Reductive Cyclisation of Azidolactams with $Bu_3P/LiAlH_4$

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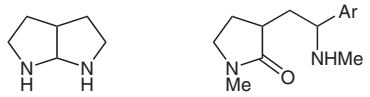
Abstract: Octahydropyrrolo[2,3-*b*]pyrroles were synthesised by treatment of azidolactams successively with tri-*n*-butylphosphine and $LiAlH_4$.

Key words: azides, lactams, aminals, bicyclic Compounds, heterocycles

The octahydropyrrolo[2,3-*b*]pyrrole ring system (**1**, Figure 1) has not been extensively studied, although a benzo-fused congener is found in a diverse range of alkaloids. Indeed, other than benzo-fused and 2,5-dioxo analogues (in which both rings are lactams), there is only one literature synthesis of compounds of this type. This route, reported by Thorsett et al. in 1978, involves reduction of amino-lactams such as **2** with diisobutylaluminium hydride in Et_2O.[1]

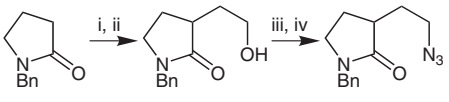


1 **2**

Figure 1

As part of a study towards the synthesis of alkaloids of the sarain class, we were interested in developing routes to simple octahydro[2,3-*b*]pyrroles in which the two nitrogen atoms were differentially protected. In this paper, we report a variation of Thorsett's chemistry, which utilises azido- rather than amino-lactams.

The starting point for these studies was *N*-benzylpyrrolidinone (**3**). Deprotonation with lithium hexamethyldisilazide followed by treatment with allyl bromide gave the α-allylated product in moderate yield (Scheme 1).[2] Ozonolysis with a $NaBH_4$ work-up gave alcohol **4**,[3] which was subjected to mesylation and azide displacement to afford alkyl azide **5**.



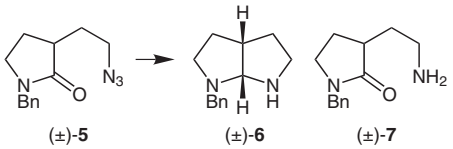
3 (±)-**4** (±)-**5**

Scheme 1 *Reagents and conditions:* (i) LHMDS, THF, –78 °C, then allyl bromide, –78 °C to r.t., 40%; (ii) O_3, MeOH, –78 °C, then $NaBH_4$, –78 °C, 84%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 97%; (iv) NaN_3, DMSO, 60 °C, 76%.

Initial attempts to convert azide **5** into the desired bicycle **6** used $LiAlH_4$ at low temperature (Scheme 2; Table 1). Under these conditions amine **7**, resulting from reduction of the azide, was the major product, and no evidence was seen for reduction of the lactam carbonyl.[4] Attempts to convert **7** to **6** with hydride reducing agents proved unsuccessful.

Conducting the reduction of **5** at room temperature resulted in formation of some of the desired bicycle **6**, together with amine **7**; however, the reaction was not clean, and several other products were apparent in the ^1H NMR spectrum of the crude reaction mixture. Similar results were obtained when either DIBAL[1] or Red-Al®[5] was used.

Successful reductive cyclisation was achieved by treating azide **5** sequentially with tri-*n*-butylphosphine and $LiAlH_4$. Under these conditions, clean cyclisation was observed, and the bicycle **6** could be isolated in 54% yield. The compound was identified as the *cis*-fused isomer by the coupling constant of 7.0 Hz between the ring junction protons.[6] No evidence was seen for formation of any of the *trans*-fused isomer.



(±)-**5** (±)-**6** (±)-**7**

Scheme 2

Bicycle **6** could be protected as a *p*-toluenesulfonamide derivative **8**, by reaction with *p*-toluenesulfonyl chloride and Et_3N, or as a formamide by heating a solution of **6** in ethyl formate (Scheme 3).

