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Aust. J. Chem. **2011**, *64*, 1327–1338

Cyclizations using Selenium Chemistry for Substituted 3-Hydroxypiperidines and 3-Hydroxypyrrolidines

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The development of new methods for the stereoselective synthesis of nitrogen heterocycles is of current interest because of increasing demands for the syntheses of biologically important alkaloids and related compounds. It is shown that selenium-induced cyclization of 4-hydroxy-5-pentenylamines occurs regio- and stereo-selectively to afford *cis*-3-hydroxy-2-phenylselenomethylpyrrolidines, whereas 5-hydroxy-6-hexenylamines cyclize and give *trans*-3-hydroxy-2-phenylselenomethylpiperidines, with some compounds forming stable hydrates. In all cases cyclization proceeds regioselectively to give only the exo adducts with moderate to good diastereoselectivity. The reaction appeared to be under kinetic control as product ratios did not alter with time and the separated diastereomers did not interconvert when resubjected to the reaction conditions. These phenylseleno-substituted compounds could be transformed to diols by substitution of the corresponding selenone with a hydroxide ion. Substituted pyrrolidines and piperidines were thus afforded from unsaturated protected amines by electrophilic activation with Se^{II}, followed by oxidation of the intermediate to Se^{VI} and substitution with nucleophiles.

Manuscript received: 14 February 2011.
Manuscript accepted: 27 April 2011.
Published online: 23 August 2011.

Introduction

The inherent versatility of selenium compounds lies in their ability to act as both an electrophile and as a nucleophile. The phenylselenide anion is a good nucleophile[2] and has been used to displace halide and sulfonate anions[3] and cleave esters and lactones.[4] The phenylselenide anion also undergoes conjugate addition to α,β-unsaturated carbonyl compounds and, with tributyl phosphine, converts alcohols directly into alkyl phenyl selenides.[5] In marked contrast, organoselenium species containing a good leaving group (e.g., Cl, Br, I, O_2CCF_3, and phthaloyl (Phth)) can serve as extremely reactive, soft electrophiles.[2,6,7] Organoselenium moieties can thus be introduced into a variety of organic substrates as nucleophiles or as electrophiles, using very mild conditions and usually in high yield. Addition of selenium to an organic compound is usually carried out using the phenylselanyl halides, phenylselanyl phthalimide, phenylseleninic acid, or diphenyldiselenide. Phenylselenenyl halides react instantaneously with double bonds to give anti-Markovnikov adducts, which isomerize rapidly at room temperature in polar solvents, or slowly at low temperatures in non-polar solvents,[8] to the thermodynamically more stable Markovnikov adducts.[9] This isomerization involves the reversible formation of an episelenonium ion and is dependent upon the solvent, temperature, and nature of the counter anion of the selenium reagent used.

The cyclofunctionalization[10] of unsaturated carbamates and unsaturated amides using phenylselanyl halides has been reported to afford pyrrolidine and piperidine derivatives in high yield. The use of selenium reagents as mediators of stereoselective cyclization of these substrates, however, has received comparatively little attention.[11] Ninoi et al.[12] have reported that cyclization of an optically active pentenyl amide with phenylselanyl chloride gave the pyrrolidine **1a** with 25 % enantiomeric excess and Clive et al.[13] have reported that cyclization of a 5-hexenyl carbamate with phenylselanyl chloride gave only the *cis*-2,6 disubstituted piperidine **1b** (Scheme 1).

Diastereoselective intramolecular addition of heteronucleophiles directed by an allylic hydroxy group has been employed in the syntheses of a variety of natural products and their synthetic intermediates.[11,14–23] Accordingly, we wished to determine if selenium induced cyclizations of unsaturated N-protected amines possessing an allylic hydroxy group could afford products with defined stereochemistry. We have reported in previous communications[24,25] that such reaction with hexenyl- and pentenyl-N-protected amines proceeds regio- and stereoselectively to afford cyclized dihydroxyphenylselenated adducts. The concomitant incorporation of the synthetically useful phenylseleno group could then enable ready elaboration of these products; for example, by substitution of a higher oxidation state Se^{VI} selenone derivative. More recently, it has been reported that the selenone group can be exploited in the conversion of allylic alcohols by dihydroxyselenides from β-hydroxy epoxides,[26] stereoselective synthesis of substituted cyclopropanes by organocatalytic Michael addition to vinyl selenones,[27] and Michael additions to α-substituted cyanoacetates with α,β-unsaturated selenones in the presence of bifunctional urea and thiourea organocatalysts to provide adducts with

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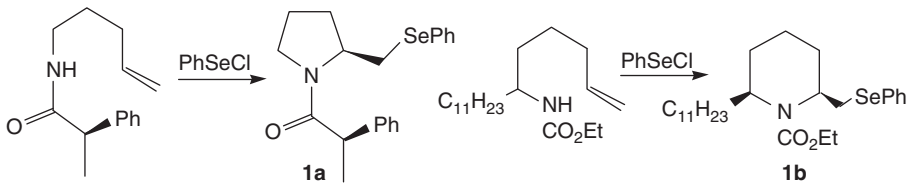
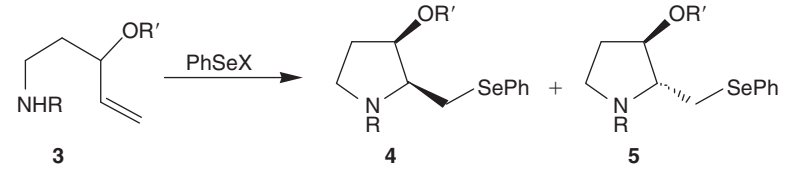


Scheme 1.



a: R = CO_2Et, R′ = H **b**: R = Boc, R′ = H **c**: R = Ts, R′ = H
d: R = Ac, R′ = H **e**: R = Ac, R′ = Ac **f**: R = CO_2Et, R′ = Ac
g: R = CO_2Et, R′ = TBDPS **h**: R = Ac, R′ = $COCF_3$ **i**: R = Boc, R′ = $COCF_3$

Scheme 2.

all-carbon quaternary stereocenters.[28] We show herein that substituted hydroxy-pyrrolidines and -piperidines can be readily made from N-protected hydroxy-unsaturated amines by electrophilic activation with Se^{II}, followed by oxidation of the intermediate to Se^{VI} and subsequent displacement of this leaving group.

Results and Discussion

Cyclization of N-Protected 3-Hydroxy-4-pentenylamines

As unsaturated amines are known[3,29] to react directly upon nitrogen with selenium electrophiles, it was necessary to synthesize the N-protected analogues of 3-hydroxy-4-pentenylamine[30] **2** for cyclization studies. A variety of different N-protecting groups, conferring differing degrees of nucleophilicity and differing steric environments to the nitrogen atom, were employed in these studies (Scheme 2). The carbamates **3a** and **3b** and the sulfonamide **3c** were synthesized from **2** using standard techniques.[31] Attempts to synthesise the amide **3d** directly from **2** using a variety of methods always resulted in concomitant formation of the acetate **3e**, thus **3d** was prepared by selective hydrolysis[32] of the ester moiety of **3e** with barium hydroxide.

Cyclizations were routinely carried out using a slight excess of the phenylselanyl halide in the presence of dry silica gel as catalyst,[13] and anhydrous potassium carbonate as a non-nucleophilic acid scavenger. As addition of phenylselanyl halides is a reversible process,[13,33] an acid trap was required to prevent competing addition of acid formed as an adjunct to cyclization to the free alkene. The orange colour of phenylselanyl chloride was discharged immediately upon addition to a solution of the alkenes **3a**–**3d** in dichloromethane at −78 °C, and the reaction mixtures were then warmed to room temperature. Examination of the reaction mixtures by reverse phase high-performance liquid chromatography (HPLC) revealed the rapid conversion of starting material into distinct, UV-active products and enabled accurate determination of reaction times and product ratios. In all cases cyclization proceeds regioselectively to give only the five membered ring adducts and with good diastereoselectivity (Table 1). The reaction appears to be under kinetic control as product ratios did not alter with time and the separated diastereomers did not interconvert when resubjected to the reaction conditions.

The rate and stereoselectivity of the reaction was enhanced by the use of more polar solvents, which suggests that the rapid formation[34] of an intermediate selenonium ion is responsible for the fast, stereoselective reaction observed. Tiecco et al. have reported[35] that the presence of nucleophilic halide ions is sometimes responsible for a decrease in stereoselectivity of selenium-induced cyclizations. Alkyl phenyl selenides may also react with phenylselanyl halides[36] affording deselenation products and complex mixtures. It was thought the reagents phenylselanyl sulfate[35] and phenylselanyl phthalimide,[37] which do not suffer from these complications, may provide a greater stereoselectivity. However, when **3a** was reacted with phenylselanyl sulfate no increase in stereoselectivity was observed. Reaction with phenylselanyl phthalimide gave only starting materials, although HPLC and thin-layer chromatography (TLC) analysis indicated that selenium-containing intermediates had formed. It is possible that the phthalimido group is too bulky to allow the approach of the neighbouring phenylseleno moiety, thus formation of a selenonium ion is sterically hindered and cyclization cannot occur (Scheme 3).

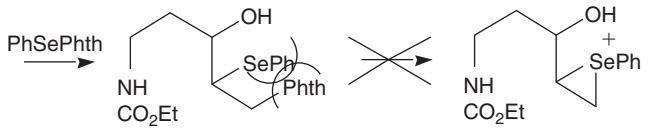
Effect of Hydrogen Bonding and N-Protecting Group

The allylic hydroxy group plays an important role in the stereoselective *cis* cyclization of 3-hydroxy-4-pentenamides,[20,23,30] 3-hydroxy-4-pentenoic acids,[38] and 4-pentene-1,3-diols.[19] It has been proposed[19,22] that a transition state characterized by an intramolecular hydrogen bonded six-membered ring directs attack of the electrophile to the *syn* face of the double bond. Reaction of the O-protected derivatives of **3a**, i.e., the acetate **3f** and the silyl ether **3g**, under the conditions described above resulted in complete loss of stereoselectivity and necessitated much greater reaction times (Table 1). The type of N-protecting group employed also had a marked effect on the stereoselectivity of the reaction. The carbamates **3a** and **3b** and the sulfonamide **3c** were of comparable reactivity, however, when the amide **3d** was subjected to reaction with phenylselanyl bromide in chloroform, none of the *trans* isomer **5d** could be detected by HPLC or ^1H NMR analysis. The diasteromeric purity of the

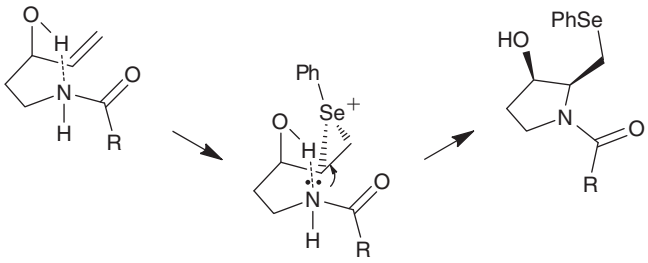
Table 1. Selenium-induced cyclization of N-protected 3-hydroxy-4-pentenylamines

Substrate	PhSe(X)	X = Reaction conditions[A]	Product ratio (yield [%])[B]
3a	Cl	CH_2Cl_2, a, 4 h	**4a**/**5a** 75/25 (88)
		$CHCl_3$, b, 30 min	85/15 (88)
		Dioxan, b, 40 min	76/24 (83)
	Br	CH_2Cl_2, a, 2 h	79/21 (95)
		$CHCl_3$, b, 20 min	87/13 (95)
	SO_4	CH_2Cl_2, a, 4 h	72/28 (84)
3b	Cl	CH_2Cl_2, a, 4 h	**4b**/**5b** 74/26 (56)
	Br	CH_2Cl_2, a, 2 h	80/20 (60)
		$CHCl_3$, b, 20 min	88/12 (70)
3c	Cl	CH_2Cl_2, a, 3 h	**4c**/**5c** 64/36 (83)
	Br	CH_2Cl_2, a, 2 h	66/34 (85)
		$CHCl_3$, b, 20 min	72/28 (84)
3d	Cl	CH_2Cl_2, a, 24 h	**4d**/**5d** 90/10 (21)[C]
	Br	CH_2Cl_2, a, 16 h	>99/<1 (23)
		$CHCl_3$, b, 1 h	>99/<1 (40)
3f	Br	$CHCl_3$, b, 48 h	**4f**/**5f** 50/50 (60)
3g	Br	$CHCl_3$, b, 1 h	**4g**/**5g** 60/40 (68)

[A] a = −78 °C 10 min to RT, b = 0 °C 10 min to RT.
[B] Yield refers to isolated yield, product ratios determined by HPLC analysis.
[C] Determined by HPLC: none of the *trans* isomer could be isolated.



