Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 597–604

TETRAHEDRON: *ASYMMETRY*

Intramolecular amidomercurations under allylic control: a stereoselective synthesis of (+)-pseudohygroline and (+)-3-hydroxypyrrolizidine

Gina Enierga,[a] Maria Espiritu,[a] Patrick Perlmutter,[a,*] Ngoc Pham,[a] Mark Rose,[a] Stefan Sjöberg,[b] Neeranat Thienthong[a] and Katie Wong[a]

[a]*Department of Chemistry, Monash University, PO Box 23, Victoria 3800, Australia*
[b]*Department of Organic Chemistry, Uppsala University, Uppsala, Sweden*

Received 3 January 2001; accepted 5 February 2001

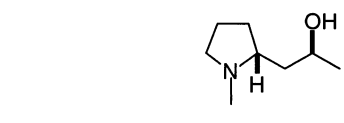
Abstract—The diastereoselectivity of intramolecular amidomercurations can be reversed by altering the remote allylic substituent of ω-alkenylcarbamates. This methodology has been applied to the synthesis of (+)-pseudohygroline and (+)-3-hydroxypyrrolizidine. © 2001 Published by Elsevier Science Ltd.

1. Introduction

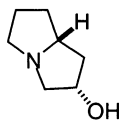
We recently reported a stereoselective synthesis of (+)-pseudohygroline **1**[1] using an intramolecular amidomercuration step under allylic control as a key reaction.[2] Herein, we report full details of this work. In addition, we describe the remarkable reversal of diastereoselection in intramolecular amidomercuration when employing a different allylic protecting group. This chemistry was applied to an enantioselective synthesis of (+)-3-hydroxypyrrolizidine **2**.[3,4]

The pyrrolidine and pyrrolizidine nuclei are found in many alkaloids, including those possessing potent pharmacological activity.[5–7] From our earlier work on stereoselective tetrahydrofuran synthesis using the intramolecular oxymercuration of (*Z*)-alkenes such as **5**, we reasoned that it should be possible to develop a general enantioselective synthetic strategy to compounds of the type **1** and **2** by using allylic control in an intramolecular amidomercuration reaction,[2,8–10] where an alkylamine residue (X = NR″) is present in the precursor **5** instead of an alcohol.

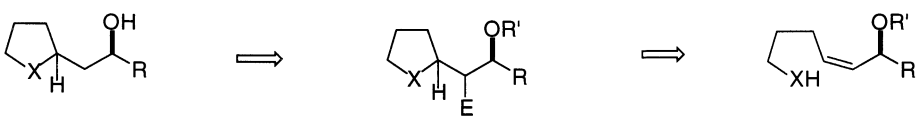
In this synthetic approach the alkene starting material has an allylic ether function remote from the locus of ring closure; oxymercuration of **5** affords the heterocycle **4** by electrophilic ring closure, which may then be further elaborated to provide the desired target **3**.



(+)-Pseudohygroline 1



(+)-3-Hydroxypyrrolizidine 2



3 **4** **5**

* Corresponding author. E-mail: patrick.perlmutter@sci.monash.edu.au

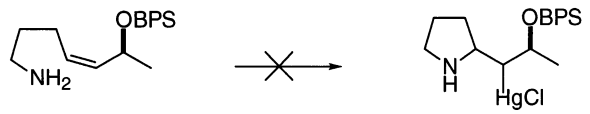
0957-4166/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0957-4166(01)00064-7

2. Results and discussion

2.1. Synthesis of (+)-pseudohygroline 1

The synthesis of **1** is outlined in Scheme 1.[8]

Wittig olefination of the silyl ether of (*S*)-lactaldehyde **6**[11] with the known ylide **7**[12] gave (*Z*)-alkene **8** in 80% yield. Reduction of the nitrile function of **8** with lithium aluminium hydride[13] then gave primary amine **9** in 83% yield. We next attempted to ring close the free amine **9** to pyrrolidine **14**; however, we only observed formation of a precipitate. None of the conditions we examined, including elevated reaction temperature, prolonged reaction times and solvent variations, proved successful.



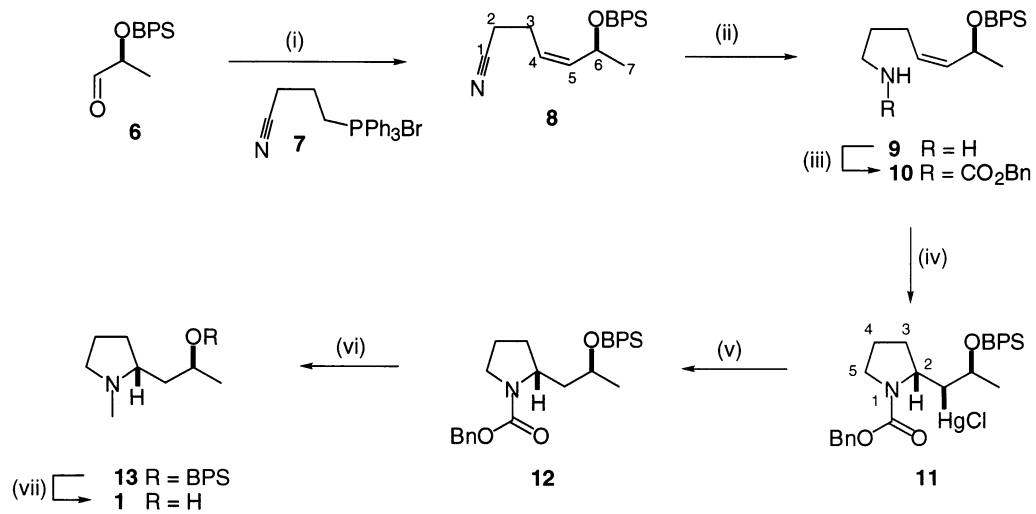
9 **14**

As it is well known that carbamates undergo intramolecular amidomercurations,[14–16] we converted **9** into its corresponding benzyl carbamate **10**. Pleasingly, **10** underwent smooth ring closure to the organomercurial **11** in a good yield (62%); additionally, the diastereoselectivity was ~12:1 in favour of the desired (2*R*)-isomer, as confirmed by X-ray crystallography. Reductive demercuration,[9,10] under radical conditions, then afforded **12** in 55% yield. The carbamate protecting group of **12** was then reduced with lithium aluminium hydride[17,18] to furnish the *N*-methyl analogue **13** in a 50% yield. Finally, removal of the silyl protecting group[19] resulted in a 50% yield and completed the synthesis to give enantiomerically pure (+)-pseudohygroline **1**.[2,20,21]