The methodology was next applied to the synthesis of a related compound bearing a vinyl substituent, which we required for our projected synthesis of the sarain core (Scheme 4). *N*-Benzylpyrrolidinone (**3**) was converted to an iminium salt by reaction with dimethyl sulfate. Treatment of this salt with the lithium alkoxide of an allylic alcohol under conditions reported by Stevenson[7] led, via sigmatropic rearrangement of **10**, to a mixture of diastere-

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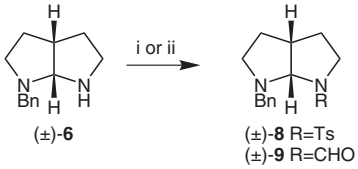
Table 1 Reductive Cyclisation of **5**

Conditions[a]	Product(s)
$LiAlH_4$, −78 °C, 10–60 min	**7**[b]
$LiAlH_4$, r.t., 10 min	**6** + **7**[c]
DIBAL, r.t., 30 min	**6** + **7**[c]
Red-Al, r.t., 30 min	**6** + **7**[c]
i) Bu_3P, r.t., 20 min ii) $LiAlH_4$, r.t., 1 h	**6** (54%)

[a] All reactions were conducted in THF solution, and worked up with potassium sodium tartrate.
[b] Major product; not isolated.
[c] Both **6** and **7** were identified as components of an intractable mixture.



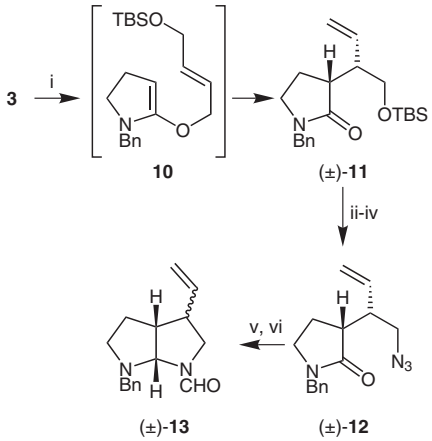
Scheme 3 *Reagents and conditions:* (i) TsCl, Et_3N, CH_2Cl_2, r.t., 64%; (ii) HCO_2Et, 60 °C, 40% from **5**.

omeric compounds from which **11** was isolated in 56% yield. The relative stereochemistry of this major diastereomer was tentatively assigned by analogy with Stevenson's work. Following removal of the silyl protecting group, the primary alcohol was converted to an azide by mesylation and nucleophilic substitution.

Cyclisation of azidolactam **12** using the conditions developed previously gave a mixture of diastereomeric products in a 2:1 ratio. Protection of the secondary amine gave an inseparable 4:1 mixture of two formamides **13**; in both compounds the ring fusion can be assigned as *cis*- on the basis of the coupling between the ring junction protons [6.6 Hz (major isomer) and 6.0 Hz (minor isomer)], and of an nOe enhancement observed in the H-3a ring junction protons on irradiation of the aminal protons. However, the relative stereochemistry of the C-3 vinyl substituent cannot be assigned.

The epimerisation observed in the cyclisation of **12** was also noted by Thorsett et al. in closely related compounds,[1] and was attributed to reversible ring-opening of the aminal system and conversion to an enamine which could be protonated from either face. Thus the epimerisation is of the ring-junction stereocenters rather than that bearing the vinyl group.

A putative mechanism for the reductive cyclisation step is outlined in Scheme 5. Tri-*n*-butylphosphine reacts with the azide moiety of **14** to generate an iminophosphorane **15**. Work-up of the reaction at this stage gives a primary amine product **16**, which suggests that further reaction of



Scheme 4 *Reagents and conditions:* (i) Me_2SO_4, 50 °C; then BuLi, $TBSOCH_2CH{=}CHCH_2OH$,[8] THF, 70 °C, 56%; (ii) TBAF, THF, 0 °C to r.t., 77%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 84%; (iv) NaN_3, DMSO, 60 °C, 74%; (v) Bu_3P, THF, r.t.; then $LiAlH_4$, r.t.; (vi) HCO_2Et, 60 °C, 25% from **12**.

15 to afford an amidine (**17**) does not occur. Instead, addition of $LiAlH_4$ leads to partial reduction of the lactam carbonyl, to give the iminium ion **18**. Cyclisation of the nucleophilic iminophosphorane nitrogen onto the iminium ion leads to bicycle **19**, and aqueous work-up cleaves the nitrogen-phosphorus bond to generate the observed product **20**, which may subsequently undergo epimerisation, and tri-*n*-butylphosphine oxide.

