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An enantioselective approach to the *Securinega* alkaloids: the total synthesis of (+)-norsecurinine and (+)-allonorsecurinine

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

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ABSTRACT

Total syntheses of (+)-norsecurinine and (+)-allonorsecurinine are described that utilize a rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration domino process for the stereoselective introduction of the tertiary alcohol moiety. Overall the employed strategy is flexible and will allow access to other members of the *Securinega* family of alkaloids.

1. Introduction

The *Securinega* alkaloids[1] are a small family of natural products isolated from the Euphorbiaceae family of plants (Fig. 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 toward 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 laboratory[16] would provide an interesting stereocontrolled approach to the desired tertiary alcohol functionality. Herein, we report the application of this domino sequence to the synthesis of (+)-norsecurinine[17] and (+)-allonorsecurinine.[9]

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

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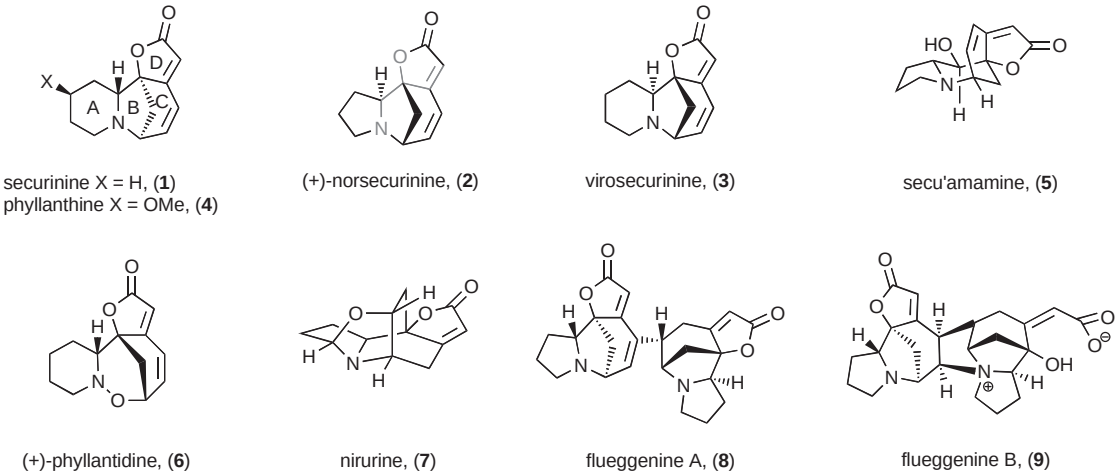
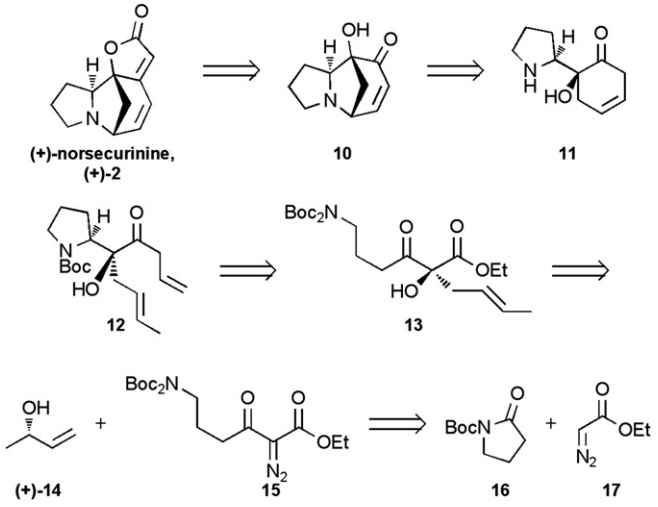


Figure 1. Selected *Securinega* alkaloids.

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.

