Total synthesis of (5*R*,6*R*,8*R*,9*S*)-(–)-5,9*Z*-indolizidine 221T using sulfinimine-derived *N*-sulfinyl β-amino ketones†

Franklin A. Davis,* Minsoo Song, Hui Qiu and Jing Chai

Received 3rd August 2009, Accepted 23rd September 2009
First published as an Advance Article on the web 26th October 2009
DOI: 10.1039/b915796d

The first total asymmetric synthesis of the poison frog alkaloid (–)-221T, a 5,6,8-trisubstituted indolizidine is described. The key core piperidine ring was constructed *via* an acid catalyzed intramolecular cascade Mannich cyclization reaction of a *N*-sulfinyl *syn*-α-methyl β-amino ketone and crotonaldehyde. The β-amino ketone was prepared *via* the reaction of prochiral lithium Weinreb amide enolate with an enantiopure *N*-2,4,6-triisopropylphenylsulfinyl imine.

Introduction

The alkaloid 5,9-*Z*-indolizidine 221T (**1**) is one of more than 800 different alkaloids isolated from the skins of poison frogs by Daly and co-workers.[1,2] This is an example of a 5,6,8-trisubstituted indolizidine of which about 70 alkaloids have been assigned to this class.[3] Of these alkaloids, only indolizidine 223A (**2**) has been prepared (Fig. 1).[4–6] Since these alkaloids were isolated in trace amounts, their structures are tentative, being based on mass spectral and FTIR data.[1] Although little is known about their biological activity, related indolizidine alkaloids are noncompetitive blockers of nicotinic acetylcholine receptor channels,[1,2,7a] and have demonstrated binding affinity for the human δ-opioid receptor.[7b]

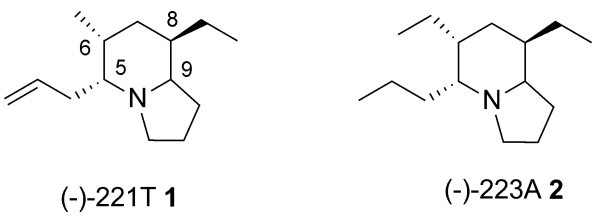


Fig. 1 Indolizidine alkaloids.

Key to the synthesis of the 5,6,8-trisubstituted indolizidines, such as (–)-221T (**1**), are efficient processes for the stereocontrolled construction of the core piperidine ring.[8] In this regard, the acid-catalyzed intramolecular Mannich cyclization reaction, a cascade reaction, between an *N*-sulfinyl β-amino ketone and an aldehyde, is a powerful method for the asymmetric synthesis of multi-substituted stereodefined piperidones (Fig. 2).[9,10] In addition to (–)-223A (**2**),[4] we have employed this methodology in highly efficient asymmetric syntheses of trisubstituted piperidine (–)-nupharamine,[11] indolizidine (–)-209B[12] and substituted tropinones.[13] The reaction of Grignard reagents with sulfinimine-derived enantiopure *N*-sulfinyl β-amino Weinreb amides readily affords the requisite *N*-sulfinyl β-amino ketones.[14] Using this protocol the first total synthesis of (5*R*,6*R*,8*R*,9*S*)-(–)-5,9*Z*-indolizidine 221T (**1**) has been achieved, demonstrating the general utility of this protocol for the synthesis of 5,6,8-trisubstituted indolizidine alkaloids.

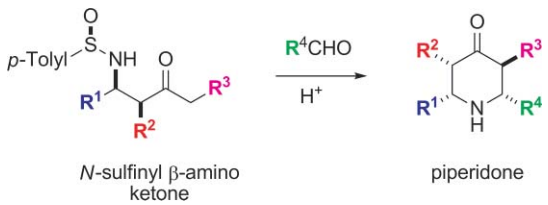


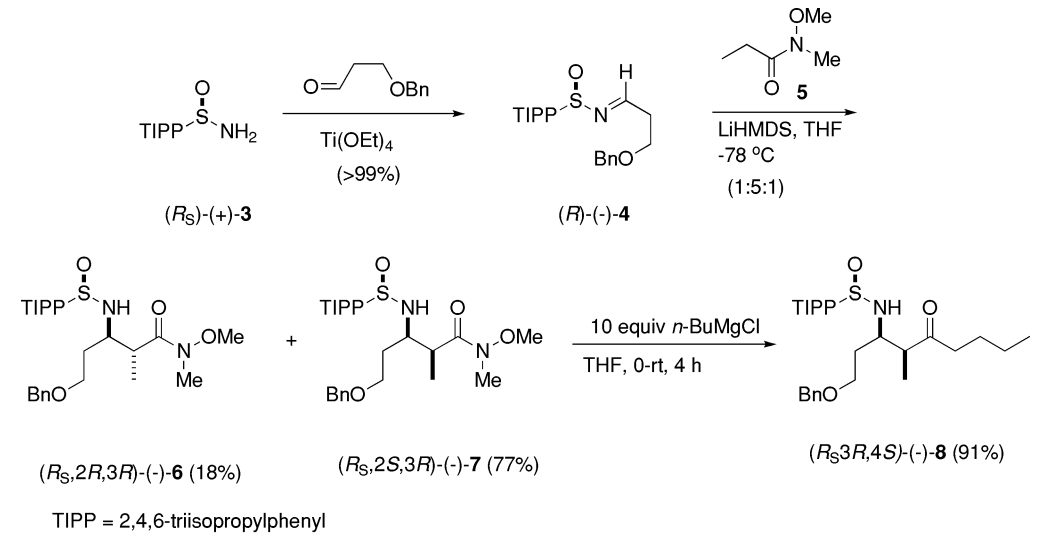
Fig. 2 Intramolecular Mannich cyclization of *N*-sulfinyl β-amino ketones and aldehydes.