Scheme 3.



Scheme 4.

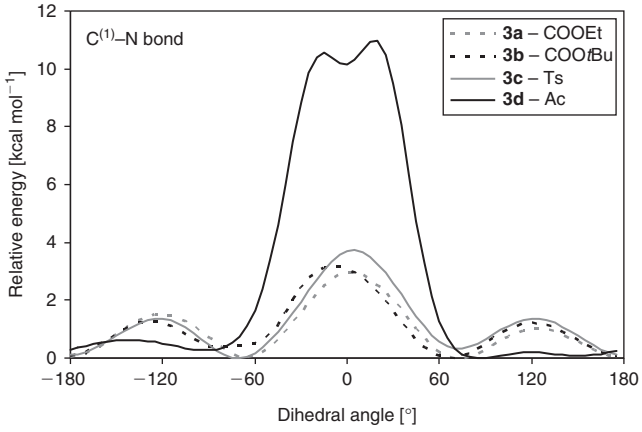


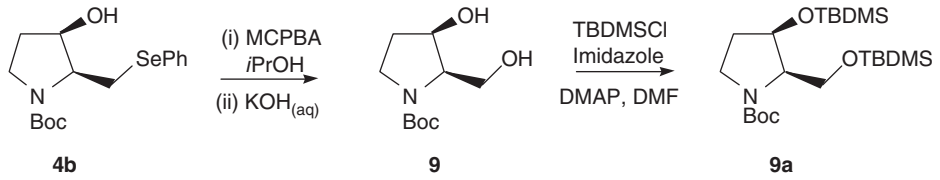
Fig. 1. Dihedral angle C–N bond energy calculation using the MM2 force field for compounds in this study with variant N-protecting groups.

product **4d** was confirmed upon examination of the ^{19}F NMR spectrum of the trifluoroacetate derivative **4h**, which showed only one peak at −0.63 ppm. The trifluoroacetates **4i** and **5i** were clearly resolvable by ^{19}F NMR at −0.32 and 2.34 ppm.

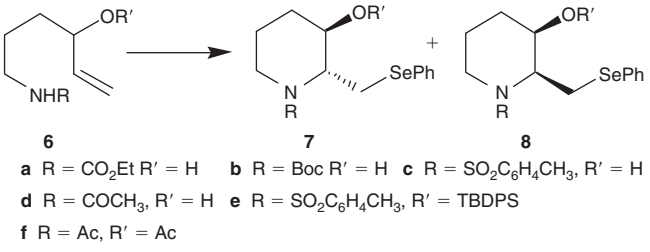
The observed reactivity towards selenium-induced cyclization of the sulfonamides, carbamates, and amides shows a general tendency: the less acidic the NH the greater the yield and the greater the double bond character of the C–N bond of the protecting group, the greater the stereoselectivity. The quite dramatic increase in stereoselectivity observed in the case of the amide **3d** may be attributed to the carbonyl group influencing which face of the double bond is attacked by selenium. This hypothesis is proposed on the basis of molecular modelling studies using a MM2 force field on the substrates **3a**, **3c**, and **3d** and on their phenylseleno adducts. In all cases there is strong hydrogen bonding depicted between the hydroxy proton and the nitrogen atom to form a six-membered ring. This interaction results in the protecting group on nitrogen shielding one face of the double bond and directs the subsequent selective stereofacial attack of selenium to this bond (Scheme 4).

The minimized energy profile from a dihedral drive about the C–N bond for the N-protected 3-hydroxy-4-pentenylamines shows that **3a**, **3b**, and **3c** have a similar energy profile, however, that of **3d** is of much higher energy, reflecting the greater double bond character of this bond.[39] There is also a significant local minimum in which hydrogen bonding is seen between the hydroxy proton and the oxygen atom of the amide further restricting rotation about the C–N bond (Fig. 1).

The *cis* pyrrolidine **4b** was converted[26] by the intermediacy of a selenone into the *cis* diol **9** in good yield by reaction with *m*-chloroperoxybenzoic acid (MCPBA) and sodium hydroxide. The diol **9** was then protected as its disilyl ether **9a** by reaction[15] with *t*-butyldimethylsilyl chloride (Scheme 5). Compounds such as **9** and **9a** are useful templates for the synthesis of a variety of alkaloids. The disilyl ether **9a** has been oxidized to β-hydroxyproline,[40] converted by an aldol



Scheme 5.



Scheme 6.

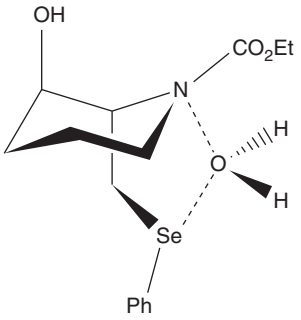
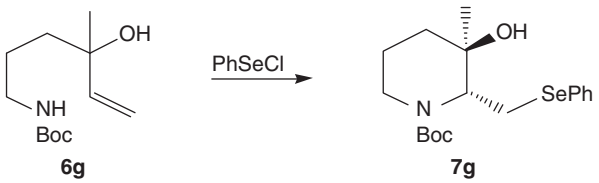


Fig. 2. Structure proposed[1] for the hydrate **11** in which water is held firmly in place by dipole–dipole interactions from the ring nitrogen (δ+ve due to the carbamate) and selenium.

Table 2. Selenium-induced cyclization of N-protected 4-hydroxy-5-hexenylamines

Substrate	Reaction conditions[A]	Product ratio **7**/**8**[B] (yield [%])
6a	a, 48 h	3/1 (57)
	b, 18 h	5/1 (61)
6b	a or b, 5 days	No reaction
6c	a, 48 h	3/1 (59)
	b, 18 h	5/1 (58)
6d	a, 48 h	3/1 (41)
6e	a, 5 days	3/1 (27)

[A]a = PhSeCl, CH_2Cl_2 −78 °C 10 min to RT, b = PhSeBr, $CHCl_3$ 0 °C 10 min to RT.
[B]Yield refers to isolated yield, product ratios were determined by HPLC ananlysis.



Scheme 7.

condensation of a chiral enolate ester into (−)-detoxinine,[41] and elaborated[15,42] to 3-hydroxyglutamic acid,[43] an amino acid component of the peptide antibiotic S-520.

Cyclization of N-Protected 4-Hydroxy-5-hexenylamines

While there have been many examples of the cyclization of N-substituted-3-hydroxy-4-pentenylamines using a variety of electrophilic reagents,[15,20,21,23,30,42] 4-hydroxy-5-hexenylamines have proved comparatively unreactive.[20,21] In the few cases in which cyclization occurred,[21] product mixtures were obtained or the reaction occurred non-stereoselectively. In fact Tamaru et al.[20] have reported that N-protected 4-hydroxy-5-hexenylamines are unreactive towards phenylselanyl chloride and phenylselanyl phthalimide. We found, however, that substrates such as the carbamate **6a**, the sulfonamide **6b**, and the amide **6d**, synthesized in an analogous manner to **3a**–**d**, were indeed cyclized upon treatment with phenylselanyl chloride in dichloromethane (Scheme 6, Table 2). These reactions proceeded with *trans*-stereoselectivity and were considerably slower than those of the 3-hydroxy-4-pentenylamines, with less stereo-selectivity. Reaction in this case may be slow because no hydrogen bonding between the hydroxy proton and the nitrogen atom may occur as this would require the formation of a thermodynamically unfavourable seven-membered ring. Similar selectivity has been described in the 6-exo selenoetherification of enantiomerically pure unsaturated diols, in which case the presence of the oxygen atom close to the intermediate seleniranium ring was reported to govern regio- and stereoselectivity, and reactions performed under kinetic and thermodynamic control both led to the same products.[44]

Upon extended reaction times, or upon exposure of the hydroxypiperidines **7a**, **7d**, and **7e** to tetrahydrofuran (THF)/water in the presence of a catalytic amount of silica gel, stable hydrates (e.g., **11**) could be isolated. The formation of a stable hydrate was most facile with the amide **7d**, slow with the carbamate **7a** and did not occur with the sulfonamide **7c**. The ability of these compounds to include water follows a general trend in accordance with the rotational barrier about the C–N and SO_2–N bonds.[39] The more double bond character the C–N bond of the protecting group possesses, the more likely it is that the compound will include water. This observation supports the hypothesis that the inclusion of water involves hydrogen bonding to the carbonyl or sulfonyl moiety of the protecting group. Unfortunately none of the hydrates were suitable for X-ray crystallographic analysis, but all gave micro-analytical data[1] consistent with the structures proposed (e.g., Fig. 2).

Although the *t*-butylcarbamate **6b** would not cyclize, the 4-hydroxy-4-methyl *t*-butylcarbamate **6g** underwent clean reaction to give a 3:1 mixture of diastereomers **7f** and **8f** in good yield (Scheme 7). Substitution at the allylic position of

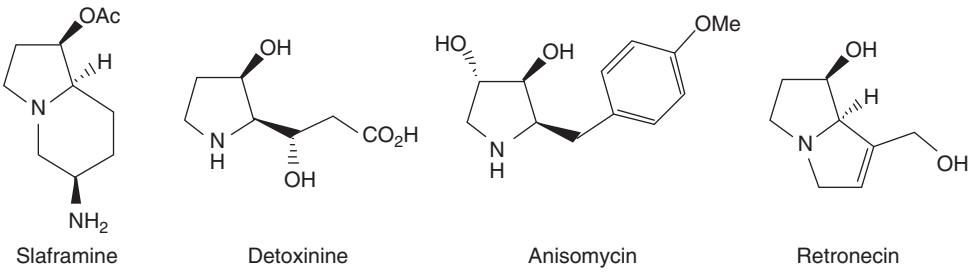


Fig. 3. Structures of slaframine, detoxinine, anisomycin, and retronecin.

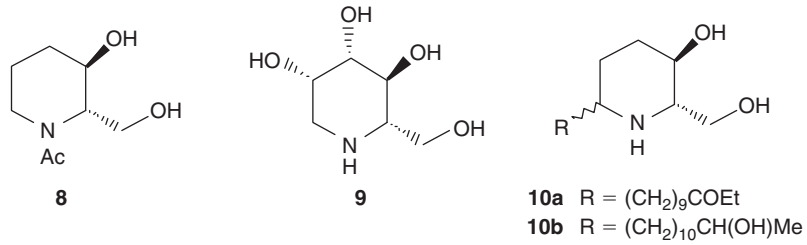


Fig. 4. Examples of polyhydroxylated piperidines with *trans* substituents at C_2 and C_3.

compounds such as **6g** has been previously reported[30] to increase the efficacy of cyclization reactions.