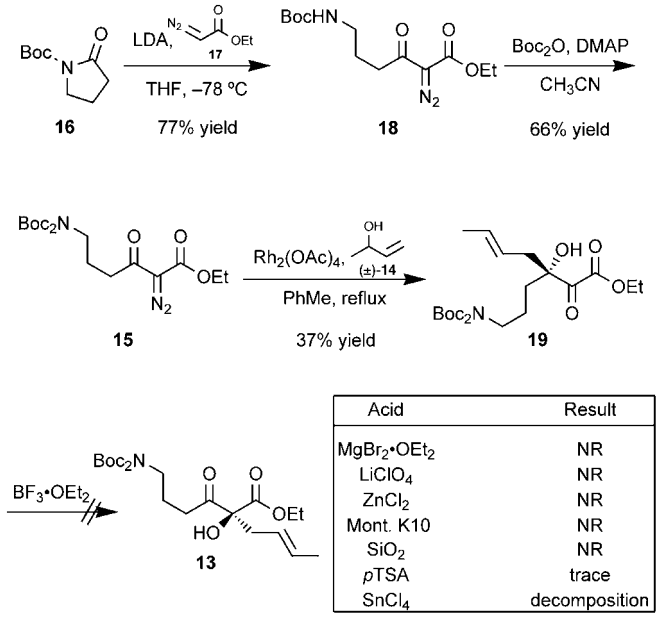


Scheme 1. Retrosynthetic analysis of (+)-norsecurinine.

2.2. Synthesis of (+)-norsecurinine

Our synthesis commenced with the opening of *N*-Boc-2-pyrrolidinone (**16**) with ethyl lithiodiazoacetate [20] 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 % $Rh_2(OAc)_4$ 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 (±)-**14** in the presence of 1 mol % $Rh_2(OAc)_4$ 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 $BF_3 \cdot Et_2O$ 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

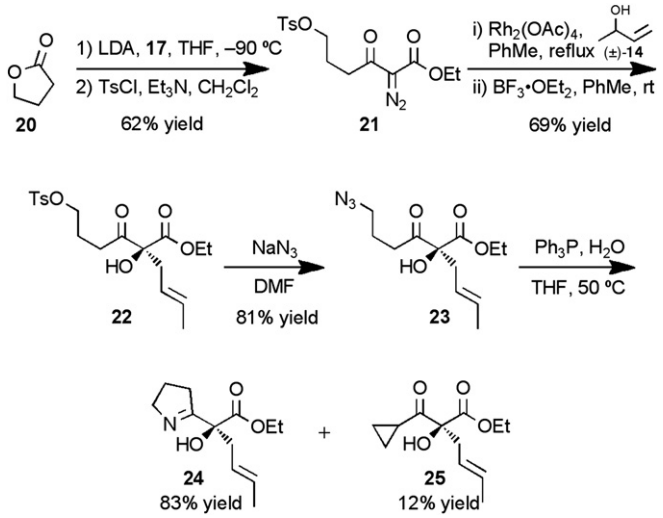


Acid	Result
$MgBr_2 \cdot OEt_2$	NR
$LiClO_4$	NR
$ZnCl_2$	NR
Mont. K10	NR
SiO_2	NR
*p*TSA	trace
$SnCl_4$	decomposition

Scheme 2. Initial investigation of the key domino process.

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 pot[22] with (±)-**14** in the presence of 0.1 mol % $Rh_2(OAc)_4$ in toluene at reflux followed by addition of $BF_3 \cdot Et_2O$ 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 sequence[23] 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.

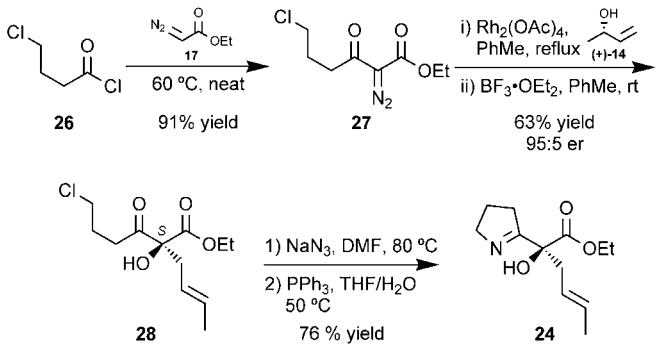
Although an effective route to imine **24** had been developed, some difficulties encountered with scale-up and variable yields for the opening of butyrolactone with ethyl lithiodiazoacetate led us to seek an alternative strategy. We found that adapting a procedure reported by Staudinger and co-workers[24] and Bestmann and



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

Kolm[25] 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 equiv (+)-**14** (98:2 er)[26] and 0.1 mol % $Rh_2(OAc)_4$, 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.