Results and discussion

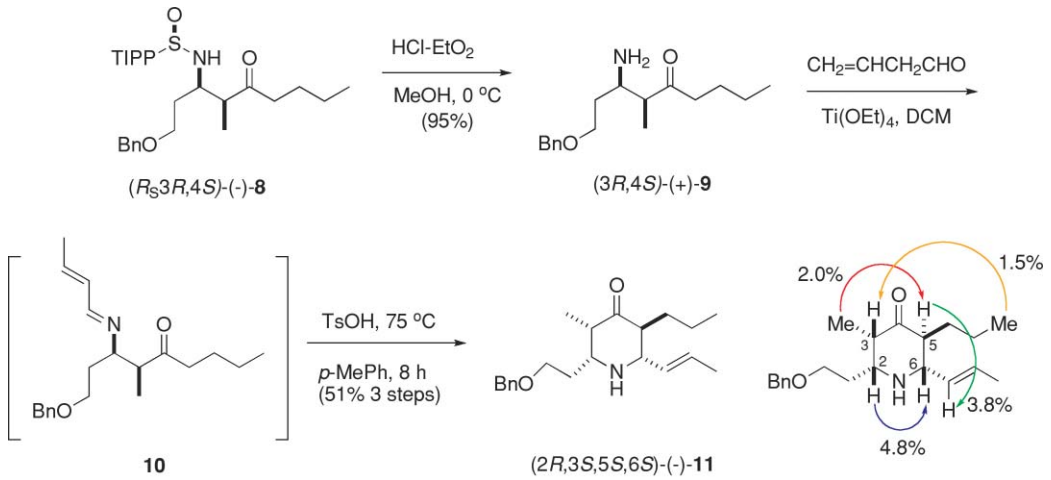
Our synthesis began with preparation of sulfinimine (*R*)-(–)-**4** by condensing (*R*)-(+)-2,4,6-triisopropylphenylsulfinamide (**3**)[16] with 3-benzyloxypropanal and $Ti(OEt)_4$ to give the sulfinimine in quantitative yield (Scheme 1). Sulfinimine (*R*)-(–)-**4**, 0.4 equiv, was added to the preformed prochiral lithium Weinreb amide enolate of *N*-methoxy-*N*-methylpropylamide (**5**), prepared at –78 °C using LiHMDS. The *syn*- and *anti*-β-amino Weinreb amides (–)-**6** and (–)-**7** were obtained in approximately a 1 : 5.1 ratio, affording the major *syn* isomer (–)-**7** in 77% isolated yield. Attempts to improve the *syn* : *anti* selectivity by varying the solvent and changing the base to LDA resulted in poorer ratios. The stereochemical assignment of (–)-**7** to the *syn* isomer was based on earlier studies where it was also demonstrated that the 2,4,6-triisopropyl (TIPP) sulfinyl auxiliary afforded the best *syn* : *anti* selectivities.[14b,15] Next, treatment of (–)-**7** with 10 equiv. of *n*-butylmagnesium chloride in THF gave *N*-sulfinyl β-amino ketone (R_S,3*R*,3*S*)-(–)-**8** in 91% yield (Scheme 1).

The conversion of (–)-**8** to piperidone (–)-**11** involved removal of the sulfinyl auxiliary (HCl–Et_2O) to give an amine hydrochloride salt, which was neutralized with aqueous NaOH to give amino ketone (3*R*,4*S*)-(+)-**9** in 95% yield. However, upon purification, the amine rapidly decomposed and was used in crude form. Next, the amine was treated with crotonaldehyde and $Ti(OEt)_4$ to give imine **10**. The imine decomposed on attempted purification and was simply passed through a pad of Celite prior to subjecting it to the intramolecular Mannich cyclization (IMC) reaction. Under optimized conditions, the crude imine was heated in toluene with

Department of Chemistry, Temple University, Philadelphia, PA, 19122, USA. E-mail: fdavis@temple.edu; Fax: +1 215-204-0478; Tel: +1 215-204-0477
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR data for all new compounds. See DOI: 10.1039/b915796d



Scheme 1

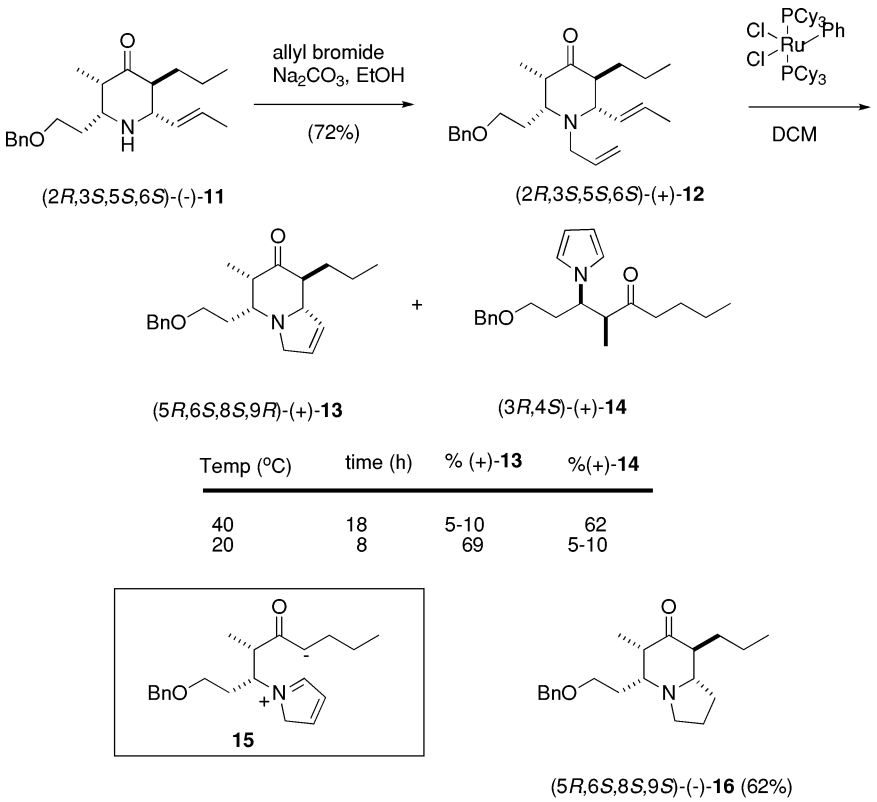


Scheme 2

2 equiv. of anhydrous *p*-toluenesulfonic acid at 75 °C for 8 h to give piperidone (2*R*,3*S*,5*S*,6*S*)-(−)-**11** in 51% yield for the three step sequence (Scheme 2). Use of toluenesulfonic acid hydrate, longer or shorter reaction times, and lower temperatures all resulted in poor yields (30–40%) of the piperidone. The structure of (−)-**11** was based on the fact that the IMC reaction of β-amino ketones and aldehydes gives piperidones where the C-2 and C-6 substituents have a *cis* relationship and NOE studies (Scheme 2).[4,11,12]