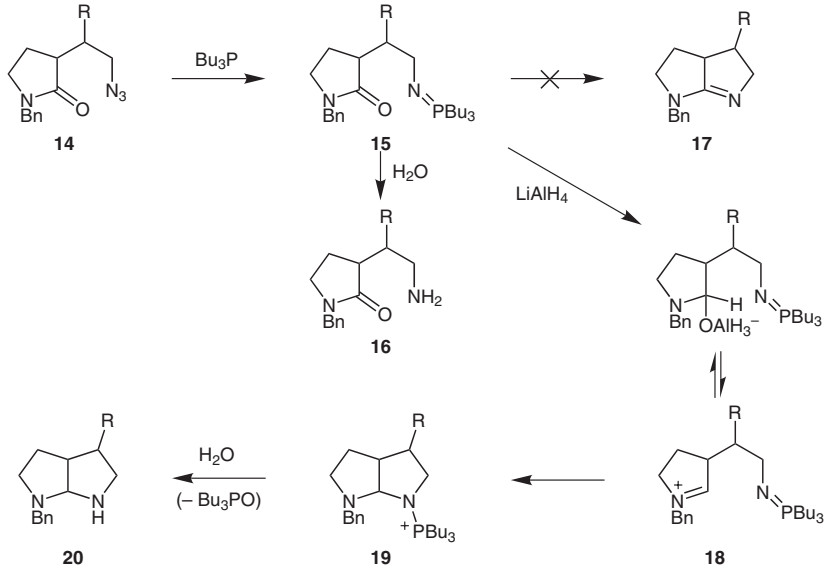
In conclusion, we have developed a novel method for cyclisation of γ-lactams bearing a 2-azidoethyl side-chain to octahydropyrrolo[2,3-*b*]pyrroles. The conversion is effected by successive treatment with tri-*n*-butylphosphine and $LiAlH_4$; use of either reagent alone, or of various other metal hydride reducing agents, is ineffective.

IR spectra were recorded as $CHCl_3$ casts on a SHIMADZU FT-IR 8700 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AMX300, AMX400 or AVANCE500 spectrometers. Flash chromatography was carried out on silica gel (40–63 μm) or neutral alumina (grade III, 50–200 μm). All reagents were obtained from commercial sources and were used without further purification. Reactions were performed under an inert atmosphere of N_2, using anhyd solvents. Alcohol **4** was prepared by known procedures.[2,3]

(3*RS*)-3-(2-Methanesulfonyloxyethyl)-1-(phenylmethyl)pyrrolidin-2-one

3-(2-Hydroxyethyl)-1-(phenylmethyl)pyrrolidin-2-one (**4**, 1.1 g, 5.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. Et_3N (1.4 mL, 10 mmol) was added dropwise, followed by methanesulfonyl chloride (0.78 mL, 10 mmol) dropwise and the resulting solution was stirred at 0 °C for 3 h. Water (20 mL) and brine (10 mL) were added followed by CH_2Cl_2 (100 mL) and the organic layer was separated. The aqueous layer was extracted further with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; EtOAc–petroleum ether, 1:1) afforded the title mesylate (1.38 g, 97%).

IR: 2924, 1678, 1433, 1352, 1173 cm^{-1}.



Scheme 5 Proposed mechanism of reductive cyclisation.

^{1}H NMR (300 MHz): δ = 1.65–1.73 (m, 1 H), 1.83–1.90 (m, 1 H), 2.24–2.33 (m, 2 H), 2.59–2.64 (m, 1 H), 3.02 (s, 3 H), 3.19–3.24 (m, 2 H), 4.40–4.50 (m, 4 H), 7.20–7.34 (m, 5 H).

^{13}C NMR (75 MHz): δ = 25.3, 31.2, 37.3, 38.5, 44.8, 46.8, 68.3, 127.6, 128.1, 128.7, 136.3, 175.3.

MS (CI): *m*/*z* (%) = 298 (20) [MH$^+$], 202 (25), 91 (25), 40 (100).

HRMS: *m*/*z* [MH$^+$] calcd for $C_{14}H_{20}NO_4S$: 298.1113; found: 298.1115.