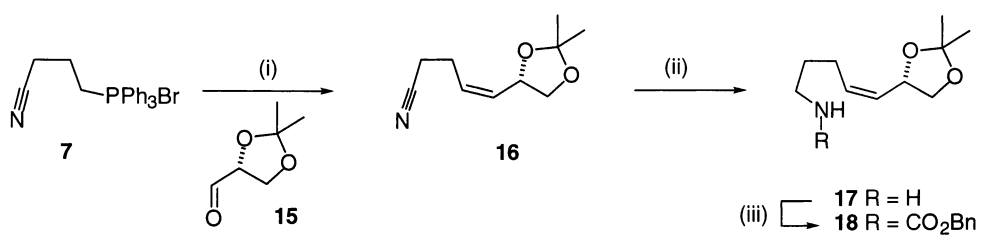
2.2. Synthesis of (+)-3-hydroxpyrrolizidine

The synthesis of (+)-3-hydroxypyrrolizidine **2** involved a similar sequence to that for **1**, leading to **18** as an important target intermediate. Wittig olefination[11] of D-glyceraldehyde acetonide **15** with the ylide derived from **7**[12] gave a new alkene, **16**, in 70% yield. Carbamate **18** was then prepared by reduction and protection in 62% yield from **16** (Scheme 2).

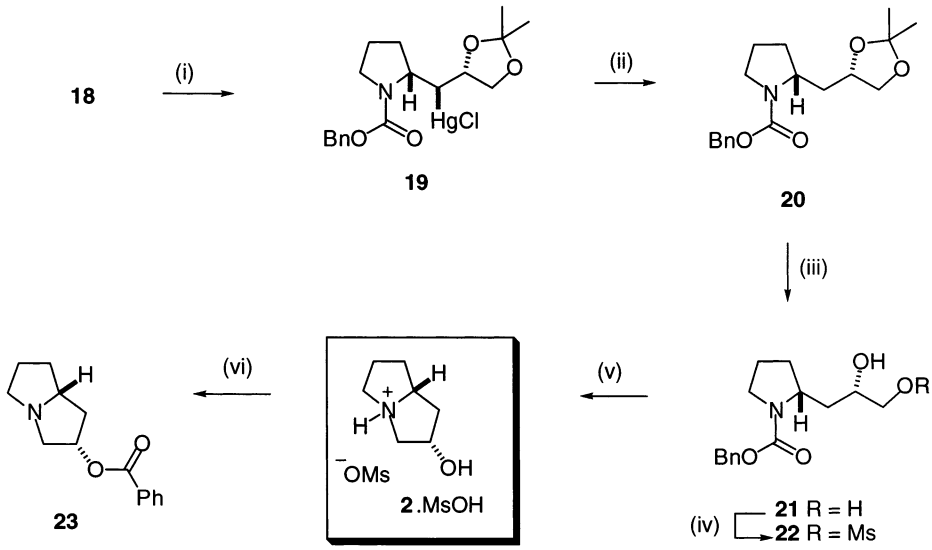
Ring closure of **18**, using the same conditions as those used for the closure of **10**, provided pyrrolidine **19** with >10:1 diastereoselectivity and in an excellent yield (82%). Reductive demercuration[2,9,10] of **19** afforded **20** in 73% yield and was followed by removal of the acetonide protecting group with aqueous acetic acid[22] to give **21** in 73% yield. Selective mesylation[23] at the primary alcohol generated the activated precursor for the second ring closure, **22**, in 72% yield. Catalytic hydrogenation of **22** removed the benzyloxycarbonyl protecting group, and the resultant free amine spontaneously displaced mesylate to yield **2**[24] in 91% yield. The pyrrolizidine **2** (obtained as its mesylate salt)



Scheme 1. (i) $NaN(TMS)_2$, 80%; (ii) $LiAlH_4$, Et_2O, 83%; (iii) BnOCOCl, Et_3N, 43%; (iv) (a) $Hg(OAc)_2$, CH_2Cl_2, rt; (b) aq. NaCl 62%; (v) Bu_3SnH, AIBN, toluene, 55%; (vi) $LiAlH_4$, Et_2O, 50%; (vii) NH_4F, MeOH 50%.



Scheme 2. (i) $NaN(TMS)_2$, 70%; (ii) $LiAlH_4$, Et_2O, 94%; (iii) BnOCOCl, Et_3N, 66%.



Scheme 3. (i) (a) $Hg(OAc)_2$, CH_2Cl_2, rt; (b) aq. NaCl 82%; (ii) Bu_3SnH, AIBN, toluene, 73%; (iii) aq. AcOH, rt, 77%; (iv) MsCl (1 equiv.), CH_2Cl_2, Et_3N, 72%; (v) Pd–C, H_2, 91%; (vi) $(PhCO)_2O$, pyridine, 70%.

proved to be quite difficult to purify. Consequently, it was converted into the benzoate **23** in 70% yield, which was readily purified by column chromatography (Scheme 3).