To prepare the unsaturated indolizidine from (−)-**11**, the idea was to allylate the piperidone nitrogen and use ring-closing metathesis (RCM) to generate the pyrrolidine ring. Allylation of (−)-**11** with 10 equiv. of allyl bromide/Na_2CO_3 in ethanol and heating gave amino diene (+)-**12** in 72% yield (Scheme 3). The amino diene (+)-**12** was heated at 40 °C in DCM with the Grubbs "first generation" catalyst[16] for 18 h to give a blue colored solution. However, less then 10% of the desired unsaturated indolizidine (+)-**13** was detected. Unexpectedly, the major product was keto pyrrole (+)-**14**, isolated in 62% yield (Scheme 3). The structure of the pyrrole is based on HRMS data, and the 2,5- and 3,4-pyrrole protons at δ 6.5 ppm and δ 6.0 ppm, respectively. When the temperature and time were reduced to rt and to 8 h, it was possible to isolate the unsaturated indolizidine (+)-**13** in about 69% yield, but contaminated with the pyrrole.

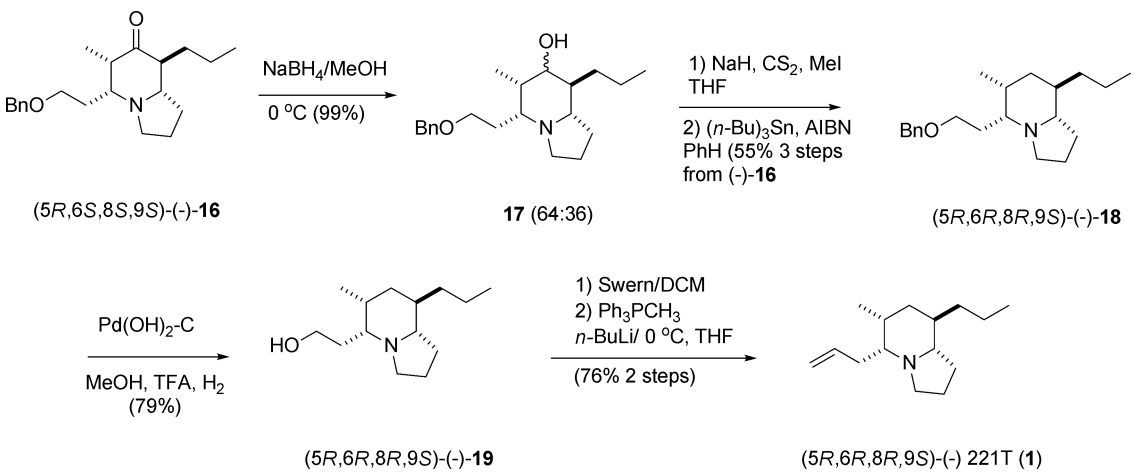
When (+)-**13** was heated at 80 °C in benzene for 16 h, a 4 : 1 mixture of **13** : **14** resulted, and with the Grubbs catalyst at 40 °C in DCM for 16 h, a 1 : 6 ratio of **13** : **14** was obtained. The formation of the pyrrole (+)-**14** is consistent with a retro-Mannich reaction of (+)-**13** affording species **15**, which aromatizes to the pyrrole. Pyrrole formation in the RCM of diallylamines has been reported.[17] Here, the Grubbs catalyst apparently isomerizes the alkene and functions as a dehydrogenation reagent. This does not appear to be what is happening in the formation of pyrrole (+)-**14** from (+)-**13** because the transformation can be thermally induced. We suggest that the Grubbs catalyst promotes the retro-Mannich reaction by associating with the piperidone oxygen. Because it was difficult to isolate (+)-**13** free of the pyrrole the mixture was hydrogenated (H_2/Pd–C) to give (5*R*,6*S*,8*S*,9*S*)-(−)-**16** in 62% yield (Scheme 3).



Scheme 3

With (–)-**16** in hand, removal of the C-7 oxo group was accomplished by reduction with $NaBH_4$ to give a mixture of isomeric alcohols **17** in quantitative yield. The crude alcohols were subjected to the Barton–McCombie radical deoxygenation reaction, giving indolizidine (5*R*,6*R*,8*R*,9*S*)-(–)-**18** in 55% yield for the two steps (Scheme 4). Deprotection of the benzyloxy group (TFA, 20% $Pd(OH)_2$, H_2, 1 atm) gave alcohol (5*R*,6*R*,8*R*,8a*S*)-(–)-**19** in 79% yield. Swern oxidation gave an aldehyde, which was not stable to purification and was carried on to the next step in crude form. A Wittig reaction (Ph_3PCH_3/*n*-BuLi) was used to install the methylene group, completing the first total synthesis of (5*R*,6*R*,8*R*,9*S*)-(–)-5,9*Z*-Indolizidine 221T (**1**) (Scheme 4).

In conclusion, we have accomplished the first total synthesis of (5*R*,6*R*,8*R*,9*S*)-(–)-5,9*Z*-indolizidine 221T (**1**) in 15 steps with a 4.4% overall yield. Highlights of the synthesis include a novel intramolecular Mannich cyclization cascade reaction of a sulfinimine-derived *syn*-α-methyl *N*-sulfinyl-β-amino ketone (–)-**8**, prepared form *N*-sulfinyl β-amino Weinreb amide (–)-**7**.



Scheme 4

Experimental

General information

All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), and toluene were purified by filtration on a Glass Contour Solvent System. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 and a Varian 300 MHz NMR spectrometer. $CDCl_3$ was used as a solvent and TMS as an internal standard. NOE studies were done after assigning the chemical shifts of protons and carbons using COSY, HECTOR(HMQC) and DEPT experiments. Optical rotations were measured on a PerkinElmer 341 instrument. HRMS were obtained on a G ZAB2SE high resolution mass spectrometer.