(3*RS*)-3-(2-Azidoethyl)-1-(phenylmethyl)pyrrolidin-2-one (5)
A solution of 3-(2-methanesulfonyloxyethyl)-1-(phenylmethyl)pyrrolidin-2-one (0.57 g, 2.0 mmol) and sodium azide (0.39 g, 6.0 mmol) in dimethyl sulfoxide (5 mL) was stirred at 60 °C for 2 h and then cooled to r.t. Water (10 mL) was added followed by EtOAc (100 mL) and the organic layer was separated. The aqueous layer was extracted further with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; EtOAc–petroleum ether, 1:2) afforded azidolactam **5** (0.42 g, 86%).

IR: 2932, 2097, 1678, 1427, 1261 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.56–1.72 (m, 2 H), 2.11–2.27 (m, 2 H), 2.48–2.59 (m, 1 H), 3.16–3.20 (m, 2 H), 3.40–3.53 (m, 2 H), 4.42 (d, *J* = 14.8 Hz, 1 H), 4.45 (d, *J* = 14.8 Hz, 1 H), 7.19–7.34 (m, 5 H).

^{13}C NMR (75 MHz): δ = 25.2, 30.8, 39.5, 44.7, 46.8, 46.6, 127.6, 128.1, 128.7, 136.5, 175.6.

MS (CI): *m*/*z* (%) = 245 (50) [MH$^+$], 217 (85), 189 (50), 91 (100).

HRMS: *m*/*z* [MH$^+$] calcd for $C_{13}H_{17}N_4O$: 245.1402; found: 245.1399.

(3*RS*)-3-(2-Aminoethyl)-1-(phenylmethyl)pyrrolidin-2-one (7)
Azidolactam **5** (0.20 g, 0.82 mmol) and triphenylphosphine (0.26 g, 0.98 mmol) were dissolved in anhyd THF (2 mL) and stirred at r.t. for 30 min. Water (0.5 mL) was added dropwise and the resulting solution was stirred for 16 h at r.t. The solvent was removed in vacuo and flash chromatography (SiO_2; MeOH–CH_2Cl_2, 1:4) afforded aminolactam **7** (0.14 g, 76%).

IR: 3358, 2926, 2870, 1674, 1583, 1495, 1437, 1304 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.42 (br s, 2 H), 1.48–1.70 (m, 2 H), 1.94–2.04 (m, 1 H), 2.11–2.23 (m, 1 H), 2.48–2.58 (m, 1 H), 2.73–2.95 (m, 2 H), 3.10–3.22 (m, 2 H), 4.42 (d, *J* = 14.7 Hz, 1 H), 4.45 (d, *J* = 14.7 Hz, 1 H), 7.18–7.33 (m, 5 H).

^{13}C NMR (75 MHz): δ = 25.1, 35.4, 39.8, 40.2, 44.9, 46.8, 127.5, 128.1, 128.7, 136.6, 176.6.

MS (CI): *m*/*z* (%) = 219 (100) [MH$^+$], 202 (75), 175 (85), 91 (40).

HRMS: *m*/*z* [MH$^+$] calcd for $C_{13}H_{19}N_2O$: 219.1497; found: 219.1494.

(3a*RS*,6a*SR*)-*cis*-1-(Phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole (6)
Tri-*n*-butylphosphine (1.0 mL, 4.1 mmol) was added to a solution of azidolactam **5** (0.5 g, 0.2 mmol) in anhyd THF (25 mL) and the mixture was stirred at r.t. for 20 min. $LiAlH_4$ (1 M in THF, 1.2 mL, 1.2 mmol) was added dropwise and the resulting solution was stirred at r.t. for 1 h. Potassium sodium tartrate tetrahydrate (1 M in water, 20 mL) was added dropwise and the mixture was stirred at r.t. for 30 min. The mixture was then saturated with solid NaCl and extracted with EtOAc (2 × 400 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (Al_2O_3; petroleum ether then EtOAc–petroleum ether, 1:5) afforded bicycle **6** (0.22 g, 54%).

IR: 2956, 2792, 1484, 1452, 1101 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.38–1.45 (m, 1 H), 1.47–1.53 (m, 1 H), 1.68–1.79 (m, 2 H), 1.90–1.98 (m, 1 H), 2.30–2.36 (m, 1 H), 2.58–2.65 (m, 1 H), 2.74–2.79 (m, 1 H), 2.81–2.93 (m, 2 H), 3.64 (d, *J* = 13.0 Hz, 1 H), 3.84 (d, *J* = 13.0 Hz, 1 H), 4.10 (d, *J* = 7.0 Hz, 1 H), 7.19–7.34 (m, 5 H).