X-Ray crystal structure analysis revealed that the relative stereochemistry of **19** is as shown in Fig. 1. Clearly, ring closure proceeded with the opposite sense of diastereoselection to that for **10**. This is the most remarkable 'reversal' of diastereoselection in all our studies so far on intramolecular oxy-[8–10] and amido-[2] mercurations and obviously reflects the influence of an allylic dioxolane moiety on this process.

2.3. Diastereoselectivity in intramolecular amidomercurations

Previously we have argued that, where the remote allylic substituent is a bulky silyl ether, the diastereocontrol is determined by the approach of the metal ion (possibly ^+HgOAc or an incipient form) to the less hindered face of the most stable conformation of the alkene.[8–10] This conformation (**I**, Fig. 2) contains the smallest allylic substituent (H-6) in plane and is closest to the allylic methylene protons (H-3a and H-3b). Naturally, this assumes that the most stable conformation is also the major reacting conformation. This simple model, as shown in Fig. 2, accounts for the observed diastereoselection associated with all the intramolecular oxymercurations we have so far studied, as well as the closure of carbamate **10**. However, in the case of **18**, the dioxolane clearly reacts via a different conformation to those of the related allylic TBS ethers. Given the stereochemical outcome of this particular closure, it appears reasonable to propose that this case involves the approach of the metal ion to a conformation resembling **II** (Fig. 2). In conformation **II** the dioxolane oxygen attached to C-(6) occupies the most hindered position. This renders the *Si*-face more sterically hindered when compared to the *Re*-face.

3. Conclusion

We have demonstrated that a similar sequence of reactions involving the intramolecular amidomercuration reaction of an allylic ether leads to useful, enantiomerically pure intermediates for pyrrolidine and pyrrolizidine synthesis. In addition, we have shown that the nature of the *O*-protecting group of the allylic ether can dramatically influence the diastereoselectivity of intramolecular amidomercuration reactions.

4. Experimental

4.1. (4*Z*,6*S*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-4-heptenenitrile 8

Sodium bis(trimethylsilyl)amide (1 M in THF, 4.5 mL, 4.5 mmol) was added to a stirred suspension of phos-

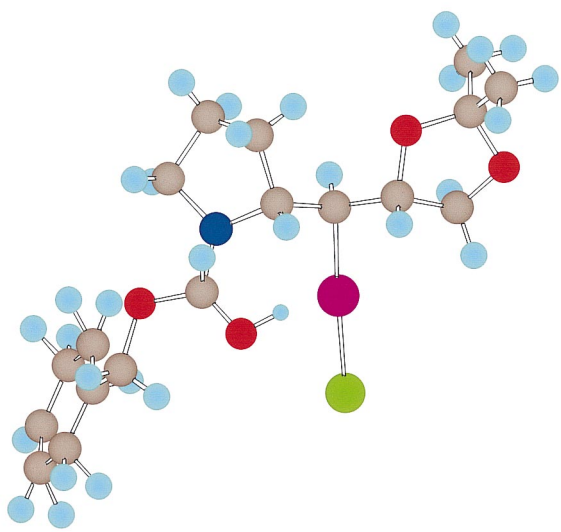
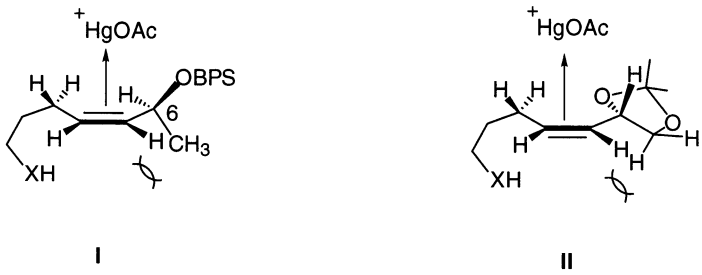


Figure 1. X-Ray crystal structure of **19**.



I II

Figure 2.

phonium salt **7** (1.60 g, 3.9 mmol) in THF (35 mL) under nitrogen at 0°C. The bright orange mixture was stirred for 30 min. A solution of the aldehyde **6**[11] (600 mg, 1.92 mmol) in THF (10 mL) was added. The reaction mixture was then stirred for a further 4 h at 0°C, poured into ether (110 mL) and the mixture washed with satd NaCl (2×35 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by pre-column and preparative TLC (ethyl acetate–hexane 1:8, $R_f = 0.3$). Nitrile **8** was obtained as a colourless liquid (0.563 g, 80%). IR ν_{max} (cm^{-1}): 2963 (CN). ^1H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H, *t*-Bu), 1.22 (d, 3H, $J = 6.2$ Hz, 3×H-7), 1.8–2.0 (m, 4H, 2×H-2 and 2×H-3), 4.5 (m, 1H, H-6), 5.13 (m, 1H, H-4), 5.63 (m, 1H, H-5), 7.38–7.48 (m, 6H, Ph), 7.63–7.74 (m, 4H, Ph). Anal. calcd for $C_{23}H_{29}NOSi$: C, 75.98; H, 8.04; N, 3.85. Found: C, 76.03; H, 8.11; N, 3.79%.

4.2. (4*Z*,6*S*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-4-heptenamine 9

To a stirred suspension of $LiAlH_4$ (0.212 g, 5.64 mmol) in anhydrous ether (4.8 mL) was added a solution of the nitrile **8** (1.365 g, 3.75 mmol) in ether (12 mL) at room temperature. The reaction mixture was heated under reflux for 2.5 h and then left to cool to rt. Sodium sulfate decahydrate was added in portions until effervescence ceased. The mixture was filtered and the solid was washed with ether. The combined organic solvents were evaporated to give the amine **9** as an oil (1.152 g, 83%). IR ν_{max} (cm^{-1}): 3356 (NH_2). ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (s, 9H, *t*-Bu), 1.16 (d, 3H, $J = 6.2$ Hz, 3×H-7), 1.2–1.39 (m, 2H, 2×H-2), 1.63 (m, 2H, 2×H-3), 2.47 (m, 2H, 2×H-1), 4.56 (m, 1H, H-6), 5.16 (m, 1H, H-4), 5.50 (m, 1H, H-5), 7.25–7.44 (m, 6H, Ph), 7.65–7.69 (m, 4H, Ph). EIMS *m*/*z* 368 (M^+). Anal. calcd for $C_{23}H_{33}NOSi$: C, 75.15; H, 9.05; N, 3.81. Found: C, 71.23; H, 9.01; N, 3.35%.