Assignation of Stereochemistry

The stereochemistry of the isomers **4a**–**d** was assigned as *cis* initially on the basis of the ^{13}C NMR spectra by analogy with literature values[20] and by a heteronuclear correlation (HETCOR)[45] experiment. The CSe resonance of the *cis* isomers were generally ~2 ppm further upfield than those of the *trans* isomers as a result of a γ-gauche effect.[46] A 4.15 % nuclear Overhauser effect (nOe) enhancement was observed between the protons H_2 and H_3 of **4c** and a 0.5 % enhancement for the same protons of **5c**. The pyrrolidine **4c** was obtained in crystalline form suitable for X-ray analysis,[47] which clearly depicts the *cis* relationship of the substituents at C_2 and C_3. This configuration of the substituents at C_2 and C_3 of the pyrrolidine ring is abundant in alkaloids possessing potent biological activity such as slaframine,[42,48,49] detoxinine,[41] anisomycin,[50] and retronecin[16] (Fig. 3).

The relative stereochemistry of the hydroxypiperidines was assigned on the basis of the coupling constants between H_2 and H_3. In the *cis* isomer **8c** H_2 appeared at 3.56 ppm (ddd) and H_3 at 4.09 ppm (dt) with $J_{2,3}$ 3.7. In the *trans* isomer **7c** H_2 appeared at 3.87 ppm (ddd) and H_3 at 4.43 ppm (dt) with $J_{2,3}$ 9.5. These coupling constants compare favourably with the values calculated by application of the Karplus equation[51] to the energy minimized structures of **8c**: H_2H_3 3.7 Hz and **7c**: H_2H_3 8.7 Hz. The stereochemistry was confirmed by a series of nOe experiments in which a 13.7 % enhancement was seen between the H_2 and H_3 protons of **8c**, and only a 2.6 % enhancement for the same protons of **7c**. The stereochemistry of **7f** was elucidated from a nOe enhancement observed between the acetate methyl resonance and the two diastereotopic hydrogens adjacent to selenium. No enhancement was observed to the proton adjacent to nitrogen.

Polyhydroxylated piperidines with *trans* substituents at C_2 and C_3, such as the acetamide[52] **8** deoxymannojirimycin[53] **9**, and the prosopis alkaloids prosopinine **10a** and prosopine[54] **10b** also possess potent biological activity (Fig. 4).

Conclusion

Development of new methods for the stereoselective synthesis of nitrogen heterocycles is of current interest because of increasing demands for the syntheses of biologically important alkaloids and related compounds. Polyhydroxylated nitrogen heterocycles are found abundantly in nature and constitute a major class of glucosidase inhibitors. Compounds such as detoxinine, anisomycin, retronecin, slaframine, swainsonine, and castanospermine effect highly specific inhibition of a variety of trimming glucosidases and show little cytotoxicity *in vitro* or *in vivo*.[55] They have been used, or implicated for use, as antihyperglycemic compounds, inhibitors of tumour metastasis, anti-obesity drugs, fungistatic compounds, insect antifeedants, and antivirals.[56] We have developed a novel route to establish the core nitrogen heterocycle with moderate control of stereochemistry to afford 3-hydroxypiperidines and 3-hydroxypyrrolidines suitable for further elaboration.

Experimental

^1H NMR, ^{13}C NMR, and all two-dimensional NMR spectra were obtained on a Bruker ACP-300 (7.05T) spectrometer. Double-quantum filtered correlation spectroscopy (DQF-COSY) spectra were recorded at a constant 20 °C in phase sensitive mode using time proportional phase incrementation[57] to give quadrature detection in f_1. Routinely 2048 data points were recorded in f_1 and 512 in f_2, with 64 transients at each value of t_1. nOe samples were degassed by freeze–pump–thawing (4 cycles) and run at a constant 20 °C. ^1H NMR spectra were recorded as solutions in deuterochloroform, using tetramethylsilane as an internal standard unless otherwise specified. ^{77}Se NMR spectra were obtained on the 300 MHz Bruker ACP-300 at 57.2 MHz with a spectroscopic width of 100 kHz and a digital resolution of 6 Hz per point using diphenyldiselenide (δ 463) as an external standard. ^{19}F NMR spectra were obtained at on the 300 Bruker

ACP-300 at 282 MHz using trifluoroacetic acid (δ 0) as an external standard. NMR data are reported as follows: chemical shift (δ) (multiplicity, coupling constant(s) J [Hz], relative integral) where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above.

Electron impact mass spectra were recorded at 70 eV on an AEI 3074 mass spectrometer. Fast atom bombardment mass spectra and collisional activation mass analyzed ion kinetic energy spectroscopy (CA-MIKES) spectra were recorded on a V.G. ZAB 2HF mass spectrometer. Melting points were recorded on a Kofler hot-stage apparatus equipped with a Reichert microscope, and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Infrared spectra were recorded on a Jasco A-102 spectrometer as nujol mulls or liquid films, or as solutions where indicated.

Preparative chromatography was performed using Merck Kieselgel PF254 silica using, unless otherwise stated, a Chromatotron 7924T (Harrison Research, Palo Alto/TC Research, California), eluting with a gradient of light petroleum/ethyl acetate. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) eluting with a gradient of light petroleum/ethyl acetate. HPLC was carried out using a Waters Model 501 solvent delivery system and a U6K injector with a Waters Model 481 absorbance detector. Analyses were performed using a Waters Z-module with a Waters Radial-PAK C18 reverse phase cartridge (10 cm × 8 mm) eluting with a methanol/water gradient. All organic extracts were dried over anhydrous sodium sulfate unless otherwise specified. Phenylselanyl phthalimide was synthesized according to the method of Nicolaou et al.[37] MCPBA was recrystallized from dichloromethane/light petroleum and was 85 % pure as determined by epoxidation of a stoichiometric amount of cyclohexene.

Ethyl N-*(3-Hydroxy-4-pentenyl)carbamate (**3a**)*

To an emusified mixture of the amine **2** (1.01 g, 10 mmol) in water (30 mL) at 0 °C was added ethyl chloroformate (0.65 g, 6 mmol). The emulsion was stirred at 0 °C for 5 min and then a second portion of ethyl chloroformate (0.65 g, 6 mmol) was added, followed immediately by a solution of sodium hydroxide (0.5 g, 1.2 mmol) in water (5 mL). The mixture was stirred at 0 °C for a further 1.5 h, and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with 1 N hydrochloric acid (10 mL), and then 10 % sodium bicarbonate (10 mL). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate **3a** (1.53 g, 89 %) as a light yellow oil. bp 115–118 °C, 0.013 mm (block). Calc. for $C_8H_{18}NO_3$: C 55.47, H 8.73, N 8.09. Found: C 55.18, H 8.58, N 8.30 %. δ_H 5.87 (ddd, J 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.79 (s, 1H, NH), 5.24 (dd, J 1.8, 17.1, 1H, C*H*$_a$H$_b$=CH), 5.08 (dd, J 1.8, 10.6, 1H, CH$_a$*H*$_b$=CH), 4.19 (s, 1H, OH), 4.17 (m, 1H, C*H*OH), 4.08 (q, J 6.9, 2H, C*H*$_2$CH$_3$), 3.29 (m, 2H, CH_2N), 1.71 (m, 2H, CH_2), 1.22 (t, J 6.9, 3H, CH_3). ν_{max}/cm^{-1} 3600, 3450, 1705, 1510. *m/z* 174 (M + H), 156 (M–OH), 102 (M–CO_2Et).

N-*(3-Hydroxy-4-pentenyl)-4-toluenesulfonamide (**3b**)*

To a stirred mixture of the amine **2** (505 mg, 5 mmol) in dry pyridine (10 mL) under nitrogen at 0 °C was added portion-wise tosyl chloride (1.05 g, 5.5 mmol). The mixture was stirred at this temperature for 4 h, diluted with ethyl acetate (40 mL), and washed with 1 N hydrochloric acid (2 × 40 mL), followed by 10 % sodium bicarbonate (20 mL). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue recrystallized (ethyl acetate/ether/light petroleum) to give the sulfonamide **3b** (1.11 g, 88 %) as white needles, mp 70–71.5 °C. Anal. Calc. for $C_{12}H_{17}NO_3S$: C 56.45, H 6.71, N 5.49. Found: C 56.38, H 6.68, N 5.46 %. δ_H 7.75 (d, J 8.2, 2H), 7.30 (d, J 8.2, 2H), 6.91 (s, 1H, NH), 5.79 (ddd, J 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.18 (dd, J 1.8, 17.1, 1H, C*H*$_a$H$_b$=CH), 5.08 (dd, J 1.8, 10.6, 1H, CH$_a$*H*$_b$=CH), 4.24 (m, 1H, C*H*OH), 3.80 (br s, 1H, OH), 3.08 (m, 2H, CH_2N), 2.42 (s, 3H, ArCH_3), 1.71 (m, 2H, CH_2). ν_{max}/cm^{-1} 3350, 3250, 1160, 815. *m/z* 256 (M + H), 238 (M–OH), 184 (M–C_4H_6OH), 155 (M–SO_2PhCH$_3$).

t-*Butyl* N-*(3-Hydroxy-4-pentenyl)carbamate (**3c**)*

To an emusified mixture of the amine **2** (101 mg, 1 mmol) in water (10 mL) at 0 °C was added portion-wise 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON, 271 mg, 1.1 mmol) followed by a solution of sodium hydroxide (44 mg, 1.1 mmol) in water (1 mL). The mixture was warmed to room temperature and stirred for a further 6 h. The mixture was then diluted with ethyl acetate (20 mL) and washed with hydrochloric acid (2 × 10 mL), followed by 10 % sodium bicarbonate (10 mL). The organic phase was separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the carbamate **3c** (133 mg, 68 %) as a colourless oil, bp 108 °C, 0.01 mm (block). Anal. Calc. for $C_{10}H_{19}NO_3$: requires C 59.67, H 9.52, N 6.96. Found: C 59.36, H 9.59, N 6.79 %. δ_H 5.87 (ddd, J 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.42 (br s, 1H, NH), 5.24 (dd, J 1.8, 17.1, 1H, C*H*$_a$H$_b$=CH), 5.08 (dd, J 1.8, 10.6, 1H, CH$_a$*H*$_b$=CH), 4.18 (m, 1H, C*H*OH), 4.03 (s, 1H, OH), 3.32 (m, 1H, CH$_a$N), 3.15 (m, 1H, CH$_b$N), 1.64 (m, 2H, CH_2), 1.44 (s, 9H). ν_{max}/cm^{-1} 3340, 1685, 1520. *m/z* 202 (M + H), 145 (M–*t*Bu), 101 (M–CO_2*t*Bu).

N-*(3-Hydroxy-4-pentenyl)acetamide (**3d**)*

A mixture of the acetate **3e** (400 mg, 2.1 mmol) and barium hydroxide (680 mg, 2.1 mmol) in methanol (20 mL) was stirred at room temperature for 1 h. The solution was filtered through celite, the celite washed with methanol (10 mL), and the solvent removed under reduced pressure to give the amide **3d** (300 mg, 100 %) as a colourless oil, bp 142 °C, 0.02 mm (block). Anal. Calc. for $C_7H_{13}NO_2$: C 58.89, H 9.15, N 9.78. Found: C 58.89, H 9.11, N 10.15 %. δ_H 6.45 (s, 1H, NH), 5.87 (ddd, J 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.24 (dd, J 1.8, 17.1, 1H, C*H*$_a$H$_b$=CH), 5.08 (dd, J 1.8, 10.6, 1H, CH$_a$*H*$_b$=CH), 4.17 (m, 1H, C*H*OH), 3.56 (s, 1H, OH), 3.24 (dt, J 8.3, 1.8, 1H, CH$_a$N), 3.18 (dt, J 8.3, 1.8, 1H, CH$_b$N), 1.99 (s, 3H, CH_3), 1.72 (m, 1H), 1.62 (m, 1H). ν_{max}/cm^{-1} 3250, 1630, 1540. *m/z* (FAB) 144 (M + H), 126 (M–OH).

