sugimoto N, Horii Z, Tamura Y. Chem. Ind 1964:1263–1264.
- Iketubosin GO, Mathieson DWM. J. Pharm. Pharmacol 1963;15:810. [PubMed: 14134116]
- Alibes R, Balbe M, Busque F, de March P, Elias L, Figueredo M, Font J. Org. Lett 2004;6:1813–1816. [PubMed: 15151421]
- (a). Alibes R, Bayon P, de March P, Figueredo M, Font J, Garcia-Garcia E, Gonzalez-Galvez D. Org. Lett 2005;7:5107–5109. [PubMed: 16235969] (b) Bardaji GG, Canto M, Alibes R, Bayon P,

Busque F, de March P, Figueredo M, Font J. J. Org. Chem 2008;73:7657–7662. [PubMed: 18781804] (c) Carson CA, Kerr MA. Angew. Chem. Int. Ed 2006;45:6560–6563. (d) Dhudshia B, Cooper BFT, Macdonald CLB, Thadani AN. Chem. Commun 2009:463–465. (e) Heathcock CH, Vongeldern TW. Heterocycles 1987;25:75–78. (f) Honda T, Namiki H, Kudoh M, Nagase H, Mizutani H. Heterocycles 2003;59:169–187. (g) Honda T, Namiki H, Kudoh M, Watanabe N, Nagase H, Mizutani H. Tetrahedron Lett 2000;41:5927–5930. (h) Horii Z, Hanaoka M, Imanishi T, Iwata C. Chem. Pharm. Bull 1972;20:1774–1775. (i) Horii Z, Hanaoka M, Yamawaki Y, Tamura Y, Saito S, Shigematsu N, Kotera K, Yoshikawa H, Sato Y, Nakai H, Sugimoto N. Tetrahedron 1967;23:1165–1174. (j) Jacobi PA, Blum CA, Desimone RW, Udodong UES. Tetrahedron Lett 1989;30:7173–7176. (k) Liu P, Hong S, Weinreb SM. J. Am. Chem. Soc 2008;130:7562–7563. [PubMed: 18491903] (l) Magnus P, Rodriguez-Lopez J, Mulholland K, Matthews I. Tetrahedron 1993;49:8059–8072. (m) Saito S, Yoshikawa H, Sato Y, Nakai H, Sugimoto N, Horii ZI, Hanaoka M, Tamura Y. Chem. Pharm. Bull 1966;14:313–314. [PubMed: 5908765]