^{13}C NMR (75 MHz): δ = 30.7, 33.8, 41.6, 45.1, 52.0, 57.2, 83.2, 126.8, 128.2, 128.9, 139.6.

MS (CI): *m*/*z* (%) = 203 (100) [MH$^+$], 159 (30), 91 (25).

HRMS: *m*/*z* calcd [MH$^+$] for $C_{13}H_{19}N_2$: 203.1548; found: 203.1545.

(3a*RS*,6a*SR*)-*cis*-1-(4-Methylphenylsulfonyl)-6-(phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole (8)
Bicycle **6** (0.27 g, 1.3 mmol) was dissolved in CH_2Cl_2 (10 mL). Et_3N (0.4 mL, 2.9 mmol) was added dropwise followed by 4-methylphenylsulfonyl chloride (0.56 g, 2.9 mmol) and the resulting solution was stirred at r.t. for 1 h. Water (10 mL) was added, followed by CH_2Cl_2 (100 mL) and the organic layer was separated. The organic extract was dried ($MgSO_4$) and concentrated in vacuo. Flash

chromatography (SiO_2; MeOH–CH_2Cl_2, 1:49) afforded sulfonamide **8** (0.30 g, 64%).

IR: 3028, 2963, 1452, 1344, 1303, 1217 cm^{-1}.

^1H NMR (400 MHz): δ = 1.19–1.29 (m, 1 H), 1.36–1.45 (m, 2 H), 1.86–1.95 (m, 1 H), 2.40 (s, 3 H), 2.26–2.40 (m, 1 H), 2.56–2.65 (m, 2 H), 3.28 (td, *J* = 12.2, 5.6 Hz, 1 H), 3.59 (dd, *J* = 12.2, 7.5 Hz, 1 H), 3.98 (d, *J* = 13.8 Hz, 1 H), 4.03 (d, *J* = 13.8 Hz, 1 H), 5.03 (d, *J* = 6.8 Hz, 1 H), 7.19–7.32 (m, 7 H), 7.73 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz): δ = 21.5, 29.9, 32.3, 42.0, 48.0, 50.5, 55.5, 84.7, 126.7, 127.1, 128.1, 128.8, 129.7, 137.4, 139.3, 143.1.

MS (CI): *m*/*z* (%) = 357 (100) [MH^+], 201 (85), 91 (50).

HRMS: *m*/*z* [MH^+] calcd for $C_{20}H_{25}N_2O_2S$: 357.1637; found: 357.1633.

(3a*RS*,6a*SR*)-*cis*-6-(Phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole-1-carboxaldehyde (9)

Azidolactam **5** (0.5 g, 2.1 mmol) was converted to bicycle **6** as described above. The crude mixture was dissolved in ethyl formate (4 mL, 50 mmol) and the resulting mixture was heated to reflux for 6 h. The solution was cooled and concentrated in vacuo. Flash chromatography (Al_2O_3; EtOAc–petroleum ether, 1:2) afforded formamide **9** (0.18 g, 40% from **5**).

IR: 3445, 2939, 2872, 1674, 1385 cm^{-1}.

^1H NMR (500 MHz, major rotamer): δ = 1.54–1.61 (m, 1 H), 1.71–1.76 (m, 1 H), 1.85–1.91 (m, 1 H), 2.08–2.12 (m, 1 H), 2.58–2.63 (m, 1 H), 2.72 (dt, *J* = 9.3, 6.6 Hz, 1 H), 2.90–2.96 (m, 1 H), 3.10 (td, *J* = 11.5, 6.7 Hz, 1 H), 3.68 (d, *J* = 13.4 Hz, 1 H), 3.87 (d, *J* = 13.4 Hz, 1 H), 3.99–4.04 (m, 1 H), 4.75 (d, *J* = 6.7 Hz, 1 H), 7.20–7.35 (m, 5 H), 8.06 (s, 1 H).

^{13}C NMR (125 MHz): δ = 30.5, 31.5, 41.2, 42.4, 51.7, 55.5, 80.9, 127.2, 128.4, 128.9, 138.3, 161.2.