(*R*)-(+)-2,4,6-Triisopropylphenylsulfinamide (**3**) and *N*-methoxy-*N*-methylpropylamide (**5**) were prepared as previously described.[16] 3-Benzyloxypropanal was purchased from Aldrich.

(*R*)-(−)-*N*-(3-(Benzyloxy)propylidene)-2,4,6-triisopropylbenzenesulfinamide (4)

In a 1000 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed (*R*)-(+)-**3** (3.56 g, 13.3 mmol) and 3-benzyloxypropanal (2.30 g, 14.0 mmol) in DCM (200 mL). The mixture was cooled to 0 °C and $Ti(OEt)_4$ (13.8 mL, 66.5 mmol) was added. The solution was warmed to rt and stirred for 4 h. At this time, the reaction mixture was diluted with DCM (300 mL), the solution was vigorously stirred and H_2O (13.8 mL) was added dropwise. The mixture was filtered through a Celite pad, washed with DCM (100 mL) and the combined organic phases concentrated. Flash chromatography (20% Et_2O–hexane) provided 5.44 g (99%) of a colorless oil; $[\alpha]_D^{20}$ −139.1 (*c* 0.83, $CHCl_3$); IR (neat) 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.40 (t, J = 4.8 Hz, 1H), 7.30 (m, 5H), 7.07 (s, 2H), 4.53 (s, 2H), 3.76 (m, 4H), 2.86 (m, 3H), 1.25 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 165.9, 152.8, 149.7, 138.0, 134.5, 128.5, 127.8, 123.0, 73.3, 66.3, 36.8, 34.5, 27.9, 24.5, 24.0, 23.8 (one carbon could not be identified due to overlap). HRMS calcd for $C_{25}H_{36}NO_2S$ (M + H) 414.2467. Found 414.2450.

(R_S,2*S*,3*R*)-(−)-*N*-Methoxy-*N*,2-dimethyl-3-(2,4,6-triisopropylphenylsulfinamido)-5-benzyloxypentanamide (7)

In a 100 mL, oven-dried, single-neck round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed LiHMDS (13.85 mL, 13.85 mmol, 1.0 M solution in THF), and a solution of *N*-methoxy-*N*-methylpropylamide (**5**) (1.62 g, 13.85 mmol) in THF (40.0 mL) was added at −78 °C *via* cannula. The solution was stirred for 2 h at −78 °C at which time sulfinimine (*R*)-(−)-**4** (2.29 g, 5.54 mmol) in THF (16.0 mL) was added dropwise. The reaction mixture was stirred for 1 h at this temperature and quenched by addition of sat. aqueous NH_4Cl (10 mL). The solution was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (2 × 20 mL), dried ($MgSO_4$) and concentrated. Chromatography (50% Et_2O–hexanes) provided 2.26 g (77%) of a colorless oil as the major isomer and 0.529 g (18%) of a colorless oil as a minor isomer. Major isomer: $[\alpha]_D^{20}$ −27.6 (*c* 0.975, $CHCl_3$); IR (neat) 2961, 2869, 1652, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 7.05 (s, 2H), 5.16 (d, J = 8.0 Hz, 1H), 4.45 (s, 2H), 3.95 (bs, 2H), 3.74 (m, 4H), 3.57 (m, 3H), 3.20 (s, 3H), 2.87 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.28 (d, J = 6.6 Hz, 3 H), 1.23 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 176.1, 151.6, 147.4, 138.8, 138.6, 128.4, 127.6, 127.5, 123.0, 73.0, 67.8, 61.6, 56.9, 40.5, 34.4, 32.0, 31.3, 28.5, 24.4, 24.3, 23.9, 13.6. HRMS calcd for $C_{30}H_{47}N_2O_4S$ (M + H) 531.3257. Found 531.3280.

(R_S,2*R*,3*R*)-(−)-*N*-Methoxy-*N*,2-dimethyl-3-(2,4,6-triisopropylphenylsulfinamido)-5-benzyloxypentanamide (6)

Minor isomer: $[\alpha]_D^{20}$ −48.6 (*c* 1.05, $CHCl_3$); IR (neat) 2961, 2869, 1653, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 7.05 (s, 2H), 4.90 (d, J = 8.4 Hz, 1H), 4.51 (d, J = 2.4 Hz, 2H), 4.02 (bs, 2H), 3.80 (m, 1H) 3.65 (m, 2H), 3.52 (s, 3H), 3.11 (m, 4H), 2.86 (m, 1H), 2.16 (m, 1H), 1.96 (m, 1H), 1.23 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 166.6, 151.6, 147.4, 139.2, 138.6, 128.6, 128.0, 127.8, 123.1 73.4, 67.7, 61.5, 58.6, 40.2, 34.5, 33.8, 32.5, 28.6, 24.8, 24.4, 24.0, 15.1. HRMS calcd for $C_{30}H_{47}N_2O_4S$ (M + Na) 531.3257. Found 531.3280.

N-[(R_S,3*R*,4*S*)-(−)-1-(Benzyloxy)-4-methyl-5-oxononan-3-yl]-2,4,6-triisopropyl-benzenesulfinamide (8)

In a 25 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed (−)-**6** (2.07 g, 3.95 mmol) in THF (50 mL), and the solution was cooled to 0 °C. To the solution was added *n*-butylmagnesium chloride (19.7 mL, 39.5 mmol, 2.0 M solution in THF) *via* syringe, and the reaction mixture was stirred for 2 h at rt, quenched by addition of sat. aqueous NH_4Cl (5 mL) at 0 °C and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), and concentrated. Chromatography (50% hexanes–EtOAc) provided 1.89 g (91%) of a colorless oil; $[\alpha]_D^{20}$ −42.6 (*c* 0.47, $CHCl_3$); IR (neat) 2960, 2869, 1700, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 7.04 (s, 2H), 5.20 (d, J = 8.8 Hz, 1H), 4.42 (s, 2H), 3.90 (bs, 2H), 3.66 (m, 1H), 3.51 (m, 2H), 3.23 (m, 1H), 2.86 (dq, J = 6.8 Hz, 1H), 2.48 (m, 2H), 1.88 (m, 2H), 1.53 (m, 2H), 1.22 (m, 23 H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.9, 151.1, 146.8, 138.2, 137.9, 127.9, 127.1, 127.0, 122.5, 72.6, 67.0, 56.9, 50.0, 41.0, 33.9, 31.7, 28.0, 25.2, 23.9, 23.8, 23.3, 21.9, 13.5, 13.3. HRMS calcd for $C_{32}H_{50}NO_3S$ (M + H) 528.3511. Found 528.3487.