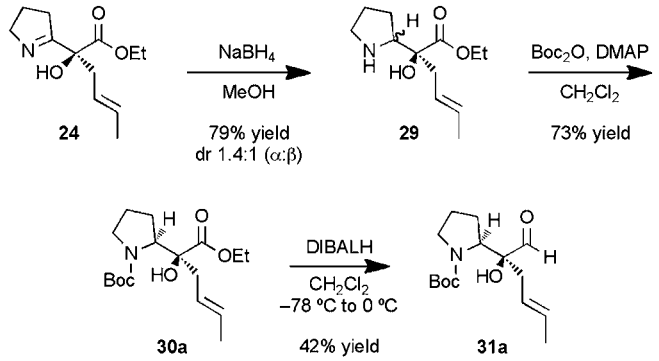
Proceeding forward, imine **24** was reduced with $NaBH_4$ in MeOH to yield an inseparable mixture of diastereomeric amino esters **29**, which were directly converted to *tert*-butyl carbamates **30** with Boc_2O and DMAP (Scheme 5). The derived carbamates proved separable by simple column chromatography and the major isomer



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

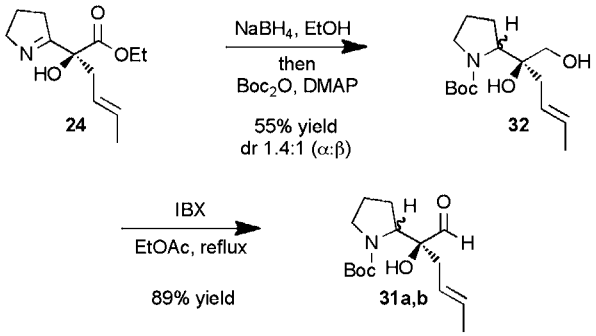
(**30a**) was reduced to aldehyde **31a** by treatment with DIBALH at low temperature, albeit in moderate yield. Warming the reaction above 0 °C resulted in a complex mixture of products.

To circumvent this problem we found that reduction of imine **24** with $NaBH_4$ 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]



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

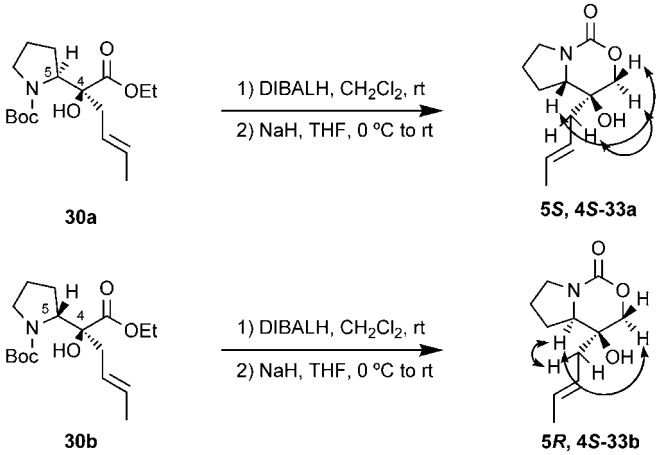
Prior to continuing with the synthesis, the stereochemical outcome of the $NaBH_4$ reduction was delineated (Scheme 7). To this end, carbamate esters **30a** and **30b** were individually subjected to DIBALH at room temperature and the resulting crude diols were treated with NaH in THF. Nuclear Overhauser Effect (NOE) analysis of cyclic carbamates **5*S*, 4*S*-33a**, and **5*R*-4*S*-33b** revealed the illus-



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

trated stereochemical relationships (relevant NOEs indicated with double headed arrows).