MS (EI): *m*/*z* (%) = 230 (20) [MH^+], 172 (22), 158 (50), 91 (100).

HRMS: calcd *m*/*z* [MH^+] for $C_{14}H_{19}N_2O$: 230.1414; found: 230.1416.

(3*RS*,3′*SR*)-3-(4-*tert*-Butyldimethylsilyloxybut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one (11)[9]

Dimethyl sulfate (0.27 mL, 2.85 mmol) was added dropwise to lactam **3** (0.50 g, 2.85 mmol) and the mixture was stirred at 50 °C for 3 h. A second equivalent of dimethyl sulfate (0.27 mL, 2.85 mmol) was added dropwise and stirring at 50 °C was continued for 1 h.

In a separate flask, *n*-BuLi (1.6 M in hexanes, 4.9 mL, 6.3 mmol) was added dropwise to a solution of (*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol[8] (1.15 g, 5.71 mmol) in anhyd THF (20 mL) and the mixture was stirred at r.t. for 1 h. The resulting THF alkoxide solution was added in one portion to the lactam–dimethyl sulfate reaction mixture, and the resulting solution was stirred at 70 °C for 3 h. The solution was cooled and concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (50 mL) and washed with sat. aq $NaHCO_3$ (5 mL) and brine (5 mL). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; EtOAc–petroleum ether, 1:9) afforded lactam **11** (571 mg, 56%) as a single diastereoisomer, which was tentatively assigned as (3*RS*,3′*SR*).

IR: 2960, 2880, 1666, 1435, 1194 cm^{-1}.

^1H NMR (400 MHz): δ = 0.04 (s, 6 H), 0.86 (s, 9 H), 1.82–1.92 (m, 1 H), 2.00–2.08 (m, 1 H), 2.48–2.54 (m, 1 H), 2.79 (td, *J* = 8.9, 3.5 Hz, 1 H), 3.08–3.17 (m, 2 H), 3.73 (dd, *J* = 10.0, 6.3 Hz, 1 H), 3.92 (dd, *J* = 9.9, 7.0 Hz, 1 H), 4.38 (d, *J* = 14.7 Hz, 1 H), 4.43 (d, *J* = 14.7 Hz, 1 H), 5.08–5.14 (m, 2 H), 5.70–5.79 (m, 1 H), 7.19–7.31 (m, 5 H).

^{13}C NMR (75 MHz): δ = 18.3, 22.2, 25.9, 42.0, 45.0, 46.6, 48.3, 64.2, 117.7, 127.4, 128.2, 128.6, 136.7, 136.9, 175.1.

MS (CI): *m*/*z* (%) = 360 (100) [MH^+], 302 (55), 228 (20), 91 (20).

HRMS: *m*/*z* [MH^+] calcd for $C_{21}H_{34}NO_2Si$: 360.2360; found: 360.2359.

(3*RS*,3′*SR*)-3-(4-Hydroxybut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one[9]

To a stirred solution of lactam **11** (302 mg, 0.84 mmol) in THF (1.5 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (1 M in THF, 1.0 mL, 1.0 mmol). The resulting solution was warmed to r.t. and stirred for 2 h, then concentrated in vacuo, diluted with EtOAc (20 mL) and washed with sat. aq $NaHCO_3$ (4 mL). The organic extract was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography [SiO_2; EtOAc–petroleum ether (40–60) 1:1] afforded the title alcohol (154 mg, 75%).

IR: 3403, 2928, 2856, 1686, 1429, 1258, 1094 cm^{-1}.

^1H NMR (400 MHz): δ = 1.81–1.90 (m, 1 H), 2.02–2.13 (m, 1 H), 2.43–2.48 (m, 1 H), 2.85 (td, *J* = 9.0, 3.0 Hz, 1 H), 3.17–3.24 (m, 2 H), 3.78 (dd, *J* = 11.1, 5.4 Hz, 1 H), 3.88 (dd, *J* = 11.1, 4.1 Hz, 1 H), 4.38 (d, *J* = 14.6 Hz, 1 H), 4.47 (d, *J* = 14.6 Hz, 1 H), 5.13–5.20 (m, 2 H), 5.84 (dt, *J* = 17.0, 10.1 Hz, 1 H), 7.19–7.34 (m, 5 H).