N-*(3-Acetoxy-4-pentenyl)acetamide (**3e**)*

To a mixture of the amine **2** (101 mg, 1 mmol) and triethylamine (404 mg, 4 mmol) in dry tetrahydrofuran (THF, 10 mL) under nitrogen at 0 °C was added acetyl chloride (286 mL, 4 mmol) dropwise over 2 min. The resultant solution was warmed to room temperature and stirred overnight. The solvent was then removed under reduced pressure, the residue diluted with ethyl acetate (20 mL), washed with 1 N hydrochloric acid (2 × 10 mL), followed by 10 % sodium bicarbonate (10 mL). The organic phase was separated, dried, the the solvent removed

under reduced pressure and the residue chromatographed to give the acetate **3e** (142 mg, 77 %) as a colourless oil, bp 135 °C, 0.06 mm (block). Anal. Calc. for $C_9H_{15}NO_3$: 185.1052; HRMS found: 185.1056. δ_H 5.9 (s, 1H, NH), 5.80 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.32 (m, 1H), 5.25 (dd, *J* 1.8, 17.1, 1H, C$H_a$$H_b$=CH), 5.19 (dd, *J* 1.8, 10.6, 1H, $CH_a$$H_b$=CH), 3.46 (m, 1H, CH_aN), 3.08 (m, 1H, CH_bN), 2.09 (s, 3H, $OCOCH_3$), 1.98 (s, 3H, $NCOCH_3$), 1.83 (m, 2H, CH_2). ν_{max}/cm^{-1} 3300, 1735, 1650, 1240. *m/z* 185 ($M^{+\prime}$), 126 (M–$OCOCH_3$).

Ethyl N*-(3-Acetoxy-4-pentenyl)carbamate (**3f**)*

To a stirred mixture of the carbamate **3a** (692 mg, 4 mmol) and triethylamine (505 mg, 5 mmol) in dry THF (20 mL) under nitrogen at 0 °C was added acetyl chloride (430 mL, 6 mmol) dropwise over 2 min. The mixture was warmed to room temperature and stirred for a further 24 h. The solvent was removed under reduced pressure, and the residue redissolved in ethyl acetate (50 mL), washed with 1 N hydrochloric acid (2 × 10 mL), followed by 10 % sodium bicarbonate (10 mL). The organic phase was separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the acetate **3f** (688 mg, 80 %) as a colourless oil, bp 101 °C, 0.02 mm (block). Anal. Calc. for $C_{24}H_{33}NO_3Si$: C 71.03, H 8.08, N 2.40. Found: C 71.15, H 8.18, N 2.40 %. δ_H 5.80 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.34 (m, 1H, C*H*OH), 5.22 (dd, *J* 1.8, 17.1, 1H, C$H_a$$H_b$), 5.19 (dd, *J* 1.8, 10.6, 1H, $CH_a$$H_b$=CH), 5.06 (br s, 1H, NH), 4.10 (q, *J* 6.9, 2H, C$H_2$$CH_3$), 3.31 (m, 1H), 3.11 (m, 1H), 2.08 (s, 3H, $COCH_3$), 1.83 (m, 2H), 1.23 (t, *J* 6.9, 3H, CH_3). ν_{max}/cm^{-1} 3350, 1730, 1715, 1225. *m/z* 216 (M + H), 156 (M–OAc), 102 (M–OAc–CO_2Et).

Ethyl N*-(3-*t*-Butyldiphenylsilyloxy-4-pentenyl) carbamate (**3g**)*

A mixture of the carbamate **3a** (519 mg, 3 mmol), imidazole (450 mg, 7.5 mmol), dimethylaminopyridine (80 mg, 0.6 mmol), and *t*-butyldiphenylsilyl chloride (1.24 g, 4.5 mmol) in dry *N*,*N*-dimethylformamide (DMF, 10 mL) was stirred at room temperature for 24 h. The mixture was diluted with ether (10 mL), washed with saturated sodium chloride (10 mL), 5 % hydrochloric acid (2 × 5 mL), 10 % sodium bicarbonate (5 mL), and again with saturated sodium chloride (10 mL). The organic phase was separated, dried, and the solvent removed under reduced pressure to give the silyl ether **3g** (1.22 g, 99 %) as a colourless oil, bp 120 °C, 0.02 mm (block). Anal. Calc. for $C_{24}H_{33}NO_3Si$: C 71.01, H 8.08, N 2.40. Found: C 71.15, H 8.18, N 2.40 %. δ_H 7.7–7.2 (m, 10H), 5.80 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.19 (br s, 1H, NH), 5.01 (dd, *J* 1.8, 17.1, 1H, C$H_a$$H_b$=CH), 4.98 (dd, *J* 1.8, 10.6, 1H, $CH_a$$H_b$=CH), 4.27 (m, 1H, C*H*OH), 4.03 (q, *J* 6.9, 2H, C$H_2$$CH_3$), 3.20 (m, 2H, CH_2N), 1.60 (m, 2H), 1.26 (t, *J* 6.9, 3H, CH_3), 1.06 (s, 9H). ν_{max}/cm^{-1} 3460, 1700, 1530. *m/z* 354 (M–*t*Bu), 200 (M–Ph_2*t*Bu), 172 (M–$SiPh_2$*t*Bu).

*Ethyl 2(*R**)-Phenylselenomethyl-3(*R**)-hydroxypyrrolidine-1-carboxylate (**4a**) and Ethyl 2(*S**)-phenylselenomethyl-3(*R**)-hydroxypyrrolidine-1-carboxylate (**5a**)*

Method B: To a solution of the carbamate **3a** (173 mg, 1 mmol), dry silica (250 mg), and anhydrous potassium carbonate (250 mg) in dry chloroform (10 mL) under nitrogen at 0 °C was added a solution of phenylselanyl chloride (230 mg, 1.2 mmol) in dry chloroform (3 mL) dropwise over 5 min. The mixture was stirred at 0 °C for 10 min, and then at room temperature for 30 min. The solution was filtered through celite, the celite washed with ethyl acetate, the filtrate concentrated under reduced pressure, and the residue chromatographed to give the *cis* pyrrolidine **4a** as white crystals (272 mg, 83 %), mp 89–90 °C. Anal. Calc. for $C_{14}H_{19}NO_3Se$: C 51.22, H 5.83, N 4.27. Found: C 51.17, H 5.64, N 4.25 %. δ_H ($CDCl_3$, 50 °C) 7.57 (m, 2H), 7.28 (m, 3H), 4.54 (m, 1H, H_3), 4.10 (q, *J* 6.9, 2H, C$H_2$$CH_3$), 3.69–3.42 (m, 3H), 3.47 (dd, *J* 12.3, 3.6, 1H, H_{6a}), 3.08 (dd, *J* 12.3, 10.9, 1H, H_{6b}), 2.51 (br s, 1H, OH), 1.94 (m, 2H, $H_{4a}$$H_{4b}$), 1.22 (t, *J* 6.9, 3H, CH_3). δ_C ($CDCl_3$, 50 °C) 155.4 (C=O), 132.3, 131.6, 129.1, 126.6 (Ar), 72.1 (C_3), 61.1 (CH_2O), 44.6 (C_6), 32.5 (C_2), 32.0 (C_5), 25.4 (C_4), 14.6 (CH_3). ν_{max}/cm^{-1} 3420, 1670, 1580, 1480. *m/z* 329 ($M^{+\prime}$), 172 (M–SePh), 158 (M–CH_2SePh). Further elution gave the *trans* pyrrolidine **5a** as a light yellow oil (41 mg, 12 %). δ_H ($CDCl_3$, 50 °C) 7.54 (m, 2H), 7.24 (m, 3H), 4.35 (m, 1H, H_3), 4.09 (q, *J* 6.9, 2H, C$H_2$$CH_3$), 3.85 (m, 1H, H_2), 3.63–3.40 (m, 2H, $H_{5a}$$H_{5b}$), 3.30 (dd, *J* 12.3, 3.0, 1H, H_{6a}), 2.63 (br s, 1H, OH), 2.55 (dd, *J* 12.3, 11.8, 1H, H_{6b}), 2.04 (m, 1H, H_{4a}), 1.88 (m, 1H, H_{4b}), 1.24 (t, *J* 6.9, 3H, CH_3). δ_C ($CDCl_3$, 50 °C) 155.8 (C=O), 134.9, 132.1, 130.5, 129.1 (Ar), 74.2 (C_3), 61.1 (CH_2O), 44.6 (C_6), 31.4 (C_2), 30.0 (C_5), 27.9 (C_4), 14.5 (CH_3). ν_{max}/cm^{-1} 3350, 1660, 1580, 1480. *m/z* 329 ($M^{+\prime}$), 172 (M–SePh), 158 (M–CH_2SePh).

t*-Butyl 2(*R**)-Phenylselenomethyl-3(*R**)-hydroxypyrrolidine-1-carboxylate (**4b**) and* t*-Butyl 2(*S**)-Phenylselenomethyl-3(*R**)-hydroxypyrrolidine-1-carboxylate (**5b**)*

Using method B with the carbamate **3c** (201 mg, 1 mmol), dry silica (250 mg), anhydrous potassium carbonate (250 mg), and phenylselanyl chloride (230 mg, 1.2 mmol) gave the *cis* pyrolidine **4b** as translucent needles (219 mg, 62 %), mp 101–103 °C. Anal. Calc. for $C_{16}H_{23}NO_3Se$: C 53.93, H 6.51, N 3.93. Found: C 54.01, H 6.83, N 4.08 %. δ_H ($CDCl_3$, 50 °C) 7.63 (m, 2H), 7.10 (m, 3H), 4.49 (m, 1H, H_3), 3.96 (m, 1H, H_2), 3.51 (m, 2H, $H_{5a}$$H_{5b}$), 3.38 (dd, *J* 12.3, 3.6, 1H, H_{6a}), 3.02 (dd, *J* 12.3, 11.8, 1H, H_{6b}), 2.09 (br s, 1H, OH), 1.88 (m, 2H, $H_{4a}$$H_{4b}$), 1.36 (s, 9H). δ_H ($CDCl_3$, 50 °C) 154.6 (C=O), 133.1, 131.5, 129.2, 127.5 (Ar), 88.1 (CMe_3), 74.0 (C_3), 43.3 (C_6), 32.4 (C_2), 30.6 (C_5), 28.7 (C_4), 28.4 (CH_3). ν_{max}/cm^{-1} 3410, 1660, 1460. *m/z* 355 ($M^{+\prime}$), 138 (M–SePh), 124 (M–CH_2SePh). Further elution gave the *trans* pyrrolidine **5b** as a light yellow oil (39 mg, 8 %). δ_H ($CDCl_3$, 50 °C) 7.63 (m, 2H), 7.14 (m, 3H), 4.31 (m, 1H, H_3), 3.73 (m, 1H, H_2), 3.50 (m, 1H, H_{5a}), 3.32 (m, 1H, H_{5b}), 3.19 (dd, *J* 12.3, 3.2, 1H, H_{6a}), 2.85 (br s, 1H, OH), 2.51 (dd, *J* 12.3, 11.6, 1H, H_{6b}), 1.95 (m, 1H, H_{4a}), 1.76 (m, 1H, H_{4b}), 1.37 (s, 9H). δ_C ($CDCl_3$, 50 °C) 154.4 (C=O), 132.9, 131.9, 129.0, 127.1 (Ar), 87.8 (CMe_3), 75.1 (C_3), 65.3 (CMe_3O), 44.6 (C_6), 30.9 (C_2), 30.2 (C_5), 29.6 (C_4), 28.5 (CH_3). ν_{max}/cm^{-1} 3400, 1660, 1460. *m/z* 355 ($M^{+\prime}$), 138 (M–SePh), 124 (M–CH_2SePh).