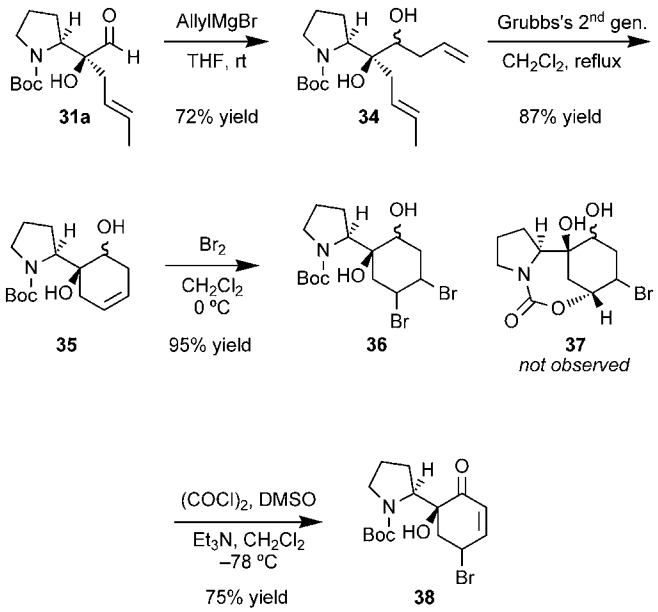
Having assigned the stereochemistry, the synthesis continued with alkylation of aldehyde **31a** using allylmagnesium bromide to furnish **34** followed by ring-closing metathesis using Grubbs's second generation catalyst to provide cyclohexene **35** as a mixture of diastereomers (Scheme 8). Given that the newly produced hydroxyl stereocenter would eventually undergo oxidation, the mixture of diastereomers was advanced without separation. Adopting a strategy used by Liras and co-workers for their synthesis of (±)-securinine,[15] cyclohexene **35** was treated with Br_2 at 0 °C to yield dibromide **36** as a single diastereomer



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

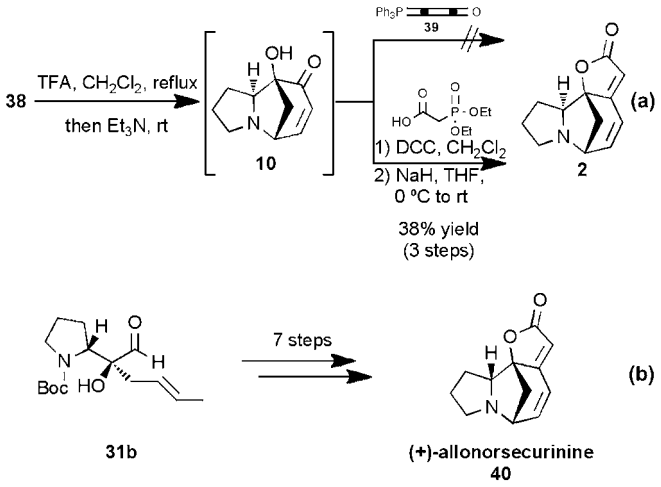
based on ^{1}H NMR analysis. We found that dropwise addition of Br_2 at 0 °C was essential to avoid the formation of **37** obtained from attack of the carbamate carbonyl on the secondary bromide.[29] After some experimentation, we found that Swern oxidation of alcohol **36** supplied enone **38** in good yield. During their syntheses of (−)-securinine, Honda and co-workers[13] and Figueredo and co-workers[11] 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 Et_3N 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 co-workers also noted the recalcitrance of a similar substrate toward acylation with the Bestmann reagent.[12] Consequently, we turned to a two step procedure involving DCC mediated acylation of the tertiary alcohol with diethylphosphonoacetic



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

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).



Scheme 9. Endgame strategy.

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] (Triphenylphosporanylidene)-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 CH_2Cl_2) and are reported as wavenumber (cm^{-1}). High-resolution mass spectrometry was conducted on an Agilent 6210 TOF LCMS. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 400 or 300 spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ 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-tert-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 h 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 $NaHCO_3$ (satd 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 $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.66 (br s, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{13}H_{22}N_3NaO_5$ $[M+Na]^+$: 322.1373, found: 322.1375.