(2*R*,3*S*,5*S*,6*S*,*E*)-(−)-2-(2-(Benzyloxy)ethyl)-3-methyl-6-(prop-1-enyl)-5-propylpiperidin-4-one (11)

(a) In a 250 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed (−)-**8** (1.71 g, 3.24 mmol) in anhydrous MeOH (103 mL). The solution was cooled to 0 °C, HCl (6.5 mL, 12.98 mmol, 2.0 M solution in Et_2O) was added *via* syringe, and the reaction mixture was stirred for 20 min at 0 °C. At this time, enough aqueous NaOH solution was added at 0 °C to bring the pH of the solution to 9. The mixture was extracted with DCM (2 × 20 mL), the combined organic phases washed with brine

(2 × 20 mL), dried ($NaSO_4$), and concentrated. The crude amine (+)-**9** was used in the next step without further purification.

(b) In a 250 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed crude (+)-**9** in DCM (52 mL), crotonaldehyde (2.76 mL, 32.5 mmol), and $Ti(OEt)_4$ (3.31 mL, 16.25 mmol) were added at 0 °C *via* syringe. The reaction mixture was stirred for 3 h at rt, diluted with DCM (100 mL), stirred vigorously, and quenched by dropwise addition of sat. $NaHCO_3$ (6.62 mL). The mixture was filtered through a Celite pad and the Celite was washed with DCM (100 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). The crude imine **10** was carried on to the next step without further purification.

(c) In a 250 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed anhydrous TsOH (1.04 g, 6.48 mmol), and a solution of the crude imine **10** in anhydrous toluene (103 mL) was added *via* a cannula. At this time the reaction mixture was warmed to 75 °C, stirred for 8 h, cooled to rt, and diluted with Et_2O (20 mL). Enough sat. aq. $NaHCO_3$ solution was added until the aqueous phase reached pH 8, at which time the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic phases were washed with brine (2 × 20 mL), dried ($MgSO_4$) and concentrated. Chromatography (10% EtOAc–hexanes) gave 0.545 g (51%) of a yellow oil; $[\alpha]_D^{20}$ −5.7 (*c* 0.667, $CHCl_3$); IR (KBr) 3343, 1707, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (m, 5H), 5.57 (dq, $J = 6.4$, 15.2 Hz, 1H), 5.41 (ddq, $J = 1.6$, 8.4, 15.2 Hz, 1H), 4.48 (m, 2H), 3.65 (m, 1H), 3.59 (m, 1H), 2.97 (dd, $J = 8.4$, 10.2 Hz, 1H), 2.61 (ddd, $J = 2.4$, 8.6, 10.8 Hz, 1H), 2.27 (ddq, $J = 1.1$, 6.4, 10.8, 1H), 2.16 (ddd, $J = 1.1$, 6.5, 10.2, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.69 (dd, $J = 1.6$, 6.4 Hz, 3H), 1.61 (m, 1H), 1.36 (m, 1H), 1.16 (m, 2H), 0.98 (d, $J = 6.4$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H), the NH proton was partially overlapped with peak at δ 2.27; ^{13}C NMR ($CDCl_3$) δ 211.3, 138.4, 132.7, 128.6, 128.5, 127.8, 127.5, 73.2, 68.7, 65.3, 62.6, 55.9, 50.9, 34.0, 27.6, 21.2, 17.9, 14.6, 10.3. HRMS calcd for $C_{21}H_{32}NO_2$ (M + H) 330.2433. Found 330.2428.

Upon irradiation of the C-2 proton at δ 2.55 ppm, a positive NOE was observed on the C-6 proton at δ 2.91 (4.8%), indicating a *cis*-relationship between the C-2 and the C-6 protons. Upon irradiation of the C-3 methyl at δ 0.92 ppm, a positive NOE was observed on the C-5 proton at δ 2.11 (2.0%), indicating the *trans* relationship between the C-3 methyl group and the C-5 proton. Upon irradiation of the C-5 methyl group at δ 0.79 ppm, a positive NOE was observed on the C-6 proton at δ 2.91 (1.5%), indicating a *cis*-relationship between the C-5 methyl group and the C-6 proton. Upon irradiation of the C-5 proton at δ 2.11, a positive NOE was observed on the C-6 vinyl proton at δ 5.35 (3.8%), indicating a *cis*-relationship between the C-5 and the C-6 vinyl protons.

(3*R*,4*S*)-(+)-3-Amino-1-(benzyloxy)-4-methylnonan-5-one (9)

An analytical sample was purified by chromatography (5% MeOH–CH_2Cl_2, 0.5% Et_3N) to give a colorless oil that slowly decomposed on standing: $[\alpha]_D^{20}$ +32.6 (*c* 0.35, $CHCl_3$); IR (neat) 3386, 2933, 2870, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.50 (s, 2 H), 3.59 (m, 2 H), 3.26 (dt, $J = 4.8$, 8.4 Hz, 1 H), 2.56 (dq, $J = 4.8$,6.8 Hz, 1 H), 2.45 (m, 2 H), 1.63 (m, 2 H), 1.52 (m, 2 H), 1.28 (m, 4 H), 1.06 (d, $J = 6.8$ Hz, 3 H), 0.90 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.6, 138.7, 128.7, 127.98, 127.95, 73.4, 68.5, 51.8, 50.4, 42.1, 35.9, 26.1, 22.7, 14.2, 10.7. HRMS calcd for $C_{17}H_{28}NO_2$ (M + H) 278.2120. Found 278.2111.