*2-(*R**)-Phenylselenomethy-3(*R**)-hydroxypyrrolidine-1-tosylate (**4c**) and 2-(*S**)-Phenylselenomethy-3(*R**)-hydroxypyrrolidine-1-tosylate (**5c**)*

Method A: To a stirred mixture of the sulfonamide **3b** (254 mg, 1 mmol), dry silica (250 mg), and anhydrous potassium carbonate (250 mg) in dry dichloromethane (10 mL) under nitrogen at −78 °C was added a solution of phenylselanyl chloride (230 mg, 1.2 mmol) in dry dichloromethane (3 mL) dropwise over 5 min. The mixture was stirred at −78 °C for 10 min, and then at room temperature for 3 h. The solution was fitered through celite, the celite washed with ethyl acetate, the filtrate concentrated under reduced pressure and the residue chromatographed to give a mixture of the *cis* and *trans* pyrrolidines **4c**

and **5c** which was fractionally recrystallized (ethyl acetate/ether/light petroleum) to give **4c** as translucent needles, mp 110–112 °C. Anal. Calc. for $C_{18}H_{21}NO_3SSe$: C 52.68, H 5.16, N 3.41. Found: C 52.36, H 5.15, N 3.47 %. δ_H 7.62 (m, 2H), 7.37 (m, 3H), 7.44 and 7.37 (d, *J* 8.2, 4H, C_6H_4), 4.37 (m, 1H, H_3), 3.71 (dd, *J* 12.3, 3.6, 1H, H_{6a}), 3.56 (dt, *J* 5.8, 10.8, 1H, H_{5a}), 3.46 (ddd, *J* 11.8, 3.6, 4.0, 1H, H_2), 3.44 (dt, *J* 5.8, 10.8, 1H, H_{5b}), 3.20 (dd, *J* 12.3, 11.8, 1H, H_{6b}), 2.38 (s, 3H, $ArCH_3$), 2.34 (br s, 1H, OH), 1.66 (m, 1H, H_{4a}), 1.17 (m, 1H, H_{4b}). δ_C 144.1, 133.9, 129.4, 127.2 (Ar), 71.8 (C_3), 63.7 (C_7), 47.7 (C_2), 32.6 (C_5), 26.7 (C_4), 20.6 (MePh). nOe (% enhancement): H_2H_3 (4.1), H_2H_{6a} (1.6), H_2H_{6b} (0.8), H_3OH (2.4), H_3H_{4a} (3.0), H_3H_{4b} (1.8), $H_{4a}H_{4b}$ (11.0), $H_{6a}H_{6b}$ (17.5). ν_{max}/cm^{-1} 3400, 1660, 1580, 1480. *m/z* 411 ($M^{+\prime}$), 255 (M–SePh), 241 (M–CH_2SePh). The supernatant of the recrystallization was then concentrated and the residue recrystallized to give **5c** as white crystals, mp 139–141 °C. δ_H 7.80 (m, 2H), 7.63 (m, 3H), 7.37 and 7.24 (d, *J* 8.2, 4H, C_6H_4), 4.04 (dt, *J* 6.4, 12.9, 1H, H_3), 3.73 (dd, *J* 12.3, 8.9, 1H, H_{6a}), 3.63 (dt, *J* 6.5, 10.6, 1H, H_{5a}), 3.51 (ddd, *J* 6.4, 1.8, 8.9, 1H, H_2), 3.43 (dd, *J* 12.3, 1.8, 1H, H_{6b}), 3.06 (dt, *J* 6.5, 10.6, 1H, H_{5b}), 2.41 (s, 3H, $ArCH_3$), 2.30 (br s, 1H, OH), 1.91 (m, 1H, H_{4a}), 1.61 (m, H_{4b}). δ_C 147.2, 131.4, 129.8, 127.4 (Ar), 71.1 (C_3), 59.7 (C_7), 46.9 (C_2), 32.4 (C_5), 27.7 (C_4), 22.0 (MePh). nOe (% enhancement): H_2H_3 (0.5), H_2H_{6a} (1.5), H_2H_{6b} (0.8), H_3OH (2.3), H_3H_{4a} (3.0), H_3H_{4b} (1.5), $H_{4a}H_{4b}$ (10.1), $H_{6a}H_{6b}$ (17.0). ν_{max}/cm^{-1} 3400, 1660, 1580, 1480. *m/z* 411 ($M^{+\prime}$), 255 (M–SePh), 241 (M–CH_2SePh).

N-*Acetyl-2(*R**)-phenylselenomethyl-3(*R**)-hydroxypyrrolidine (**4d**)*

Using method B with the amide **3d** (143 mg, 1 mmol), dry silica (250 mg), anhydrous potassium carbonate (250 mg), and phenylselanyl chloride (230 mg, 1.2 mmol) gave the *cis* pyrrolidine **4d** as white crystals, mp 150–151 °C. Anal. Calc. for $C_{13}H_{17}NO_2Se$: C 52.35, H 5.75, N 4.70. Found: C 52.18, H 5.68, N 4.62 %. δ_H 7.63 (m, 2H), 7.22 (m, 3H), 4.50 (dt, *J* 5.1, 5.6, 1H, H_3), 3.70 (dd, *J* 12.2, 3.5, 1H, H_{6a}), 3.61 (m, 3H), 3.09 (dd, *J* 12.2, 9.9, 1H, H_{6b}), 3.08 (br s, 1H, OH), 2.05 (m, 2H, $H_{4a}H_{4b}$), 1.99 (s, 3H, $COCH_3$). δ_C 206.5 (C=O), 132.2, 130.0, 128.4, 125.1 (Ar), 69.6 (C_3), 60.1 (C_6), 45.2 (C_2), 32.0 (C_5), 28.7 (C_4), 21.8 (CH_3). ν_{max}/cm^{-1} 3400, 1630, 1060. *m/z* 299 ($M^{+\prime}$), 142 (M–SePh), 128 (M–CH_2SePh).

*Ethyl 2′(*R**)-Phenylselenomethyl-3′(*R**)-acetoxypyrrolidine-1-carboxylate (**4f**) and Ethyl 2′(*S**)-(Phenylselenomethyl)-3′(*R**)-O-acetoxypyrrolidine-1-carboxylate (**5f**)*

Using method B with the carbamate **3f** (215 mg, 1 mmol), dry silica (500 mg), anhydrous potassium carbonate (500 mg), and phenylselanyl bromide (283 mg, 1.2 mmol) gave a 1:1 mixture of the *cis* and *trans* pyrrolidines as a viscous yellow oil (220 mg, 60 %). HRMS: 371.0616; $C_{16}H_{21}NO_4Se$ requires 371.0636. ν_{max}/cm^{-1} 1720, 1690, 1520, 1240. *m/z* 371 ($M^{+\prime}$), 328 (M-$COCH_3$), 200 (M-CH_2SePh). δ_H ($CDCl_3$, 50 °C) **4f**: 7.57 (m, 2H), 7.28 (m, 3H), 5.03 (m, 1H, H_3), 4.10 (q, *J* 6.9, 2H, CH_2CH_3), 3.69–3.42 (m, 3H), 3.47 (dd, *J* 12.3, 3.6, 1H, H_{6a}), 3.08 (dd, *J* 12.3, 10.9, 1H, H_{6b}), 2.02 (s, 3H, $COCH_3$), 1.94 (m, 2H, $H_{4a}H_{4b}$), 1.22 (t, *J* 6.9, 3H, CH_3). **5f**: 7.54 (m, 2H), 7.24 (m, 3H), 4.96 (m, 1H, H_3), 4.09 (q, *J* 6.9, 2H, CH_2CH_3), 3.85 (m, 1H, H_2), 3.63–3.40 (m, 2H, $H_{5a}H_{5b}$), 3.30 (dd, *J* 12.3, 3.0, 1H, H_{6a}), 2.55 (dd, *J* 12.3, 11.8, 1H, H_{6b}), 2.10 (s, 3H, $COCH_3$), 2.04 (m, 1H, H_{4a}), 1.88 (m, 1H, H_{4b}), 1.24 (t, *J* 6.9, 3H, CH_3).

*Ethyl 2′(*R**)-(Phenylselenomethyl)-3′(*R**)-(t-butyldiphenylsilyloxy)pyrrolidine-1-carboxylate (**4g**) and Ethyl 2′(*S**)-(Phenylselenomethyl)-3′(*R**)-(t-butyldiphenylsilyloxy)pyrrolidine-1-carboxylate (**5g**)*

Using method B with the carbamate **3g** (205 mg, 0.5 mmol), dry silica (250 mg), anhydrous potassium carbonate (250 mg), and phenylselanyl bromide (130 mg, 0.55 mmol) gave a 3:2 mixture of the pyrrolidines **4g** and **5g** as a viscous yellow oil (192 mg, 68 %). HRMS: 567.1707; $C_{30}H_{37}NO_3SeSi$ requires 567.1708. ν_{max}/cm^{-1} 1690, 1580, 1480, 1420, 1100. *m/z* 567 ($M^{+\prime}$), 490 (M–Ph), 434 (M–*t*BuPh), 411 (M–SePh). δ_H ($CDCl_3$, 50 °C) **4g**: 7.70 and 7.32 (m, 10H), 7.57 (m, 2H), 7.28 (m, 3H), 4.41 (m, H_3), 4.10 (q, *J* 6.9, 2H, CH_2CH_3), 3.69–3.42 (m, 3H), 3.47 (dd, *J* 12.3, 3.6, 1H, H_{6a}), 3.08 (dd, *J* 12.3, 10.9, 1H, H_{6b}), 1.94 (m, 2H, $H_{4a}H_{4b}$), 1.22 (t, *J* 6.9, 3H, CH_3), 1.11 (s, 9H). **5g**: 7.70 and 7.32 (m, 10H), 7.54 (m, 2H), 7.24 (m, 3H), 4.30 (m, 1H, H_3), 4.09 (q, *J* 6.9, 2H, CH_2CH_3), 3.85 (m, 1H, H_2), 3.63–3.40 (m, 2H, $H_{5a}H_{5b}$), 3.30 (dd, *J* 12.3, 3.0, 1H, H_{6a}), 2.55 (dd, *J* 12.3, 11.8, 1H, H_{6b}), 2.04 (m, 1H, H_{4a}), 1.88 (m, 1H, H_{4b}), 1.24 (t, *J* 6.9, 3H, CH_3), 1.06 (s, 9H).