*4.2.2. Bis-tert-butylcarbamate **15**.* To a solution of **18** (300 mg, 1.00 mmol) and DMAP (12 mg, 0.010 mmol) in CH_3CN (1 mL) was added Boc_2O (240 mg, 1.10 mmol) as a solution in CH_3CN (1 mL). The reaction was refluxed for 10 h. Upon completion the mixture was diluted with EtOAc (5 mL) and H_2O (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 $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{29}N_3NaO_7$ $[M+Na]^+$: 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 $Rh_2(OAc)_4$ (0.6 mg, 0.0014 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 min 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{37}NNaO_8$ $[M+Na]^+$: 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-oxohexanoate[33] (3.30 g, 16.5 mmol) and Et_3N (4.00 mL, 28.9 mmol) in CH_2Cl_2 (37 mL). The reaction was stirred at room temperature for 9 h before adding $NaHCO_3$ (satd 20 mL) and extracting the aqueous layer with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{19}N_2O_6S$ $[M+H]^+$: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 $Rh_2(OAc)_4$ (12.4 mg, 0.028 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 min the reaction was cooled to room temperature before adding $BF_3{\cdot}Et_2O$ (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 (2×); ^{1}H NMR ($CDCl_3$, 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 $C_{19}H_{26}NaO_7S$ $[M+Na]^+$: 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; ^{1}H 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 $C_8H_{12}ClN_2O_3$ $[M+H]^+$: 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 $Rh_2(OAc)_4$ (10.2 mg, 0.023 mmol). The mixture was immediately placed in an oil bath preheated to 120 °C. After 15 min the reaction was cooled to room temperature before adding $BF_3{\cdot}Et_2O$. 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; ^{1}H 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 $C_{12}H_{19}ClO_4Na$ $[M+Na]^+$: 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 (4×50 mL). The organic layers were then washed with water (5×50 mL), and brine (1×50 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 h. 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, two steps) as a clear, pale yellow oil. R_f=0.24 70:30 hexanes/EtOAc; ^{1}H 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 (CDCl3, 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 $C_{12}H_{20}NO_3$ $[M+H]^+$: 226.1437, found: 226.1441. $[\alpha]_D^{22}$ −25.9 (*c* 1.48, $CHCl_3$).

Compound (−)-**25**: R_f=0.43 85:15 hexanes/EtOAc; ^{1}H 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 $C_{12}H_{19}O_4$ $[M+H]^+$: 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 h, 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 diasteromeric 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, two 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 $C_{15}H_{28}NO_4$ $[M+H]^+$: 286.2013, found: 286.2016.

Compound (−)-**30a**: clear, colorless oil; R_f=0.52 70:30 hexanes/EtOAc; ^{1}H 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 $C_{17}H_{30}NO_5$ $[M+H]^+$: 328.2118, found: 328.2122. $[\alpha]_D^{22}$ −43.0 (*c* 0.82, $CHCl_3$).

Compound (+)-**30b**: white solid; R_f=0.61 70:30 hexanes/EtOAc; ^{1}H 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 $C_{17}H_{30}NO_5$ $[M+H]^+$: 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 μL, 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**. Compounds (±)-**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, two steps), respectively, after purification by flash chromatography (gradient elution, 90:10 to 70:30 hexanes/EtOAc).

Compound (±)-**33a**: ^{1}H 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 $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1281, found: 212.1284.

Compound (±)-**33b**: ^{1}H 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 $C_{11}H_{18}NO_3$ $[M+H]^+$: 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 IBX[28] (6.20 g, 22.2 mmol). The mixture was refluxed open to the atmosphere for 6 h. 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.

Compound (+)-**31a**: R_f=0.35 95:5 CH_2Cl_2/EtOAc; ^{1}H 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 $C_{15}H_{25}NO_4Na$ $[M+Na]^+$: 306.1676, found: 306.1672. $[\alpha]_D^{22}$ +39.3 (c 2.68, $CHCl_3$).

Compound (−)-**31b**: R_f=0.48 95:5 CH_2Cl_2/EtOAc; ^{1}H 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 $C_{15}H_{25}NO_4Na$ $[M+Na]^+$: 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 Et_2O, 10.6 mL, 10.6 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min before warming to room temperature and stirring for 1 h more. The reaction was quenched with satd NH_4Cl (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 $MgSO_4$, 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.