4.3. *N*-(Benzyloxycarbonyl)-(4*Z*,6*S*)-6-[(*tert*-butyldiphenylsilyl)oxy]-4-heptenamine 10

Benzyl chloroformate (0.30 mL, 2.05 mmol) was added dropwise to a solution of amine **9** (503 mg, 1.37 mmol) and triethylamine (0.60 mL, 4.31 mmol) in THF under a nitrogen atmosphere. The reaction mixture was stirred overnight at rt. The mixture was filtered and the solid washed with ether. The carbamate was extracted with ether. The ether solution was then washed with saturated aqueous NaCl, dried (Na_2SO_4) and evaporated in vacuo. Purification using radial chromatography (ethyl acetate–hexane 1:2, $R_f = 0.47$) gave the carbamate **10** as an oil (112 mg, 43%). $[\alpha]_D$ +3.8 (*c* 1.8, $CHCl_3$). IR ν_{max} (cm^{-1}): 3342 (NH), 1731 (CO). ^1H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H, *t*-Bu), 1.16 (d, 3H, $J = 6.0$ Hz, 3×H-7), 1.35 (m, 2H, 2×H-2), 1.59–1.68 (m, 2H, 2×H-3), 2.97 (dd, 2H, $J = 12.0$, 6.0 Hz, 2×H-1), 4.49–4.56 (m, 2H, H-6 and NH), 5.07–5.28 (m, 3H, CH_2Ph and H-4), 5.53 (t, 1H, $J = 8.6$ Hz, H-5), 7.28–7.41 (m, 4H, Ph), 7.63–7.68 (m, 9H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1 (C-2), 24.4 (C-3), 24.6 (C-7), 26.9 (*t*-Bu), 29.5 (Si-C), 40.6 (C-1), 65.8 (C-6), 66.5 (CH_2Ph), 127.0, 127.4, 127.5, 128.1, 128.5, 129.4, 129.5, 134.2, 134.4, 135.4, 135.8, 135.9, 136.6 (C-4, C-5 and Ph), 156.2 (CO). Anal. calcd for $C_{31}H_{39}NO_3Si$: C, 74.21; H, 7.83; N, 2.79. Found: C, 74.28; H, 7.80; N, 2.60%.

4.4. *N*-(Benzyloxycarbonyl)-(2*R*)-2-[(1*S*,2*S*)-1-chloromercurio-2-((*tert*-butyldiphenylsilyl)oxy)prop-1-yl]-pyrrolidine 11

A solution of carbamate **10** (51 mg, 0.10 mmol) in chloroform (1 mL) was added to $Hg(OAc)_2$ (36 mg, 0.1 mL) dissolved in chloroform (1 mL). The mixture was left to stir for 2 days at rt. Saturated aqueous sodium chloride was added and the reaction was stirred for a further 15 min. The reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was then dried (Na_2SO_4) and evaporated in vacuo. Purification by preparative TLC (diethyl ether–hexane 1:2, $R_f = 0.40$) gave the cyclised product **11** as an oil (43 mg, 62%). $[\alpha]_D$ +2.8 (*c* 1.8, $CHCl_3$). IR ν_{max} (cm^{-1}): 3070 (NH), 1668 (CO). ^1H NMR (200 MHz, $CDCl_3$): δ 1.11 (s, 9H, *t*-Bu), 1.15 (d, 3H, $J = 6.0$ Hz, 3×H-3′), 1.23–1.33 (m, 2H, 2×H-4), 1.54 (m, 2H, 2×H-3), 2.26 (d, 1H, $J = 11.0$ Hz, H-1′), 3.25–3.45 (m, 2H, 2×H-5), 4.16–4.18 (m, 2H, H-2 and H-2′), 5.12 and 5.26 (AB quartet, 2H, $J = 12.3$ Hz, CH_2Ph), 7.31–7.43 (m, 11H, Ph), 7.65–7.74 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (C-4), 23.5 (C-3), 27.2 (*t*-Bu), 31.1 (Si-C), 46.7 (C-5), 59.9 (C-1′), 67.4 (CH_2Ph), 68.4 (C-2), 70.6 (C-2′), 127.6, 127.9, 128.2, 128.5, 128.6, 129.8, 130.0, 133.4, 134.2, 136.1, 136.2, 136.6 (Ph), 155.5 (CO).

4.5. *N*-(Benzyloxycarbonyl)-(2*R*)-2-[(2*S*)-2-((*tert*-butyldiphenylsilyl)oxy)prop-1-yl]pyrrolidine 12