*2(*R**)-Phenylselenomethyl-3(*R**)-trifluoroacetoxypyrrolidine-1-acetate (**4h**)*

To a stirred mixture of the alcohol **4d** (18 mg, 0.06 mmol) and triethylamine (9 mg, 0.09 mmol) in dry dichloromethane (2 mL) under nitrogen was added trifluoroacetic anhydride (15 mg, 0.072 mmol) and the mixture stirred at room temperature for 24 h. The solution was washed with 10 % hydrochloric acid (5 mL), 10 % sodium bicarbonate (5 mL), dried, and the solvent removed under reduced pressure to give the trifluoroacetate **4h** as a colourless oil (15 mg, 63 %). HRMS: 395.0249; $C_{15}H_{16}NO_3F_3Se$ requires 395.0247. δ_H 7.59 (m, 2H), 7.24 (m, 3H), 5.68 (dt, *J* 5.0, 4.7, 1H, H_3), 4.44 (ddd, *J* 5.0, 10.3, 3.7, 1H, H_2), 3.89 (dd, *J* 12.8, 3.7, 1H, H_{6a}), 3.65 (m, 2H, $H_{5a}H_{5b}$), 2.93 (dd, *J* 12.8, 10.3, 1H, H_{6b}), 2.2–2.0 (m, 2H), 2.03 (s, 3H, CH_3). δ_F −0.63. ν_{max}/cm^{-1} 1770, 1685, 1400, 1150. *m/z* 395 ($M^{+\prime}$), 298 (M–$COCF_3$).

t-*Butyl 2(*R**)-Phenylselenomethyl-3(*R**)-trifluoroacetoxypyrrolidine-1-carboxylate (**4i**) and* t-*Butyl 2(*S**)-Phenylselenomethyl-3(*R**)-trifluoroacetoxypyrrolidine-1-carboxylate (**5i**)*

To a stirred 1:1 mixture of the alcohols **4b** and **5b** (62 mg, 0.26 mmol) and triethylamine (26 mg, 0.26 mmol) in dry dichloromethane (2 mL) under nitrogen was added trifluoroacetic anhydride (555 mg, 0.26 mmol) and the mixture stirred at room temperature for 24 h. The solution was washed with 10 % hydrochloric acid (5 mL), 10 % sodium bicarbonate (5 mL), dried, and the solvent removed under reduced pressure to give a 1:1 mixture of the trifluoroacetates **4i** and **5i** as a colourless oil (73 mg, 89 %). HRMS: 453.0649; $C_{18}H_{22}NO_4F_3Se$ requires 453.0666. ν_{max}/cm^{-1} 1775, 1685, 1390, 1160. *m/z* 453 ($M^{+\prime}$), 396 (M–*t*Bu), 380 (M–*t*BuO), 356 (M–$COCF_3$), 240 (M–*t*Bu–SePh). δ_H **4i**: 7.56 (m, 2H), 7.26 (m, 3H), 5.51 (m, 1H, H_3), 4.02 (m, 1H, H_2), 3.56 (m, 2H, $H_{5a}H_{5b}$), 3.28 (dd, *J* 3.2, 12.8, 1H, H_{6a}), 2.69 (dd, *J* 11.6, 12.8, 1H, H_{6b}), 2.3–1.8 (m, 2H), 1.37 (s, 9H). **5i**: 7.56 (m, 2H), 7.26 (m, 3H), 4.40 (m, 1H, H_3), 3.80 (m, 1H, H_2), 3.6–3.4 (m, 2H, $H_{5a}H_{5b}$), 3.30 (dd, *J* 3.2, 12.8, 1H, H_{6a}), 2.60 (dd, *J* 11.6, 12.8, 1H, H_{6b}), 2.3–1.8 (m, 2H), 1.36 (s, 9H). δ_F **4i**: −0.32, **5i**: 2.14.

Ethyl N*-(4-Hydroxy-5-hexenyl)carbamate (**6a**)*

To an emulsified mixture of 6-amino-3-methylhex-1-ene-3-ol (690 mg, 6 mmol) in water (50 mL) at 0 °C was added ethyl chloroformate (450 mg, 4.5 mmol). The mixture was stirred at this temperature for 5 min and then 30 % sodium hydroxide (1.08 g, 9 mmol) was added followed immediately by a second portion of ethyl chloroformate (450 mg, 4.5 mmol). The mixture was stirred at room temperature for 2 h and then extracted with ethyl acetate (30 mL). The organic extracts were washed with 1 N hydrochloric acid (10 mL), 10 % sodium bicarbonate (10 mL), dried, the solvent removed under reduced pressure, and the residue chromatographed to give the carbamate **6a** as a yellow oil (765 mg, 68 %). bp 108 °C, 0.1 mm (block). Anal. Calc. for $C_9H_{17}NO_3$: C 57.93, H 9.15, N 8.48. Found: C 57.97, H 9.36, N 8.66 %. δ_H 5.87 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.79 (s, 1H), 5.24 (dd, *J* 1.8, 17.1, 1H, CH_aH_b=CH), 5.08 (dd, *J* 1.8, 10.6, 1H, CH_aH_b=CH), 4.82 (s, 1H, NH), 4.11 (q, *J* 6.9, 2H, CH_2), 3.21 (m, 2H, CH_2N), 1.91 (m, 2H), 1.58 (m, 2H), 1.23 (t, *J* 6.9, 3H, CH_3). ν_{max}/cm^{-1} 3340, 1690, 1550, 1260. *m/z* 188 (M + H), 170 (M–OH).

t*-Butyl* N*-(4-Hydroxy-5-hexenyl)carbamate (**6b**)*

A mixture of 6-amino-3-methylhex-1-ene-3-ol (0.92 g, 8 mmol), triethylamine (1.21 g, 12 mmol), and BOC-ON (2.21 g, 9 mmol) in dioxan (20 mL) and water (20 mL) was stirred at room temperature for 24 h. The solution was diluted with ethyl acetate (40 mL) and the organic phase separated, washed with 10 % sodium hydroxide solution, the solvent removed under reduced pressure, and the residue distilled to give the carbamate **6b** as a yellow oil (0.92 g, 53 %). bp 105 °C, 0.02 mm (block). Anal. Calc. for $C_{11}H_{21}NO_3$: C 59.71, H 9.83, N 7.51. Found: C 59.66, H 10.01, N 7.22 %. δ_H 5.82 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.18 (dd, *J* 1.4, 17.1, 1H, CH_aH_b=CH), 5.02 (dd, *J* 1.4, 10.6, 1H, CH_aH_b=CH), 4.80 (br s, 1H, NH), 4.11 (m, 1H, C*H*OH), 3.15 (m, 2H, CH_2N), 2.69 (br s, 1H, OH), 1.6–1.4 (m, 4H), 1.43 (s, 9H). ν_{max}/cm^{-1} 3340, 1690, 1525. *m/z* (FAB) 215 ($M^{+\prime}$), 159 (M–*t*Bu), 142 (M–*t*BuO).

N*-(4-*H*ydroxy-5-hexenyl)-4-toluenesulfonamide (**6c**)*

To a stirred mixture of 6-amino-3-methylhex-1-ene-3-ol (690 mg, 6 mmol) in dry pyridine (40 mL) under nitrogen at 0 °C was added tosyl chloride (1.33 g, 7 mmol) portion-wise. The mixture was stirred at this temperature for 4 h, diluted with ethyl acetate (40 mL), and washed with 1 N hydrochloric acid (2 × 40 mL), followed by 10 % sodium bicarbonate (20 mL). The organic phase was separated, dried, the solvent removed under reduced pressure, and the residue recrystallized (ethyl acetate/ether/light petroleum) to give the sulfonamide **6c** as a white solid (1.15 g, 71 %). mp 51–53 °C. Anal. Calc. for $C_{13}H_{19}NO_3S$: C 57.97, H 7.11, N 5.20. Found: C 61.24, H 7.16, N 5.33 %. δ_H 7.75 (d, *J* 8.2, 2H), 7.30 (d, *J* 8.2, 2H), 5.79 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.18 (dd, *J* 1.8, 17.1, 1H, CH_aH_b=CH), 5.08 (dd, *J* 1.8, 10.6, 1H, CH_aH_b=CH), 4.85 (s, 1H, NH), 4.08 (m, 1H, C*H*OH), 2.97 (m, 2H, CH_2N), 2.90 (s, 1H, OH), 2.43 (s, 3H, $ArCH_3$), 1.59 (m, 2H), 1.57 (m, 2H). ν_{max}/cm^{-1} 1640, 1600, 1500, 1320, 1155. *m/z* 270 (M + H), 252 (M–OH), 155 (M–$SO_2C_6H_4CH_3$).

*Compound **6d***

N*-4-(Hydroxy-5-hexenyl)acetamide*

A mixture of the acetate **6f** (0.92 g, 4.6 mmol) and barium hydroxide (1.47 g, 4.6 mmol) in methanol (20 mL) was stirred at room temperature for 1 h. The solution was filtered through celite, the celite washed with methanol (10 mL), and the solvent removed under reduced pressure to give the amide **6d** (0.72 g, 100 %) as a colourless oil. bp 145 °C, 0.02 mm (block). HRMS: 157.1098; $C_8H_{15}NO_2$ requires 157.1102. δ_H 6.41 (s, 1H, NH), 5.80 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.17 (dd, *J* 1.8, 17.1, 1H, CH_aH_b=CH), 5.12 (dd, *J* 1.8, 10.6, 1H, CH_aH_b=CH), 4.14 (m, 1H, C*H*OH), 3.54 (m, 1H, OH), 3.28 (m, 2H, CH_2N), 1.98 (s, 3H, CH_3), 1.7–1.5 (m, 4H). ν_{max}/cm^{-1} 3320, 1640, 1570. *m/z* 157 ($M^{+\prime}$), 140 (M–OH).

N*-(4-*t*-Butyldiphenylsilyloxy-5-hexenylsulfonamide)-4-toluenesulfonamide (**6e**)*

A mixture of the alcohol **6c** (269 mg, 1 mmol), imidazole (150 mg, 2.5 mmol), dimethylaminopyridine (27 mg, 0.2 mmol), and *t*-butyldiphenylsilyl chloride (413 mg, 1.5 mmol) in dry DMF (5 mL) was stirred at room temperature for 24 h. The solution was diluted with ether (5 mL), washed with saturated sodium chloride (3 mL), 10 % hydrochloric acid (5 mL), 10 % sodium bicarbonate (5 mL), and again with saturated sodium chloride (3 mL). The organic phase was separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the silyl ether **6e** as a colourless oil (504 mg, 99 %). δ_H 7.72 and 7.36 (m, 10H), 7.61 and 7.21 (d, *J* 8.2, 4H), 5.64 (ddd, J_{ax} 17.1, J_{bx} 10.6, J_{ay} 6.6, 1H, C*H*=CH_2), 4.95 (dd, J_{ab} 1.8, J_{ax} 17.1, 1H, CH_aH_b=CH), 4.92 (s, 1H, NH), 4.90 (dd, J_{ab} 1.8, J_{bx} 10.6, 1H, CH_aH_b=CH), 4.08 (m, 1H, CHOSi), 3.46 (m, 2H, CH_2N), 2.73 (m, 2H), 2.36 (s, 3H, $ArCH_3$), 1.35 (m, 2H), 1.04 (s, 9H). ν_{max}/cm^{-1} 1740, 1600, 1500, 1160. *m/z* (FAB) 507 (weak $M^{+\prime}$), 450 (M–*t*Bu), 374 (M–*t*Bu–Ph), 296 (M–$(Ph)_2$*t*Bu).