11. Gonzalez-Galvez D, Garcia-Garcia E, Alibes R, Bayon P, de March P, Figueredo M, Font J. J. Org. Chem 2009;74:6199–6211. [PubMed: 19627163]
12. Han G, LaPorte MG, Folmer JJ, Werner KM, Weinreb SM. J. Org. Chem 2000;65:6293–6306. [PubMed: 11052071]
13. Honda T, Namiki H, Kaneda K, Mizutani H. Org. Lett 2004;6:87–89. [PubMed: 14703357]
14. Leduc AB, Kerr MA. Angew. Chem. Int. Ed 2008;47:7945–7948.
15. Liras S, Davoren JE, Bordner J. Org. Lett 2001;3:703–706. [PubMed: 11259041]
16. As is often the case with discovery in synthesis, this particular transformation was serendipitously observed while attempting something different. Then graduate student Brian Stoltz working with postdoctoral student Hans-Juergen Dietrich were attempting to perform an OH insertion with allylic alcohol substrates. Our interest in the latter was actually stimulated through discussions at Yale Chemistry happy hours with a postdoctoral student from Harry Wasserman's group, Dr. Steve Coats and a good friend of his, Dr. Martin Osterhaut, who was working at Bayer in West Haven, CT. Steve and Martin, who had both spent time in Al Padwa's group, proved to be valuable sources of information regarding rhodium promoted reactions of diazoketones. The chemistry discovered by Stoltz and Dietrich played a central role in four Ph.D. theses from my group (Stoltz, Pflum, Petsch and Moniz) and clearly continues to occasionally impact our thinking. (a) Stoltz, BM. Ph.D. Thesis. Yale University; 1997. (b) Wood JL, Stoltz BM, Dietrich HJ, Pflum DA, Petsch DT. J. Am. Chem. Soc 1997;119:9641–9651.
17. Joshi BS, Gawad DH, Pelletier SW, Kartha G, Bhandary K. J. Nat. Prod 1986;49:614–620. [PubMed: 3783157]
- 18(a). Basabe P, Boder O, Marcos IS, Diez D, De Roman M, Blanco A, Urones JG. Tetrahedron 2007;63:11838–11843. (b) Kita Y, Sekihachi J, Hayashi Y, Da YZ, Yamamoto M, Akai S. J. Org. Chem 1990;55:1108–1112. (c) Krawczyk E, Koprowski M, Luczak J. Tetrahedron: Asymmetry 2007;18:1780–1787. (d) Peters R, Diolez C, Rolland A, Manginot E, Veyrat M. Heterocycles 2007;72:255–273. (e) Schobert R, Jagusch C. Synthesis-Stuttgart 2005:2421–2425.
19. Klingler, FD.; Psiorz, M. European Patent. 0576888A2. 1993.
20. Moody CJ, Taylor RJ. Tetrahedron Lett 1987;28:5351–5352.
- 21(a). Moniz, GA. Ph.D. Thesis. Yale University; 2001. (b) Wood JL, Moniz GA. Org. Lett 1999;1:371–374. [PubMed: 10822578] (c) Wood JL, Moniz GA, Pflum DA, Stoltz BM, Holubec AA, Dietrich HJ. J. Am. Chem. Soc 1999;121:1748–1749.
22. This observation was made in the original studies of this reaction. See ref. ^{16a}.
- 23(a). Gololobov YG, Kasukhin LF. Tetrahedron 1992;48:1353–1406. (b) Molina P, Vilaplana MJ. Synthesis 1994:1197–1218. (c) Staudinger H, Jules M. Helv. Chim. Acta 1919;2:635–646.
24. Staudinger H, Becker J, Hirzel H. Chem. Ber 1916:1978–1994.
25. Bestmann HJ, Kolm H. Chem. Ber 1963:1948–1958.
26. The enantiomeric ratio was determined by chiral HPLC analysis of the benzoate ester of (+)-**14** (ChiralPak IC column, 98:2 hexanes:isopropanol).
27. The enantiomeric ratio was determined by chiral HPLC analysis of azide (+)-**3** (ChiralPak IC column, 99:1 hexanes:isopropanol). The absolute stereochemistry was initially assigned in accord

with observations in previous rhodium-initiated Claisen rearrangements (see ref. ^{16b}) and is consistent with that expected for the production of (+)-norsecurinine.

- 28a). Although NaBH₄ reductions are subject to solvent effects the reactivity difference displayed by **24** in MeOH vs. EtOH was welcome but not anticipated, see: Brown HC, Narasimhan S, Choi YM. J. Org. Chem 1982;47:4702. b) For the employed IBX protocol, see: More JD, Finney NS. Org. Lett 2002;4:3001–3003. [PubMed: 12182609]
29. A similar compound was the sole product observed by Liras and coworkers.
30. Bestmann HJ. Angew. Chem. Int. Ed 1977;16:349–364.
31. Schobert R. Org. Synth 2005;82:140.
32. Still WC, Kahn M, Mitra A. J. Org. Chem 1978;43:2923–2925.
33. Moody CJ, Taylor RJ. J. Chem. Soc., Perkin Trans. 1 1989:721–731.

Figure 1.
Selected *Securinega* alkaloids

Scheme 1.
Retrosynthetic analysis of (+)-norsecurinine

Scheme 2.
Initial investigation of the key domino process

Scheme 3.
Butyrolactone-based strategy to imine **24**

Scheme 4.
Improved route to imine **24**

Scheme 5.
Initial synthesis of aldehyde **31**

Scheme 6.
Improved synthesis of aldehyde **31**

Scheme 7. Synthesis of cyclic carbamates **33a** and **33b**, and relevant nOes

Scheme 8.
Synthesis of penultimate intermediate enone **38**

Scheme 9.
Endgame strategy