^{13}C NMR (75 MHz): δ = 22.5, 45.3, 45.6, 47.0, 48.0, 65.9, 118.9, 127.7, 128.1, 128.7, 135.3, 136.1, 175.8.

MS (electrospray): *m*/*z* (%) = 268 (100) [MNa^+].

HRMS: *m*/*z* [MNa^+] calcd for $C_{15}H_{19}NO_2Na$: 268.1308; found: 268.1306.

(3*RS*,3′*SR*)-3-(4-Methanesulfonyloxybut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one[9]

To a stirred solution of (3*RS*,3′*SR*)-3-(4-hydroxybut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one (0.15 g, 0.59 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added dropwise Et_3N (0.10 mL, 1.2 mmol) and methanesulfonyl chloride (0.17 mL, 1.2 mmol), and the resulting solution was stirred at 0 °C for 3 h. Water (3 mL) and brine (3 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (50 mL + 2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; EtOAc–petroleum ether, 1:2) afforded the title mesylate (0.16 g, 84%).

IR: 2924, 1676, 1439, 1354, 1192, 1177 cm^{-1}.

^1H NMR (400 MHz): δ = 1.76–1.86 (m, 1 H), 2.05–2.13 (m, 1 H), 2.73–2.86 (m, 2 H), 3.03 (s, 3 H), 3.13–3.21 (m, 2 H), 4.35–4.46 (m, 3 H), 4.65 (dd, *J* = 9.8, 8.1 Hz, 1 H), 5.23–5.28 (m, 2 H), 5.63 (dt, *J* = 17.6, 9.4 Hz, 1 H), 7.18–7.33 (m, 5 H).

^{13}C NMR (75 MHz): δ = 21.9, 37.2, 41.3, 45.1, 45.5, 46.7, 70.6, 120.7, 127.6, 128.1, 128.7, 133.3, 136.3, 174.1.

MS (electrospray): *m*/*z* (%) = 346 (55) [MNa^+], 268 (100).

HRMS: calcd *m*/*z* [MNa^+] for $C_{16}H_{21}NO_4SNa$: 346.1084; found: 346.1083.

(3*RS*,3′*SR*)-3-(4-Azidobut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one (12)[9]

A solution of (3*RS*,3′*SR*)-3-(4-methanesulfonyloxybut-1-en-3-yl)-1-(phenylmethyl)pyrrolidin-2-one (0.15 g, 0.47 mmol) and sodium azide (91 mg, 1.4 mmol) in dimethyl sulfoxide (1.5 mL) was stirred at 60 °C for 2 h. The mixture was cooled, water (5 mL) was added and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; EtOAc–petroleum ether, 1:3) afforded azidolactam **12** (94 mg, 74%).

IR: 2874, 2097, 1682, 1439, 1263, 1194 cm^{-1}.

^1H NMR (400 MHz): δ = 1.67–1.76 (m, 1 H), 1.95–2.02 (m, 1 H), 2.46–2.53 (m, 1 H), 2.67 (td, *J* = 9.1, 3.3 Hz, 1 H), 3.04–3.11 (m, 2

H), 3.52 (dd, *J* = 12.2, 7.9 Hz, 1 H), 3.61 (dd, *J* = 12.2, 7.0 Hz, 1 H), 4.29 (d, *J* = 14.6 Hz, 1 H), 4.39 (d, *J* = 14.6 Hz, 1 H), 5.12–5.17 (m, 2 H), 5.62 (dt, *J* = 17.1, 9.3 Hz, 1 H), 7.11–7.26 (m, 5 H).

^{13}C NMR (75 MHz): δ = 22.0, 42.7, 45.0, 45.8, 46.7, 53.0, 119.4, 127.6, 128.2, 128.7, 135.6, 136.4, 174.2.

MS (FAB): *m*/*z* (%) = 271 (100) [MH$^+$].

HRMS: *m*/*z* [MH$^+$] calcd for $C_{15}H_{19}N_4O$: 271.1559; found: 271.1568.