The chloromercurial **11** (431 mg, 0.6 mmol) was dissolved in toluene (1 mL) under N_2. A solution of AIBN (8 mg) in toluene (1.4 mL) was added, followed by tributylstannane (0.43 mL). After addition of the stannane, mercury was seen to precipitate. The reaction mixture was stirred at rt for 1 h, then heated to 60°C and stirred at this temperature for 1 h. Carbon tetrachloride (0.3 mL) was added and the reaction was cooled to rt with stirring and then stirred for a further 1 h. The supernatant reaction mixture was decanted from the precipitated mercury, taken up in CH_2Cl_2–pentane (1:3) (50 mL) and washed with 5% aqueous KF solution (2×30 mL). After drying (Na_2SO_4) and filtration through silica (ethyl acetate–hexane 1:5), the mixture was evaporated in vacuo to afford the crude product as a gum. Further purification by column chromatography (ethyl acetate–hexane 1:3, $R_f=0.2$, hexane–ether 4:1) gave the carbamate **12** as a colourless gum (164 mg, 55%). $[\alpha]_D$ +10.9 (*c* 2.3, $CHCl_3$). IR ν_{max} (cm^{-1}): 1701 (CO). ^1H NMR (300 MHz, DMSO at 90°C): δ 1.01 (s, 9H, *t*-Bu), 1.10 (d, 3H, $J=5.6$ Hz, 3×H-3′), 1.46 (m, 1H, H-1′), 1.55 (m, 2H, 2×H-4), 1.70 (m, 2H, 2×H-3), 1.94 (m, 1H, H-1′), 3.15 (m, 1H, H-5a), 3.30 (m, 1H, H-5b), 3.95 (m, 2H, H-2 and H-2′), 5.01 (s, 2H, CH_2Ph), 7.22–7.40 (m, 10H, Ph), 7.60 (m, 5H, Ph). ^{13}C NMR (75 MHz, DMSO at 90°C): δ 18.7 (C-4), 22.7 (Si-C), 23.5 (C-3′), 26.9 (*t*-Bu), 30.1 (C-3), 43.9 (C-1′), 45.8 (C-5), 54.3 (C-2), 65.7 (CH_2Ph), 67.5 (C-2′), 127.4, 127.5, 127.6, 128.2, 129.5, 129.6, 133.9, 134.4, 135.3, 137.2 (Ph), 153.9 (CO). Anal. calcd for $C_{31}H_{39}NO_3Si$: C, 74.24; H, 7.78; N, 2.79. Found: C, 74.37; H, 7.62; N, 2.91%.

4.6. *N*-(Methyl)-(2*R*)-2-[(2*S*)-2-((*tert*-butyldiphenylsilyl)oxy)prop-1-yl]pyrrolidine 13

A solution of **12** (344 mg, 0.7 mmol) in ether (7 mL) was treated with $LiAlH_4$ (63 mg, 1.7 mmol). After 6 h the reaction was quenched by addition of $Na_2SO_4{\cdot}10H_2O$ (617 mg, 1.9 mmol). Water (2 mL) was added to the reaction solution, the ether layer separated and the aqueous layer extracted further with ether (2×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Following chromatography on silica (methanol–ether 1:9, $R_f=0.3$), the silyl ether **13** was obtained as a colourless oil (132 mg, 50%). $[\alpha]_D$ +31.7 (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H, *t*-Bu), 1.15 (d, 3H, $J=6.1$ Hz, 3×H-7), 1.25 (m, 2H, 2×H-2), 1.60 (m, 3H, 2×H-3 and H-5a), 1.90–2.20 (m, 3H, 2×H-1 and H-5b), 2.24 (s, 3H, CH_3N), 3.00 (t, 1H, $J=9.0$ Hz, H-4), 3.85 (m, 1H, H-6), 7.30–7.50 (m, 6H, Ph), 7.65–7.72 (m, 4H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.4 (C-2), 22.0 (Si-C), 24.8 (C-7), 27.2 (*t*-Bu), 31.2 (C-3), 40.4 (CH_3N), 44.3 (C-5), 57.1 (C-1), 63.0 (C-4), 68.4 (C-6), 127.4, 127.5, 127.6, 129.5, 129.6, 134.2, 134.9, 135.9, 136.0, 136.1 (ArH). HRMS calcd for (M+H) $C_{24}H_{36}NOSi$: 382.2566. Found: 382.2566.

4.7. (+)-Pseudohygroline 1

The silyl ether **13** (33 mg, 0.1 mmol) was dissolved in methanol (1 mL) and ammonium fluoride (38 mg, 1 mmol) was added. The reaction was stirred at rt overnight, after which the solvent was evaporated, the residue taken up in dichloromethane, stirred for 1 h and filtered. Evaporation of the dichloromethane gave the crude alkaloid **1**. Purification by chromatography on alumina (methanol–ethyl acetate 1:9, $R_f=0.25$) gave pseudohygroline **1** (7 mg, 50%) as a colourless oil. $[\alpha]_D$ +70.7 (*c* 2.0, CH_3CH_2OH); lit.[1] $[\alpha]_D$ +84.4° (*c* 3.4, CH_3CH_2OH). IR ν_{max} (cm^{-1}): 3500–3250 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (d, 3H, $J=6.1$ Hz, 3×H-3′), 1.45 (m, 3H, 2×H-4 and H-1′a), 1.80 (m, 2H, 2×H-3), 2.02 (dq, 1H, $J=12.4$, 8.0 Hz, H-1′b), 2.35–2.42 (s, 3H, CH_3N and m, 1H, H-5a), 2.72 (m, 1H, H-5b), 3.05 (dt, 1H, $J=10.6$, 6.7 Hz, H-2), 3.95 (m, 1H, H-2′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8 (C-4), 24.3 (C-3′), 30.5 (C-3), 42.8 (C-1′), 43.1 (CH_3N), 55.4 (C-5), 65.9 (C-2), 67.5 (C-2′). HRMS calcd for (M+H) $C_8H_{18}NO$: 144.1388. Found: 144.1360.