(2*R*,3*S*,5*S*,6*S*,*E*)-(+)-1-Allyl-2-(2-(benzyloxy)ethyl)-3-methyl-6-(prop-1-enyl)-5-propylpiperidin-4-one (12)

In a 50 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed piperidone (−)-**11** (0.465 g, 1.413 mmol) in absolute EtOH (40 mL). Anhydrous Na_2CO_3 (2.15 g, 20.28 mmol) and allyl bromide (1.21 mL, 14.13 mmol) were added at rt and the reaction mixture was stirred for 15 h at 70 °C. The solution was filtered through a Celite pad, the Celite was washed with DCM (2 × 10 mL) and the combined organic phases were concentrated. To the residue was added H_2O (5 mL) and the solution was extracted with DCM (2 × 20 mL). The combined organic phases were washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Chromatography (10% Et_2O–hexanes) provided 0.376 g (72%) of a yellow oil; $[\alpha]_D^{20}$ +14.5 (*c* 0.75, $CHCl_3$); IR (KBr) 1716, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.77 (m, 1H), 5.50 (dq, $J = 6.4$, 15.0 Hz, 1H), 5.27 (ddq, $J = 1.6$, 9.4, 15.0 Hz, 1H), 5.11 (m, 1H), 5.08 (s, 1H), 4.51 (s, 2H), 3.64 (dd, $J =$ 7.2, 7.2 Hz, 2H), 3.47 (dd, $J = 6.0$, 16.0 Hz, 1H), 3.29 (dd, $J = 7.0$, 16.0 Hz, 1H), 2.96 (dd, $J = 9.4$, 9.4 Hz, 1H), 2.59 (m, 1H), 2.47 (dq, $J = 6.4$, 7.2, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.71 (dd, $J = 1.6$, 6.4 Hz, 3H), 1.60 (m, 1H), 1.31 (m, 1H), 1.14 (m, 2H), 1.05 (d, $J = 6.4$ Hz, 3H), 0.84 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.9, 138.7, 133.7, 132.8, 128.9, 128.5, 127.7, 117.7, 73.3, 69.6, 66.6, 64.1, 53.4, 51.6, 48.0, 30.9, 28.6, 21.1, 17.8, 14.5, 12.5 (one unsaturated carbon could not be assigned). HRMS calcd for $C_{24}H_{36}NO_2$ (M + H) 370.2746. Found 370.2747.

(3*R*,4*S*)-(+)-1-(Benzyloxy)-4-methyl-3-(1*H*-pyrrol-1-yl)nonan-5-one (14)

In a 100 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, condenser, rubber septum and an argon balloon was placed piperidone (+)-**12** (0.340 g, 0.92 mmol) in anhydrous DCM (49 mL), and 5 mol%, Grubs "first generation" catalyst (0.038 g 0.46 mmol). The reaction mixture was heated at 40 °C for 48 h at which time the blue solution was concentrated. Chromatography (33.3% Et_2O–hexanes) to give 0.208 (69%) of a blue oil; $[\alpha]_D^{20}$ +1.5 (*c* 0.733, $CHCl_3$); IR (neat) 3446, 3031, 2958, 2870, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (m, 5H), 6.5 (t, $J = 2.2$ Hz, 2H), 6.0 (t, $J = 2.0$ Hz, 2H), 4.29 (s, 2H), 4.24 (ddd, $J = 3.6$, 10.1, 12.1 Hz, 1H), 3.25 (m, 1H), 2.94 (m, 2H), 2.12 (m, 2H), 1.81 (m, 2H), 1.23 (m, 2H), 1.05 (d, $J = 7.6$ Hz, 3H), 1.02 (m, 2H), 0.72 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.1, 138.2, 128.4, 127.7, 127.6, 119.4, 108.0, 73.2, 66.3, 58.8, 51.8, 42.4, 32.8, 25.2, 22.0, 14.5, 13.8. HRMS calcd for $C_{21}H_{29}NO_2$ (M) 327.2198. Found 327.2207.

(5*R*,6*S*,8*S*,9*S*)-(+)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propyl-5,6,8,8a-tetrahydroindolizin-7(3*H*)-one (13)

In a 250 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, condenser, rubber septum and an argon balloon was placed piperidone (+)-**12** (0.373 g, 1.011 mmol) in anhydrous DCM (50 mL), and 5 mol% Grubs "first

generation" catalyst (0.083 g, 0.46 mmol). The reaction mixture was stirred at rt for 8 h, concentrated, and applied directly to a silica gel column. Chromatography (10% Et_2O–hexanes) to give 0.227 g (69%) of a yellow oil that slowly turned blue on standing; $[\alpha]_D^{20}$ +44.7 (*c* 0.094, $CHCl_3$); IR (KBr) 3010, 2958, 2872, 2767, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (m, 5H), 6.0 (m, 1H), 5.91 (m, 1H), 4.44 (s, 2H), 3.59 (m, 3H), 3.30 (m, 2H), 2.63 (m, 1H), 2.39 (m, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.36 (m, 1H), 1.13 (m, 2H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.82 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.7, 138.6, 132.3, 129.0, 128.5, 127.7 (2C), 73.2, 72.6, 67.4, 63.3, 54.9, 52.5, 47.0, 31.9, 28.1, 21.3, 14.5, 10.8. HRMS calcd for $C_{21}H_{30}NO_2$ (M + H) 370.2746. Found 370.2747.

(5*R*,6*S*,8*S*,9*S*)-(-)-5-[2-(Benzyloxy)ethyl]-6-methyl-8-propyl-hexahydroindolizin-7(1*H*)-one (16)

(a) In a 250 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed piperidone (+)-**12** (0.340 g, 0.92 mmol) in anhydrous DCM (49 mL), and 5 mol% of Grubs "first generation" catalyst (0.083 g, 0.46 mmol) was added. The solution was stirred for 3 h at rt, concentrated, and applied directly to a short-pad silica gel column eluting with 33.3% Et_2O–hexanes. The blue colored solution was concentrated in a 50 mL single-necked round bottom flask and the unstable blue residue was carried on to the next step without further purification.