Compound (−)-**34a** (β-OH): R_f=0.44 70:30 hexanes/EtOAc; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{32}NO_4$ $[M+H]^+$: 326.2326, found: 326.2327. $[\alpha]_D^{22}$ −48.9 (c 2.02, $CHCl_3$).

Compound (−)-**34b** (α-OH): R_f=0.53 70:30 hexanes/EtOAc; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{32}NO_4$ $[M+H]^+$: 326.2326, found: 326.2327. $[\alpha]_D^{22}$ −51.9 (c 1.73, $CHCl_3$).

*4.2.13. Cyclohexene **35**.* To a solution of (−)-**34a** and (−)-**34b** (794 mg, 2.44 mmol) in CH_2Cl_2 (24 mL) was added Grubbs's second generation catalyst, and the reaction was refluxed for 1.5 h. 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.

Compound (−)-**35a** (β-OH): R_f=0.11 70:30 hexanes/EtOAc; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{26}NO_4$ $[M+H]^+$: 284.1856, found: 284.1855. $[\alpha]_D^{22}$ −80.9 (c 1.12, $CHCl_3$).

Compound (+)-**35b** (α-OH): R_f=0.21 70:30 hexanes/EtOAc; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{26}NO_4$ $[M+H]^+$: 284.1856, found: 284.1860. $[\alpha]_D^{22}$ +15.7 (c 0.74, $CHCl_3$).

*4.2.14. Dibromide **36**.* To a solution of (−)-**35a** and (+)-**35b** (602 mg, 2.12 mmol) in CH_2Cl_2 (42 mL) was added a solution of Br_2 (53.3 μL, 3.18 mmol) in CH_2Cl_2 (5 mL) dropwise at 0 °C. The reaction was stirred for 5 min before pouring into a 10% solution of $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, 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.

Compound (−)-**36a** (β-OH): white powder; R_f=0.21 70:30 hexanes/EtOAc; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{26}Br_2NO_4$ $[M+H]^+$: 442.0223, found: 442.0216. $[\alpha]_D^{22}$ −1.53 (c 1.76, $CHCl_3$).

Compound (+)-**36b** (α-OH): white foam; R_f=0.48 70:30 hexanes/EtOAc ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{26}Br_2NO_4$ $[M+H]^+$: 442.0223, found: 442.0210. $[\alpha]_D^{22}$ +7.10 (c 1.62, $CHCl_3$).

*4.2.15. Enone (−)-**38**.* Anhydrous DMSO (900 μL, 22.7 mmol) in CH_2Cl_2 (1 mL) was added to a solution of oxalyl chloride (805 μL, 5.27 mmol) in CH_2Cl_2 (12 mL) at −78 °C. The mixture was stirred for 10 min before adding a solution of (−)-**36a** and (+)-**36b** (940 mg, 2.11 mmol) in CH_2Cl_2 (7 mL) dropwise. This mixture was stirred for 10 min before adding Et_3N (2.90 mL, 21.1 mmol) and allowing the reaction to warm to room temperature. After 1 h the reaction was diluted with CH_2Cl_2 and washed with commercial bleach solution (12% $NaClO_4$, 2×15 mL). The combined aqueous layers were back extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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) $C_{15}H_{22}BrNNaO_4$ $[M+Na]^+$: 382.0624, found: 382.0624. $[\alpha]_D^{22}$ −132.3 (c 3.12, $CHCl_3$).

4.2.16. (+)-Norsecurinine ***2***. To a solution of (−)-**38** (250 mg, 0.69 mmol) in dry CH_2Cl_2 (7 mL) was added trifluoroacetic acid (550 μL, 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 CH_2Cl_2 (5 mL). Triethylamine (142 μL, 1.04 mmol) was added and the reaction was stirred at room temperature for 15 min. 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 (2×5 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 h 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 min then at room temperature for 10 min. 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, three steps) as a yellow oil. R_f=0.10 90:10 CH_2Cl_2/MeOH; ^{1}H 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; ^{1}H 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).

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra and experimental procedures for the synthesis of (+)-allonorsecurinine are available in online version at doi:10.1016/j.tet.2010.03.015.

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