4.8. (4*Z*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-pentenenitrile 16[25]

Sodium bis(trimethylsilyl)amide (1.0 M in THF, 3.9 mL, 3.9 mmol) was added dropwise to a stirred solution of the phosphonium salt **7** (1.53 g, 3.72 mmol) in THF (3.9 mL). The resultant bright yellow mixture was stirred at 0°C under a nitrogen atmosphere for 30 min. A solution of the aldehyde **15** (0.315 g, 2.4 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred for a further 4 h at 0°C and poured into a separating funnel containing diethyl ether (60 mL). The organic layer was washed with saturated aqueous sodium chloride (2×20 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (ethyl acetate–hexane 1:3) of the resulting crude oil gave the nitrile **16** ($R_f=0.3$) as a light yellow oil (0.32 g, 70%). IR ν_{max} (cm^{-1}): 2246 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.21 (m, 4H, 2×H-3 and 2×H-2), 3.60 (t, 1H, $J=8$ Hz, H-5′), 4.12–4.17 (m, 1H, H-5′), 4.81–4.86 (m, 1H, H-4′), 5.62 (m, 2H, H-4 and H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6 (C-2), 23.4 (C-3), 25.9 (CH_3), 26.8 (CH_3), 69.4 (C-5′), 71.5 (C-4′), 109.4 (CMe_2), 118.8 (C-1), 129.7 (C-4), 130.8 (C-5).

4.9. (4*Z*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-pentenamine 17

A solution of nitrile **16** (1 g, 5.52 mmol) in dry ether (5 mL) was added slowly to a stirred suspension of lithium aluminium hydride (0.9 g, 23.7 mmol) in dry ether (75 mL). The reaction mixture was heated under reflux for 2 h under nitrogen and was then allowed to cool to rt. Sodium sulfate decahydrate was slowly added in small portions until excess $LiAlH_4$ was destroyed. The reaction mixture was then filtered through Celite, washed with ether and the filtrate concentrated in vacuo to give the amine **17** as a light yellow oil (0.96 g, 94%). $[\alpha]_D$ +3.5 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 3357 (NH_2). ^1H

NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.52–1.60 (m, 2H, 2×H-2), 2.12–2.38 (m, 2H, 2×H-3), 2.49–2.68 (bs, 2H, NH_2), 2.75 (t, 2H, $J=7.3$ Hz, 2×H-1), 3.54 (t, 1H, $J=8.3$ Hz, H-5′), 4.08 (m, 1H, H-5′), 4.84–4.92 (m, 1H, H-4′), 5.44 (m, 1H, H-4), 5.62–5.70 (m, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9 (C-3), 25.8 (CH_3), 26.6 (CH_3), 33.2 (C-2), 41.3 (C-1), 69.1 (C-5′), 71.5 (C-4′), 108.6 (CMe_2), 128.2 (C-4), 131.7 (C-5).

4.10. *N*-Benzyloxycarbonyl-(4*Z*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-pentenamine 18

Benzyl chloroformate (2.4 mL, 1.62 mmol) was added dropwise to an ice-cooled solution of the amine **17** (252 mg, 1.35 mmol) and triethylamine (3 mL, 2.16 mmol) in THF (5 mL) under nitrogen. The reaction mixture was stirred overnight at rt, filtered and the solid washed with ether. The filtrate was washed with saturated aqueous sodium chloride, separated and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate–hexane 1:3, $R_f=0.7$). Carbamate **18** was obtained as a yellow oil (0.29 g, 66%). $[\alpha]_D$ −10.0 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 3364 (NH), 1706 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.65 (m, 2H, 2×H-2), 2.25 (m, 2H, 2×H-3), 3.21 (m, 2H, 2×H-1), 3.53 (t, 1H, $J=7.8$ Hz, H-5′), 4.10 (m, 1H, H-5′), 4.81 (m, 1H, H-4′), 5.10 (bs, 3H, CH_2Ph and NH), 5.41–5.50 (m, 1H, H-4), 5.56–5.66 (m, 1H, H-5), 7.30–7.39 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9 (C-3), 25.9 (CH_3), 26.7 (CH_3), 27.4 (C-2), 39.9 (C-1), 66.4 (CH_2Ph), 69.4 (C-5′), 71.6 (C-4′), 109.1 (CMe_2), 127.7, 127.9, 128.3 (Ph), 134.2 (C-4), 136.5 (C-5), 156.2 (CO). HRMS calcd for (M+Na^+) $C_{18}H_{25}NNaO_4$: 342.1681. Found: 342.1911.

4.11. *N*-Benzyloxycarbonyl-(5*R*)-5-[(*S*)-chloromercurio((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl]pyrrolidine 19

A solution of mercuric acetate (1.99 g, 6.26 mmol) in dry dichloromethane (34 mL) was added slowly to a stirred solution of carbamate **18** (1 g, 3.13 mmol). The mixture was allowed to stir for 24 h at rt, aqueous saturated NaCl was added and the mixture was stirred for an additional 15 min. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate–dichloromethane 1:4, $R_f=0.75$) of the crude residue afforded pyrrolidine **19** as a white solid (1.4 g, 82%). $[\alpha]_D$ +59.6 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 1664 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.78–1.98 (m, 4H, 2×H-3 and 2×H-4), 2.62 (dd, 1H, $J=11.6$, 5.8 Hz, CHHgCl), 3.31 (m, 2H, 2×H-2), 3.58 (t, 1H, $J=7.6$ Hz, H-5′a), 3.84–3.94 (m, 1H, H-5), 4.08 (bt, $J=5.9$ Hz, 1H, H-5′b), 4.36 (m, 1H, H-4′), 5.05 and 5.08 (ABq, 2H, $J=11.4$ Hz, CH_2Ph), 7.30–7.39 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 (C-3), 25.7 (CH_3), 27.4 (CH_3), 32.1 (C-4), 46.5 (C-2), 59.8 (C-HgCl), 60.1 (C-5), 67.5 (C-5′), 70.9 (CH_2Ph), 76.5 (C-4′), 109.2 (CMe_2), 127.2, 127.3, 128.6, 136.1 (Ph), 156.2 (CO). HRMS calcd for (M+Na^+) $C_{18}H_{24}ClHgNNaO_4$: 578.0997. Found: 578.0998. Anal. calcd for $C_{18}H_{24}ClHgNO_4$: C, 38.99; H, 4.36; N, 2.53. Found: C, 39.06; H, 4.23; N, 2.57%.