(b) To the round bottomed flask was added a magnetic stirring bar, rubber septum, and anhydrous MeOH (15 mL). To the solution was added 10 wt% Pd/C (0.184 g, 0.092 mmol) at rt. The mixture was evacuated and filled with H_2, and this sequence was repeated 5 times and the solution was stirred for 2 h at rt under an H_2 atmosphere (1 atm, H_2-filled balloon). The mixture was filtered through a Celite pad and the Celite was washed with Et_2O (20 mL). Chromatography (25% EtOAc–hexanes) provided 0.181 g (60%) of a colorless oil; $[\alpha]_D^{20}$ −12.0 (*c* 0.28, $CHCl_3$); IR (neat) 3031, 2957, 2870, 2786 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 5H) 4.48 (s, 2H), 3.63 (ddd, $J = 1.6$, 7.2, 7.4 Hz, 2H), 3.20 (ddd, $J =$ 2.4, 8.4, 8.8 Hz, 1H), 2.43 (ddq, $J = 1.2$, 6.4, 8.4, 1H), 2.24 (m, 1H), 2.0 (m, 6H), 1.80 (m, 1H), 1.68 (m, 2H), 1.54 (m, 1H), 1.37 (m, 1H), 1.15 (m, 2H), 0.99 (d, $J = 6.4$ Hz, 3H), 0.80 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.7, 138.6, 128.5, 127.6, 127.56, 73.1, 69.6, 66.3, 66.1, 55.3, 50.7, 47.2, 31.4, 30.2, 28.2, 21.4, 21.2, 14.6, 10.7. HRMS calcd for $C_{21}H_{32}NO_2$ (M+H) 330.2433. Found 330.2418.

(5*R*,6*R*,8*R*,9*S*)-(−)-5-(2-(Benzyloxy)ethyl)-6-methyl-8-propyl-octahydroindolizine (18)

(a) In a 50 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed (−)-**16** (0.110 g, 0335 mmol) in anhydrous MeOH (11.5 mL). To the solution was added $NaBH_4$ (0.101 g, 1.338 mmol) at 0 °C and the solution was stirred for 2 h at this temperature. The reaction mixture was concentrated, diluted with H_2O (3 mL), and extracted with Et_2O (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude alcohol isomers were carried on to the next step without further purification.

(b) In a 50 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed NaH (0.160 g, 2.007 mmol) in anhydrous petroleum ether (2 mL). The mixture was gently stirred for 30 s and the petroleum ether was removed by syringe. The sticky mixture was evacuated for 2 min, filled with argon, and this sequence was repeated twice. To the NaH was added THF (5.6 mL) and the crude alcohols in THF (5.6 mL). The solution was stirred for 1 h at rt, CS_2 (0.120 mL, 2.007 mmol) was added, and the solution was stirred for 2 h. At this time MeI (0.208 mL, 3.35 mmol) was added, the reaction mixture was stirred for 16 h at rt, and quenched by cautious addition of H_2O (2 mL). The solution was diluted with Et_2O (20 mL), washed with H_2O (3 × 3 mL), the organic phases were combined, washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The residue was used in the next step without further purification.

(c) In a 25 mL, oven-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon balloon was placed AIBN (0.0275 g, 0.167 mmol), and the residue from the previous step in benzene (1.4 mL) was added *via* syringe. The mixture was warmed to 85 °C and a solution of *n*-Bu_3SnH (0.33 mL, 1.23 mmol) in benzene (1.4 mL) was added using syringe drive over 3.5 h. At this time the reaction mixture was stirred for 30 min at this temperature, cooled to rt, and concentrated. Chromatography (10% Et_2O–hexanes to 50% Et_2O–hexanes) provided 0.058 g (55% for the 3 steps) of a colorless oil; $[\alpha]_D^{20}$ −61.7 (*c* 0.12, $CHCl_3$); IR (neat) 3020, 2956, 2869 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (m, 5H), 4.51 (s, 2H), 3.59 (dd, $J = 7.8$, 7.8 Hz, 2H), 3.18 (ddd, $J = 1.2$, 8.4, 8.8 Hz, 1H), 1.05–1.95 (m, 15H), 0.98 (m, 1H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.9, 128.4, 127.6, 127.5, 73.0, 70.5, 67.5, 67.4, 52.2, 40.8, 40.5, 35.7, 34.8, 31.0, 29.2, 21.0, 19.8, 18.7, 14.5. HRMS calcd for $C_{21}H_{34}NO$ (M+H) 316.2640. Found 316.2650.

2-(5*R*,6*R*,8*R*,9*S*)-(−)-6-Methyl-8-propyl-octahydroindolizin-5-yl)ethanol (19)

In a 10 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar was placed indolizidine (−)-**18** (0.055 g, 0.174 mmol) in anhydrous THF (6.8 mL) and MeOH (2.4 mL). To the solution was added 20% $Pd(OH)_2/C$ (0.551 g, 1000 wt%) and TFA (0.215 mL, 2.79 mmol). The mixture was evacuated for 30 s and filled with H_2, and this sequence was repeated 5 times. The mixture was stirred for 28 h at rt under 1 atm H_2 (hydrogen balloon). The reaction mixture was filtered through a Celite pad, and the Celite was washed with Et_2O (20 mL). The combined solutions were concentrated and washed with 5 mL of sat. $NaHCO_3$ solution until the pH of the aqueous phase was greater than 7. At this time, the solution was extracted with DCM (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Preparative TLC (6% MeOH–CH_2Cl_2) provided 0.0308 g (79%) of a yellow oil; $[\alpha]_D^{20}$ −56.2 (*c* 1.04, $CHCl_3$); IR (neat) 3394, 2956, 2870, 2781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (dt, $J = 2.8$, 11.6 Hz, 1H), 3.66 (m, 1H), 3.61 (broad t, $J =$ 8.0 Hz, 1H), 2.14 (m, 1H), 2.00 (m, 2H), 1.87 (m, 3H), 1.68 (m, 4H), 1.24 (m, 5H), 1.00 (m, 1H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.72 (q, $J = 11.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 71.0, 68.3, 59.9, 52.7, 40.3, 39.8, 35.5, 31.9, 29.1 (2C), 20.6, 19.7,

18.7, 14.5. HRMS calcd for $C_{14}H_{28}NO$ (M + H) 226.2171. Found 226.2173.