N*-(4-Acetoxy-5-hexenyl)acetamide (**6f**)*

To a mixture of 6-amino-3-methylhex-1-ene-3-ol (0.69 g, 6 mmol) and triethylamine (1.82 g, 4 mmol) in dry THF (20 mL) under nitrogen at 0 °C was added acetyl chloride (1.28 mL, 18 mmol) dropwise over 2 min. The resultant solution was warmed to room temperature and stirred overnight. The solvent was then removed under reduced pressure, the residue diluted with ethyl acetate (40 mL), and washed with 1 N hydrochloric acid (2 × 10 mL) and 10 % sodium bicarbonate (10 mL). The organic was phase separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the acetate **6f** (0.926 g, 77 %) as a colourless oil. HRMS: 199.1208; $C_{10}H_{17}NO_3$ requires 199.1190. δ_H 5.72 (s, 1H, NH), 5.80 (ddd, *J* 17.1, 10.6, 6.6, 1H, C*H*=CH_2), 5.17 (dd, *J* 1.8, 17.1, 1H, CH_aH_b=CH), 5.12 (dd, *J* 1.8, 10.6, 1H, CH_aH_b=CH), 4.20 (m, 1H, CHOAc), 3.65 (m, 2H, CH_2N), 2.40 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.9–1.7 (m, 2H), 1.6–1.5 (m, 2H). ν_{max}/cm^{-1} 1725, 1700, 1230. *m/z* 199 ($M^{+\prime}$), 140 (M–$OCOCH_3$).

t*-Butyl-(4-methylhex-5-en-4-ol)carbamate (**6g**)*

A mixture of 6-amino-3-methylhex-1-ene-3-ol (1.29 g, 10 mmol), triethylamine (1.52 g, 15 mmol), and BOC-ON (2.71 g, 11 mmol) in dioxan (20 mL) and water (20 mL) was stirred at room temperature for 24 h. The solution was washed with 10 % aqueous sodium hydroxide (2 × 20 mL) and the organic phase separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the carbamate **6g** as a yellow oil (1.47 g, 63 %). bp 128–130 °C, 0.20 mm. Anal. Calc. for $C_{12}H_{23}NO_3$: C 62.85, H 9.93, N 6.26. Found: C 62.29, H 9.93, N 6.26 %. δ_H 5.85 (dd, *J* 12.1, 17.4, 1H, C*H*=CH_2), 5.19 (dd, *J*

16.0, 1.6, 1H, CH_a=CH_2), 5.07 (dd, *J* 12.1, 1.6, 1H, CH_b=CH_2), 3.47 (s, 1H, OH), 3.08 (m, 2H, CH_2N), 1.53 (m, 4H), 1.42 (s, 9H), 1.26 (s, 3H, CH_3). δ_C 156.06 (C=O), 144.67 (**C**H=CH_2), 111.69 (CH=CH_2), 78.99 (CO_2**C**), 72.79 (C(OH)), 40.72 (CH_2N), 38.96 (C(OH)**C**H_2), 28.53 ((CH_3)$_3$), 27.63 (CH_3), 24.60 (**C**H_2CH_2N). ν_{max} (CCl_4)/cm^{-1} 3640, 3500, 3430, 1735, 1650, 1180. *m/z* 230 (M + H), 212 (M–H_2O), 173 (M–*t*Bu), 129 (M–CO_2*t*Bu).

Ethyl 2(S)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-carboxylate (**7a**) and Ethyl 2(R*)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-carboxylate (**8a**)*

Using method A with the carbamate **6a** (187 mg, 1 mmol), potassium carbonate (500 mg), dry silica (500 mg), and phenylselanyl chloride (210 mg, 1.1 mmol) gave an inseparable 3:1 mixture of the piperidines **7a** and **8a** (196 mg, 57 %) as a light yellow oil. Anal. Calc. for $C_{15}H_{21}NO_3Se$: C 52.63, H 6.18, N 4.09. Found: C 52.40, H 5.97, N 3.89 %. ν_{max}/cm^{-1} 3450, 1705, 1295. *m/z* 343 ($M^{+\prime}$), 326 (M–OH), 187 (M–SePh), 173 (M–CH_2SePh). **7a**: δ_H 7.52 (m, 2H), 7.22 (m, 2H), 4.88 (dt, *J* 9.6, 5.4, 1H, H_3), 4.10 (q, *J* 6.9, 2H, CH_2), 4.02 (ddd, *J* 9.6, 9.2, 5.5, 1H, H_2), 3.44 (dd, *J* 12.8, 9.2, 1H, H_{7a}), 3.31 (dd, *J* 12.8, 5.5, 1H, H_{7b}), 3.16 (m, 2H, $H_{6a}H_{6b}$), 2.40 (s, 1H, OH), 1.67 (m, 2H, $H_{4a}H_{4b}$), 1.58 (m, 2H, $H_{5a}H_{5b}$), 1.23 (t, *J* 6.9, 3H, CH_3). δ_C 209.1 (C=O), 156.8, 133.3, 129.3, 127.6 (Ar), 70.8 (C_3), 66.3 (CH_2O), 61.5 (C_7), 60.7 (C_2), 40.4 (C_6), 31.7 (C_4), 27.4 (C_5), 14.6 (CH_3). δ_{Se} 306.6. **8a**: δ_H 7.52 (m, 2H), 7.22 (m, 3H), 4.68 (m, 1H, H_3), 4.10, q (6.9, 2H, CH_2), 3.89 (m, 1H, H_2), 3.29 (dd, *J* 13.3, 3.5, 1H, H_{7a}), 2.64 (dd, *J* 13.3, 12.7, 1H, H_{7b}), 3.16 (m, 2H, $H_{6a}H_{6b}$), 2.40 (s, 1H, OH), 1.67 (m, 2H, $H_{4a}H_{4b}$), 1.58 (m, 2H, $H_{5a}H_{5b}$), 1.23 (t, *J* 6.9, 3H, CH_3). δ_C 210.3 (C=O), 156.8, 133.3, 129.3, 127.6 (Ar), 73.4 (C_3), 66.6 (C_7), 60.8 (CH_2O), 37.4 (C_2), 32.0 (C_6), 27.5 (C_5), 24.1 (C_4), 14.5 (CH_3). δ_{Se} 306.8.

2(S)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-*p*-toluenesulfonate (**7c**) and 2(R*)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-*p*-toluenesulfonate (**8c**)*

Using method A with the sulfonamide **6c** (269 mg, 1 mmol), potassium carbonate (500 mg), dry silica (500 mg), and phenylselanyl chloride (210 mg, 1.1 mmol) gave the *cis* piperidine **8c** as a colourless oil (63 mg, 15 %). Anal. Calc. for $C_{19}H_{23}NO_3SSe$: C 53.64, H 5.45, N 3.29. Found: C 53.62, H 5.35, N 3.16 %. ν_{max}/cm^{-1} 3450, 1600, 1580, 1500, 1150. *m/z* 425 ($M^{+\prime}$), 408 (M–OH), 268 (M–SePh), 254 (M–CH_2SePh). δ_H 7.62 and 7.22 (d, *J* 8.3, C_6H_4), 7.45 (m, 2H), 7.24 (m, 3H), 4.09 (dt, *J* 3.7, 5.6, 1H, H_3), 3.78 (dd, *J* 3.4, 14.4, 1H, H_{7a}), 3.58 (m, 1H, H_{6a}), 3.56 (ddd, *J* 11.2, 3.4, 3.7, 1H, H_2), 3.10 (dd, *J* 11.2, 14.4, 1H, H_{7b}), 2.95 (m, 1H, H_{6b}), 2.41 (s, 3H, $ArCH_3$), 2.29 (s, 1H, OH), 2.05 (m, 2H), 1.75 (m, 2H). δ_C 143.2, 133.5, 132.9, 130.0, 129.6, 129.0, 127.6, 127.0 (Ar), 68.8 (C_3), 52.6 (C_7), 47.5 (C_2), 25.4 (C_6), 23.3 (C_4), 21.4 (C_5), 19.6 ($ArCH_3$). nOe (% enhancement): H_2H_3 (13.7) Further elution gave the *trans* piperidine (**7c**) as a colourless oil (196 mg, 46 %). δ_H 7.62 and 7.22 (d, *J* 8.3, 4H, C_6H_4), 7.45 (m, 2H), 7.24 (m, 3H), 4.43 (dt, *J* 9.5, 4.8, 1H, H_3), 4.13 (s, 1H, OH), 3.87 (dt, *J* 9.5, 5.0, 1H, H_2), 3.65 (m, 1H, H_{6a}), 3.23 (dd, *J* 12.3, 5.1, 1H, H_{7a}), 2.98 (dd, *J* 12.3, 9.6, 1H, H_{7b}), 2.92 (m, 1H, H_{6b}), 2.42 (s, 3H, $ArCH_3$), 1.8–1.4 (m, 4H). δ_H 143.2, 133.5, 132.9, 130.0, 129.6, 129.0, 127.6, 127.0 (Ar), 68.9 (C_3), 57.3 (C_7), 39.5 (C_2), 27.2 (C_6), 23.9 (C_4), 23.3 (C_5), 21.5 ($ArCH_3$). nOe (% enhancement): H_2H_3 (2.6). Other spectroscopic data as for **8c**.

2(S)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-acetate Mono Hydrate (**7d**) and 2(R*)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-acetate Mono Hydrate (**8d**)*

Using method A with the amide **6d** (157 mg, 1 mmol), potassium carbonate (500 mg), dry silica (500 mg), and phenylselanyl chloride (210 mg, 1.1 mmol) gave a 3:1 mixture of **7d** and **8d** as a white solid which was recrystallized from ether/light petroleum to give **7d** as white needles (127 mg, 41 %). mp 130–132 °C. Anal. Calc. for $C_{14}H_{21}NO_3Se$: C 50.01, H 6.41, N 4.24. Found: C 49.93, H 5.93, N 3.96 %. δ_H 7.58 (m, 2H), 7.27 (m, 3H), 4.80 (m, 1H, H_3), 3.95 (m, 1H, H_2), 3.87 (dd, *J* 5.0, 4.8, 1H, H_{7a}), 3.23 (dd, *J* 5.0, 2.6, 1H, H_{7b}), 3.18 (m, 2H, $H_{6a}H_{6b}$), 1.97 (s, 3H, CH_3), 1.78 (m, 2H, $H_{4a}H_{4b}$), 1.62 (m, 2H, $H_{5a}H_{5b}$). δ_C 206.4 (C=O), 141.4, 134.6, 129.3, 127.9 (Ar), 72.9 (C_3), 64.6 (C_7), 56.9 (C_2), 39.2 (C_6), 32.4 (C_4), 26.1 (CH_3C=O), 20.1 (C_5). ν_{max}/cm^{-1} 3280, 1655, 1475. *m/z* (FAB) 333 ($M^{+\prime}$), 315 (M–H_2O), 297 (M–OH–OH_2).