4.12. *N*-Benzyloxycarbonyl-(5*R*)-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl]pyrrolidine 20

Tributylstannane (0.63 g, 2.16 mmol) was added dropwise to a stirred solution of **19** (0.3 g, 0.54 mmol) and AIBN (0.03 g, 0.18 mmol) in toluene (3 mL) under a nitrogen atmosphere. Metallic mercury immediately began to precipitate. The reaction was stirred at rt for 1 h and then at 70°C for 2 h. The mixture was allowed to cool to rt. Carbon tetrachloride (2 mL) was added and the mixture stirred for an additional 1 h. The solution was decanted from the precipitated mercury, diluted with ether (100 mL) and washed with a 5% aqueous potassium fluoride solution (2×45 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography (ethyl acetate–dichloromethane 1:4, $R_f=0.5$) gave **20** as a yellow oil (0.13 g, 73%). $[\alpha]_D$ +35.1 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 1699 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.53–1.68 (bm, 2H, 2×H-3), 1.81–1.93 (bm, 4H, 2×H-4 and 2×H), 3.38 (m, 2H, 2×H-2), 3.52 (m, 1H, H-5′a), 3.86 (m, 1H, H-5′b), 4.04 (m, 1H, H-5), 4.16 (m, 1H, H-4′), 5.10 (m, 2H, CH_2Ph), 7.32 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1 (C-3), 26.1 (CH_3), 27.3 (CH_3), 31.1 (C-4), 38.7 (CH_2), 46.4 (C-2), 54.4 (C-5), 66.8 (CH_2Ph), 67.3 (C-5′), 68.5 (C-4′), 108.2 (CMe_2), 127.6, 127.7, 128.3, 137.8 (Ph), 154.9 (CO). HRMS calcd for (M+Na^+) $C_{18}H_{25}NaO_4$: 342.1681. Found: 342.1681. Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.39; H, 7.76; N, 4.46%.

4.13. *N*-Benzyloxycarbonyl-(5*R*)-5-[(2*S*)-2,3-dihydroxyprop-1-yl]pyrrolidine 21

A 50% aqueous acetic acid solution (1 mL) was added to **20** (50 mg, 0.16 mmol) and the resulting solution was stirred at rt for 24 h. The solvent was removed under reduced pressure without heating. Toluene (0.5 mL) was added and the solvent was concentrated in vacuo. Purification of the crude mixture by flash chromatography (ethyl acetate, $R_f=0.5$) afforded the diol **21** as a yellow oil (45 mg, 77%). $[\alpha]_D$ −2.4 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 3404 (OH), 1676 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (m, 2H, H-1′), 1.63 (m, 2H, 2×H-4), 1.94 (m, 3H, 2×H-3 and OH), 3.43 (bt, $J=6.6$ Hz, 2H, 2×H-2), 3.46–3.61 (bm, 2H, 2×H-3′), 3.68 (m, 1H, H-5), 4.26 (m, 1H, H-2′), 5.15 (s, 2H, CH_2Ph), 7.36 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (C-1′), 31.3 (C-3), 39.3 (C-4), 46.5 (C-2), 54.5 (C-5), 66.5 (CH_2Ph), 67.4 (C-3′), 68.7 (C-2′), 127.9, 128.2, 128.6, 136.6 (Ph), 157.1 (CO). HRMS calcd for (M+Na^+) $C_{15}H_{21}NaO_4$: 302.1368. Found: 302.1365. Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.58; N, 5.01. Found: C, 64.34; H, 7.48; N, 4.86%.

4.14. *N*-Benzyloxycarbonyl-(5*R*)-5-[(2*S*)-2-hydroxy-3-methanesulfonyloxyprop-1-yl]pyrrolidine 22

Methanesulfonyl chloride (0.33 mL, 4.2 mmol) in dichloromethane (10 mL) was added dropwise to a stirred ice-cooled solution of the diol **21** (1.18 g, 4.2 mmol) and triethylamine (0.59 mL, 4.2 mmol) in dichloromethane (25 mL). The resulting mixture was stirred for 2 h at 0°C, after which the solvent was removed in vacuo. The residue was then diluted with dichloromethane (70 mL) and washed with ice-cold water (2×50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Flash chromatography (1:15 dichloromethane–ethyl acetate) gave the mono-mesylated product **22** as an oil (1.08 g, 72%). $[\alpha]_D$ +4.1 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 3402 (OH), 1638 (CO), 1417, 1355, 1174 (SO_3CH_3). ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (m, 2H, 2×H-1′), 1.68 (bs, 1H, OH), 1.94 (bm, 4H, 2×H-3 and 2×H-4), 3.10 (s, 3H, CH_3SO_2), 3.34 (bt, *J*=6.5 Hz, 2H, 2×H-2), 3.88 (m, 1H, H-5), 4.21 (m, 2H, 2×H-3′), 4.31 (m, 1H, H-2′), 5.15 (bs, 2H, $C\underline{H}_2Ph$), 7.36 (m, 5H, Ph). ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.5 (C-3), 31.9 (C-4), 37.7 (CH_3SO_3), 39.2 (C-1′), 46.5 (C-2), 54.1 (C-5), 66.1 (C-2′), 67.4 (C-3′), 73.3 (CH_2Ph), 128.8, 128.1, 128.5 (Ph). HRMS calcd for ($M+Na^+$) $C_{16}H_{23}NNaO_6S$: 380.1144. Found: 380.1149.