(5*R*,6*R*,8*R*,9*S*)-(−)-5, 9*Z*-Indolizidine 221T (1)

(a) In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar was placed DMSO (0.02 mL, 0.282 mmol) in DCM (0.5 mL) and $(COCl)_2$ (0.012 mL, 0.137 mmol) was added at −78 °C. After stirring for 45 min, alcohol (−)-**19** (0.026 g, 0.114 mmol) in DCM (1.9 mL) was added dropwise over 10 min using a syringe pump. After stirring for 30 min at −78 °C, the reaction mixture was quenched by addition of Et_3N (0.095 mL, 0.683 mmol), slowly warmed to rt, diluted with DCM (10 mL), washed with sat. aqueous $NaHCO_3$ (2 × 5 mL), washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The crude aldehyde was unstable and taken on to the next step without further purification.

(b) In a 5 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar was placed $Ph_3P^+CH_3I^-$ (0.144 g, 0.356 mmol) in THF (1.8 mL). To the solution was added *n*-BuLi (0.142 mL, 0.356 mmol, 2.5 M in hexanes) at 0 °C. After stirring for 30 min, a solution of the aldehyde in THF (1 mL) was added, and the reaction mixture was stirred for 4 h at rt. At this time the reaction was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (2 × 10 mL). The organic phases were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. Chromatography (3% MeOH–CH_2Cl_2, 1% Et_3N) provided 0.012 g (76% for the 2 steps) of a yellow oil; $[\alpha]_D^{20}$ −36.3 (*c* 0.08, $CHCl_3$); IR (KBr) 3394, 2956, 2870, 2781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.97 (m, 1H), 5.17 (d, $J = 6.8$ Hz, 1H), 5.14 (s, 1H), 3.91 (m, 1H), 2.82 (m, 2H), 2.6 (m, 3H), 2.46 (m, 1H), 2.25 (m, 4H), 1.98 (m, 3H), 1.29 (m, 3H), 1.02 (m, 1H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.8, 116.5, 70.9, 69.4, 52.3, 51.4, 40.6, 53.9, 53.2, 34.1, 29.3, 21.2, 19.9, 18.8, 14.7. HRMS calcd for $C_{15}H_{28}N$ (M + H) 222.2222. Found 222.2221.

Acknowledgements

We thank Dr. Charles DeBrosse, Director of Temple NMR facilities, for aid with the NOE experiments. This work was supported by a grant from the National Institutes of General Medical Sciences (GM 57870).

References

1 J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod.*, 2005, **68**, 1556–1575.
2 (*a*) H. M. Garraffo, P. Jain, J. T. F Spande and J. W. Daly, *J. Nat. Prod.*, 1997, **60**, 2–5; (*b*) J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon Press, New York, 1999, vol. 13, pp 1–161.
3 For leading references to this class of alkaloids see: J. P. Michael, C. B. de Koning and C. W. van der Westhyzen, *Org. Biomol. Chem.*, 2005, **3**, 836–847.
4 F. A. Davis and B. Yang, *J. Am. Chem. Soc.*, 2005, **127**, 8398–8407.
5 For asymmetric syntheses of 223A, see: (*a*) P. Ghosh, W. R. Judd, T. Ribelin and J. Aube, *Org. Lett.*, 2009, **11**, 4140–4141; (*b*) N. Toyooka, A. Fukutome, H. Nemoto, J. W. Daly, T. F. Spande, H. M. Garraffo and T. Kaneto, *Org. Lett.*, 2002, **4**, 1715–1717; (*c*) X. Pu and D. Ma, *J. Org. Chem.*, 2003, **68**, 4400–4405; (*d*) N. Toyooka, A. Fukutome, H. Shinoda and H. Nemoto, *Tetrahedron*, 2004, **60**, 6197–6216; (*e*) W. Zhu, D. Dong, X. Pu and D. Ma, *Org. Lett.*, 2005, **7**, 705–708.
6 For a racemic synthesis of 223A, see: (*a*) J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371–4381See also; R. Kumareswaran, J. Gallucci and T. V. RajanBabu, *J. Org. Chem.*, 2004, **69**, 9151–9158.
7 (*a*) J. W. Daly, *J. Med. Chem.*, 2003, **46**, 445–452; (*b*) P. L. Katavic, D. A. Venables, T. Rali and A. R. Carroll, *J. Nat. Prod.*, 2007, **70**, 872–875.
8 For reviews on the asymmetric synthesis of piperidines, see: (*a*) S. Laschat and T. Dickner, *Synthesis*, 2000, 1781–1813; (*b*) F-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693–3712; (*c*) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953–2989; (*d*) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701–1729.
9 F. A. Davis, *J. Org. Chem.*, 2006, **71**, 8993–9003.
10 For reviews on the Mannich reaction see: (*a*) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367–4416; (*b*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044–1070.
11 F. A. Davis and M. Santhanaraman, *J. Org. Chem.*, 2006, **71**, 4222–4226.
12 F. A. Davis and B. Yang, *Org. Lett.*, 2003, **5**, 5011–5014.
13 F. A. Davis, N. Theddu and P. M. Gaspari, *Org. Lett.*, 2009, **11**, 1647–1650.
14 (*a*) F. A. Davis, M. B. Nolt, Y. Wu, K. R. Prasad, D. Li, B. Yang, K. Bowen, S. H. Lee and J. H. Eardley, *J. Org. Chem.*, 2005, **70**, 2184–2190; (*b*) F. A. Davis and M. Song, *Org. Lett.*, 2007, **9**, 2413–2416.
15 Prochiral enolates to sulfinimnes afford the *syn* product as the major isomer. See ref. 4 and F. A. Davis, Y. Zhang and H. Qiu, *Org. Lett.*, 2007, **9**, 833–836.
16 (*a*) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450; (*b*) A. K. Chatterjee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 1751–1753.
17 (*a*) C. Yang, W. V. Murry and L. J. Wilson, *Tetrahedron Lett.*, 2003, **44**, 1783–1786; (*b*) N. Dieltiens, C. V. Stevens, D. De Vos, B. Allaert, R. Drozdzak and F. Verpoort, *Tetrahedron Lett.*, 2004, **45**, 8995–8998; (*c*) Q. Yang, X-Y. Li, H. Wu and W-J. Xiao, *Tetrahedron Lett.*, 2006, **47**, 3893–3896.