2(S)-Phenylselenomethyl-3(R*)-(t-butyldiphenylsilyloxy)-pyrrolidine-1-*p*-toluenesulfonate Mono Hydrate (**7e**) and 2(R*)-Phenylselenomethyl-3(R*)-(t-butyldiphenylsilyloxy)-pyrrolidine-1-*p*-toluenesulfonate Mono Hydrate (**8e**)*

Using method A with the sulfonamide (507 mg, 1 mmol), potassium carbonate (500 mg), dry silica (500 mg), and phenylselanyl chloride (210 mg, 1.1 mmol) gave the a 3:1 mixture of the hydrates **7e** and **8e** as white crystals (216 mg, 32 %). mp 108–113 °C. Anal. Calc. for $C_{35}H_{41}NO_3SSeSi$: C 61.74, H 6.37, N 2.00. Found: C 61.36, H 6.55, N 1.70 %. **7e**: δ_H 7.7–7.2 (m, 19H), 4.44 (t, *J* 6.2, 1H, OH_a), 4.00 (dt, *J* 1.9, 6.4, 1H, H_3), 3.90 (dd, *J* 11.4, 8.4, 1H, H_{7a}), 3.82 (dd, *J* 11.4, 6.2, 1H, H_{7b}), 3.27 (ddd, *J* 1.9, 6.2, 8.4, 1H, H_2), 2.55 (dt, *J* 6.2, 6.9, 2H, $H_{6a}H_{6b}$), 2.39 (s, 3H, $ArCH_3$), 2.03 (s, 1H, OH_b), 1.82 (m, 1H, H_{4a}), 1.47 (m, 1H, H_{4b}), 1.20 (m, 2H, $H_{5a}H_{5b}$), 1.03 (s, 9H). δ_C 143.2, 136.0, 135.8, 129.9, 129.4, 127.7, 127.6, 126.9 (Ar), 72.5 (C_3), 63.0 (C_7), 54.6 (C_2), 42.5 (C_6), 31.9 (C_4), 26.8 (CH_3), 25.9 (CMe_3), 21.4 ($ArCH_3$), 19.4 (C_5). δ_{HSe} 281. ν_{max}/cm^{-1} 1760, 1600, 1500, 1175. *m/z* 663 ($M^{+\prime}$), 607 (M–*t*Bu), 450 (M–$(Ph)_2$*t*Bu). **8e**: δ_H 7.7–7.2 (m, 19H), 4.40 (t, *J* 6.2, 1H, OH_a), 4.09 (dt, *J* 4.8, 7.2, 1H, H_3), 3.84 (dd, *J* 4.5, 5.4, 1H, H_{7a}), 3.83 (dd, *J* 4.5, 5.6, 1H, H_{7b}), 3.35 (ddd, *J* 4.8, 5.4, 5.6, 1H, H_2), 2.41 (dt, *J* 6.2, 6.8, 2H, $H_{6a}H_{6b}$), 2.40 (s, 3H, $ArCH_3$), 2.61 (s, 1H, OH_b), 1.82 (m, 1H, H_{4a}), 1.47 (m, 1H, H_{4b}), 1.20 (m, 2H, $H_{5a}H_{5b}$), 1.03 (s, 9H). δ_H 143.2, 136.0, 135.8, 129.9, 129.4, 127.7, 127.6, 126.9 (Ar), 74.1 (C_3), 62.4 (C_7), 53.6 (C_2), 42.2 (C_6), 31.4 (C_4), 26.9 (CH_3), 25.9 (CMe_3), 21.4 ($ArCH_3$), 19.4 (C_5). δ_{Se} 305.

t-*Butyl 3(R*)-Hydroxy-3-methyl-2(S*)-phenylselenomethylpiperidine-1-carboxylate (**7g**)*

Using method A with the carbamate **6g** (229 mg, 1 mmol), potassium carbonate (500 mg), dry silica (500 mg), and phenylselanyl chloride (210 mg, 1.1 mmol) gave **7g** as a white solid that was recrystallized (light petroleum/ether) to give white needles (289 mg, 75 %), mp 116–117 °C. Anal. Calc. for $C_{18}H_{27}NO_3Se$: C 56.24, H 7.08, N 3.64. Found: C 56.24, H 7.05, N 3.70 %. ν_{max} ($CDCl_3$)/cm^{-1} 3420, 1680, 1575, 1510. *m/z* 385 ($M^{+\prime}$), 170 (M–CH_3), 367 (M–OH), 308 (M–Ph). δ_H ($CDCl_3$, 50 °C) 7.62 (m, 2H), 7.26 (m, 3H), 3.99 (dd, *J* 14.3, 2.5, 1H, H_2), 3.77 (m, 1H, H_{6a}), 3.31 (dd, *J* 11.5, 14.3, 1H, H_{7a}), 3.15 (dd, *J* 11.5, 2.5, 1H, H_{7b}), 3.02 (m, 1H, H_{6b}), 2.22 (br s, 1H, OH), 2.02 (m, 1H, H_{5a}), 1.94 (m, 1H, H_{5b}), 1.67 (m, 1H, H_{4a}), 1.23 (m, 1H, H_{4b}), 1.46 (s, 3H, CH_3), 1.25 (s, 9H). δ_C ($CDCl_3$, 50 °C) 210.1 (C=O), 155.6, 134.25, 129.08, 127.65 (Ar), 79.59 (CO_2**C**),

72.48 (C_3), 58.90 (C_7), 47.30 (C_2), 45.02 (C_6), 37.86 (C_4), 32.10 (CH_3), 28.29 (($CH_3)_3$), 19.55 (C_5). nOe (% enhancement): H_2CH_3 (<0.5), $H_{7a}CH_3$ (5.2), $H_{7b}CH_3$ (5.6).

t-*Butyl 2(*R**)-(Hydroxymethyl)-3(*R**)-hydroxypyrrolidine-1-carboxylate (**9**)*

To the selenide **4b** (178 mg, 0.5 mmol) in isopropyl alcohol (40 mL) was added MCPBA (407 mg, 2 mmol) and the mixture stirred at room temperature for 1 h. A 10 % solution of sodium hydroxide (5 mL) was then added and the mixture stirred at room temperature for a further 4 h. The solution was diluted with saturated sodium bicarbonate (10 mL) and extracted with chloroform (2 × 20 mL). The combined organic extracts were washed with saturated sodium chloride (10 mL), dried, the solvent removed under reduced pressure and the residue chromatographed to give the diol **9** as a light yellow oil (64 mg, 59 %). δ_H 3.85 (br s, 1H), 3.75 (br s, 1H), 3.6–3.4 (m, 3H), 3.29 (m, 1H), 3.05 (br s, 1H), 1.95 (m, 1H), 1.63 (m, 1H), 1.46 (s, 9H). δ_C 156.3 (C=O), 80.3 ($OCMe_3$), 72.6 (C_3), 67.9 (C_6), 63.8 (C_2), 44.9 (C_5), 31.5 (C_4), 28.3 (CH_3). ν_{max}/cm^{-1} 3400, 1695, 1670. *m/z* (FAB) 219 (M + H_2), 217 (M^+), 186 (M–CH_2OH), 162 (M + H_2–*t*Bu), 144 (M–*t*BuO).

t-*Butyl 2(*R**)-(*t*-Butyldimethylsilyoxymethyl)-3(*R**)-(*t*-butyldimethylsilyoxymethyl)pyrrolidine-1-carboxylate (**9a**)*

A mixture of the diol **9** (44 mg, 0.2 mmol), imidazole (86 mg, 1.4 mmol), *t*-butyldimethylsilyl chloride (80 mg, 0.5 mmol), and DMAP (6 mg, 0.05 mmol) in dry DMF (2 mL) under nitrogen was stirred at room temperature for 24 h. The mixture was diluted with ether (3 mL), washed with saturated sodium chloride (2 mL), 10 % hydrochloric acid, 10 % sodium bicarbonate (2 mL), and again with saturated sodium chloride (2 mL). The organic phase was separated, dried, the solvent removed under reduced pressure, and the residue chromatographed to give the silyl ether **9a** as a light yellow oil (50 mg, 76 %). δ_H 4.34 (br m, 1H, H_3), 3.70 (m, 1H, H_{6a}), 3.66 (m, 1H, H_{6b}), 3.54–3.26 (m, 3H), 2.15–1.94 (m, 1H, H_{4a}), 1.70–1.80 (m, 1H, H_{4b}), 1.43 (s, 9H), 0.88 (s, 9H), 0.06–0.01 (m, 12H). ν_{max}/cm^{-1} 1695. *m/z* (FAB) 445 ($M^{+\prime}$), 388 (M–*t*Bu), 373 (M–*t*Bu–Me).

*Ethyl 2(*R**)-Phenylselenomethyl-3(*R**)-hydroxypiperidine-1-carboxylate Mono Hydrate (**11**)*

A mixture of the *trans*-selenide **7a** (23 mg, 0.067 mmol) and silica (10 mg) in THF (2 mL) and water (1 mL) was stirred at room temperature for 2 h. The solution was diluted with saturated sodium chloride and extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried and the solvent removed under reduced pressure to yield a solid that was recrystalized (ethyl acetate/ether/light petroleum) to give the hydrate **11** as white crystals (24 mg, 100 %). mp 90–91 °C. Anal. Calc. for $C_{15}H_{23}NO_4Se$: C 50.91, H 6.43, N 3.88. Found: C 51.28, H 6.38, N 3.64 %. δ_H ($CDCl_3$) 7.58 (m, 2H), 7.27 (m, 3H), 4.86 (t, *J* 6.3 [collapses to singlet upon irradiation @ 3.2 ppm], 1H, OH_a), 4.09 (q, *J* 6.9, 2H, CH_2), 3.97 (m, 1H, H_3), 3.92 (m [collapses to AB of an ABX system upon irradiation @ 3.0 ppm], 2H, $H_{7a}H_{7b}$), 3.28 (ddd, *J* 3.3, 5.0, 1.4 [collapses to d, of *J* 1.4 upon irradiation @ 3.9 ppm], 1H, H_2), 3.20 (br dt, *J* 6.3, 6.9 [collapses to br t of *J* 6.9 upon irradiation @ 4.9 ppm], 2H, $H_{6a}H_{6b}$), 3.00 (t, *J* 6.1, 1H, ROH), 1.7–1.5 (m, 4H), 1.45 (s, 1H, OH_b), 1.23 (t, *J* 6.9, 3H, CH_3). δ_H (CD_3OD) 7.58 (m, 2H), 7.25 (m, 3H), 4.05 (q, *J* 7.0, 2H, CH_2O), 3.99 (m, 1H, H_3), 3.89 (dd, *J* 11.3, 9.3, 1H, H_{7a}), 3.77 (dd, *J* 11.3, 5.0, 1H, H_{7b}), 3.19 (ddd, *J* 1.9, 5.0, 9.3, 1H, H_2), 3.10 (t, *J* 6.9, 2H, $H_{6a}H_{6b}$), 1.8–1.4 (m, 4H), 1.21 (t, *J* 7.0, 3H, CH_3). δ_C ($CDCl_3$) 218.6 (C=O), 156.9, 134.5, 129.3, 127.8 (Ar), 72.4 (C_3), 64.4 (OCH_2), 60.8 (C_7), 56.3 (C_2), 40.5 (C_6), 32.5 (C_4), 26.5 (C_5), 14.6 (CH_3). δ_C (CD_3OD) 216.4 (C=O), 157.0, 135.1, 130.1, 128.3 (Ar), 70.7 (C_3), 64.1 (C_7), 61.6 (CH_2O), 56.6 (C_2), 41.5 (C_6), 34.0 (C_4), 27.6 (C_5), 15.0 (CH_3). δ_{Se} ($CDCl_3$) 260. ν_{max} (nujol)/cm^{-1} 3350, 1705, 1515, 1210. *m/z* 361 ($M^{+\prime}$), 343 (M–H_2O).

Molecular Modeling

The dihedral angle profiles were calculated using the MM2 force field.[48] The investigation into the putative transition state of the reaction was done by *ab initio* calculations, using the program Gamess.[49] All energy calculations, structure optimizations, and transition state optimizations were done using the RHF/6-31G basis set. The starting point of the transition state investigation was the cyclic product (**5d**), by building both stereoisomers (*cis* and *trans*) of the *S*-hydroxy isomer. For both stereoisomers, both ring conformations (hydroxy in axial and equatorial orientation) were built. All four structures were pre-optimized by molecular mechanics calculations before optimizing the structure with the RHF/6-13G basis set. The search of the putative transition state was done in three steps: (a) constrain the distance between the Se and the C to 2.1 Å to form a cyclic Se and optimize the structure, (b) protonate the nitrogen and optimize the structure, and (c) use the final structure for transition state optimization (RUNTYP = SADPOINT). The final transition state structures were checked for virtual frequencies, before calculating the free energies.

Acknowledgements

The authors thank Johannes Zuegg for assistance with modelling work and an NHMRC Australia Fellowship: AF 511105 for funding.

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