4.15. (3*S*,5*R*)-3-Hydroxypyrrolizidine 2

To a solution of the mesylate **22** (200 mg, 0.56 mmol) in absolute ethanol (30 mL) was added palladium hydroxide on carbon (20%, 100 mg). The mixture was stirred under an atmosphere of hydrogen at 56 psi overnight. The suspension was filtered through Celite and the filter cake was washed with ethyl acetate (3×10 mL). The filtrate was concentrated in vacuo to give the methanesulfonic acid salt of pyrrolizidine **2** (114 mg, 91%). IR ν_{max} (cm^{-1}): 3356 (OH), 1266, 1192 (SO_3CH_3). ^1H NMR (300 MHz, CD_3OD): δ 1.90–2.40 (m, 6H, 2×H-4, 2×H-6 and 2×H-7), 2.70 (s, 3H, CH_3SO_3), 3.25 (dt, 1H, *J*=12.5, 2.1 Hz, H-2a), 3.42 (m, 1H, H-8a), 3.55 (dd, 1H, *J*=12.5, 4.3 Hz, H-2b), 3.72 (m, 1H, H-8b), 4.29 (dq, 1H, *J*=9.0, 3.9 Hz, H-5), 4.55 (sept., 1H, *J*=2.5 Hz, H-3). ^{13}C NMR (75 MHz, CD_3OD): δ 26.7 (C-7), 33.3 (C-6), 39.5 (CH_3SO_3), 39.7 (C-4), 58.1 (C-8), 61.5 (C-2), 69.2 (C-5), 72.7 (C-3). HRMS calcd for ($M+Na^+$) $C_{16}H_{23}NNaO_6S$: 128.1075. Found: 128.1070.

4.16. (3*S*,5*R*)-3-Benzoyloxypyrrolizidine 23

To a stirred solution of **2** (26 mg, 0.116 mmol) in THF (1 mL) was added benzoic anhydride (62 mg, 0.27 mmol), DMAP (2 mg) and triethylamine (40 μL, 0.29 mmol). The mixture was stirred at rt for 1 h. The suspension was filtered and the filtrate was concentrated in vacuo. The product was extracted with aqueous HCl (1 M, 3×5 mL). The aqueous layer was neutralised with $NaHCO_3$ and then extracted with ethyl acetate (2×10 mL). The organic layer was concentrated in vacuo to afford **23** as an oil (19 mg, 70%). $[\alpha]_D$ −4.6 (*c* 1.0, CH_2Cl_2). IR ν_{max} (cm^{-1}): 1716 (CO). ^1H NMR (75 MHz, $CDCl_3$): δ 1.6–2.5 (m, 5H, 2×H-6, 2×H-7 and H-4a), 2.44 (ddd, 1H, *J*=14.3, 8.2, 6.2 Hz, H-4b), 2.87 (m, 1H, H-8a), 3.05 (m, 1H, H-2a), 3.20 (ddd, 1H, *J*=10.5, 6.7, 4.4 Hz, H-8b), 3.40 (dd, 1H, *J*=12.6, 5.0 Hz, H-2b), 3.67 (m, 1H, H-5), 5.49 (m, 1H, H-3), 7.40 (m, 2H, Ph), 7.55 (m, 1H, Ph), 8.00 (m, 2H, Ph). ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.1 (C-7), 32.9 (C-6), 38.1 (C-4), 55. (C-8), 59.6 (C-2), 63.8 (C-5), 77.6 (C-3), 128.5, 129.5, 130.3, 133.0 (Ph), 166.1 (CO). HRMS calcd for ($M+H^+$) $C_{14}H_{18}NO_2$: 232.1337. Found: 232.1332.

Acknowledgements

Financial support from the Australian Research Council is gratefully acknowledged. The authors would like to thank Dr. Gary D. Fallon for determining the X-ray crystal structure of compound **19**.

References

1. Lukes, R.; Kovar, J.; Kloubeck, J.; Blaha, K. *Coll. Czech. Chem. Commun.* **1960**, *25*, 483–491.
2. Enierga, G.; Hockless, D. C. R.; Perlmutter, P.; Rose, M.; Sjoberg, S.; Wong, K. *Tetrahedron Lett.* **1998**, *39*, 2813–2814.
3. Schnekenburger, J.; Breit, E. *Arch. Pharm.* **1977**, *310*, 161–168.
4. Gundermann, H.; Wolff, C.; Schnekenburger, J. *Arch. Pharm.* **1988**, *321*, 799–802.
5. Schulz, S. *Eur. J. Org. Chem.* **1998**, *1*, 13–20.
6. Hartmann, T. *Planta* **1999**, *207*, 483–495.
7. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
8. Bratt, K.; Garavelas, A.; Perlmutter, P.; Westman, G. *J. Org. Chem.* **1996**, *61*, 2109–2117.
9. Garavelas, A.; Mavropoulous, I.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.* **1995**, *36*, 463–466.
10. Mavropoulous, I.; Perlmutter, P. *Tetrahedron Lett.* **1996**, *37*, 3751–3754.
11. Massad, S. K.; Hawkins, D. L. *J. Org. Chem.* **1983**, *48*, 5180–5182.
12. Genard, S.; Patin, H. *Bull. Soc. Chim. Fr.* **1991**, *128*, 397–406.
13. Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738–3740.
14. Harding, K. E.; Tiner, T. H. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4.
15. Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40–44.
16. Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, *12*, 1415–1419.
17. Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250.
18. Shinohara, T.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **1997**, *45*, 813–819.
19. Zhang, W.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *33*, 1177–1180.

20. Knight, D. W.; Salter, R. *Tetrahedron Lett*. **1999**, *40*, 5915–5918.
21. Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801–2810.
22. Gelas, J.; Horton, D. *Heterocycles* **1981**, *16*, 1587–1601.
23. Dolt, H.; Zabel, V. *Aust. J. Chem*. **1999**, *52*, 259–270.
24. Dobler, M.; Borschberg, H. J. *Tetrahedron: Asymmetry* **1994**, *5*, 2025–2032.
25. Jackson, D. Y. *Synth. Commun*. **1988**, *18*, 337–341.