(3*RS*,3a*RS*,6a*RS*)-*cis*- and (3*RS*,3a*SR*,6a*SR*)-*cis*-4-Ethenyl-1-(phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole

Tri-*n*-butylphosphine (0.09 mL, 0.37 mmol) was added dropwise to a stirred solution of azidolactam **12** (83 mg, 0.31 mmol) in anhyd THF and the resulting mixture was stirred for 20 min. $LiAlH_4$ (1 M in THF, 0.18 mL, 0.18 mmol) was added dropwise and the solution was stirred at r.t. for 1 h. Potassium sodium tartrate tetrahydrate (1 M in water, 3 mL) was added and the resulting mixture was stirred at r.t. for 30 min. The mixture was then saturated with solid NaCl and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo to afford the title compound, which was used without further purification.

A clean sample of the title compound (as a 2:1 ratio of diastereoisomers) was obtained by preparative TLC (SiO_2; CH_2Cl_2–MeOH, 9:1).

IR: 3368, 3030, 2958, 1674, 1465, 1456, 1147 cm^{-1}.

^{1}H NMR (400 MHz, major diastereomer): δ = 1.42–1.46 (m, 1 H), 1.86–1.98 (m, 2 H), 2.34–2.45 (m, 2 H), 2.62–2.77 (m, 3 H), 3.07 (dd, *J* = 10.2, 5.7 Hz, 1 H), 3.62 (d, *J* = 13.1 Hz, 1 H), 3.81 (d, *J* = 13.1 Hz, 1 H), 4.21 (d, *J* = 6.3 Hz, 1 H), 4.87–5.02 (m, 2 H), 5.60–5.77 (m, 1 H), 7.15–7.30 (m, 5 H).

^{13}C NMR (100 MHz): δ = 29.8, 45.8, 47.8, 50.5, 51.1, 56.0, 83.8, 113.9, 126.9, 128.2, 128.9, 139.4, 140.5.

MS (electrospray): *m*/*z* (%) = 229 (100) [MH$^+$], 228 (12) [M$^+$], 217 (46), 203 (25).

HRMS: *m*/*z* [MH$^+$] calcd for $C_{15}H_{21}N_2$: 229.1699; found: 229.1696.

(3*RS*,3a*RS*,6a*SR*)-*cis*- and (3*RS*,3a*SR*,6a*RS*)-*cis*-3-Ethenyl-6-(phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole-1-carboxaldehyde (13)

4-Ethenyl-1-(phenylmethyl)octahydropyrrolo[2,3-*b*]pyrrole (0.96 g, 4.2 mmol) was dissolved in ethyl formate (3.4 mL, 42 mmol) and the resulting mixture was heated to reflux for 2 h. The solution was concentrated in vacuo and flash chromatography (Al_2O_3; EtOAc–petroleum ether, 1:5) afforded formamides **13** (94 mg, 25%) as a 4:1 mixture of diastereomers.

IR : 3029, 2960, 1679, 1465, 1266, 1149 cm^{-1}.

^{1}H NMR (500 MHz, major rotamer of major diastereomer): δ = 1.58–1.66 (m, 1 H), 2.02–2.12 (m, 1 H), 2.43–2.49 (m, 1 H), 2.57–2.61 (m, 1 H), 2.65–2.71 (m, 1 H), 2.91–2.99 (m, 1 H), 3.57–3.61 (m, 1 H), 3.72 (d, *J* = 13.4 Hz, 1 H), 3.85 (d, *J* = 13.4 Hz, 1 H), 4.05–4.08 (m, 1 H), 4.83 (d, *J* = 6.6 Hz, 1 H), 5.06–5.16 (m, 2 H), 5.73–5.83 (m, 1 H), 7.22–7.33 (m, 5 H), 8.00 (s, 1 H).

^{13}C NMR (125 MHz): δ = 28.8, 44.6, 45.4, 47.6, 48.9, 55.8, 81.2, 117.4, 128.1, 128.4, 128.9, 138.1, 134.9, 161.5.

MS (CI): *m*/*z* (%) = 257 (100) [MH$^+$], 247 (35), 219 (70), 158 (71).

HRMS: *m*/*z* [MH$^+$] calcd for $C_{16}H_{21}N_2O$: 257.1654; found: 257.1651.

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References

(1) Thorsett, E. D.; Harris, E. E.; Patchett, A. A. *J. Org. Chem.* **1978**, *43*, 4276.
(2) Daoust, B.; Lessard, J. *Tetrahedron* **1999**, *55*, 3495.
(3) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.
(4) Amine **7** was identified in the crude reaction mixture by comparison with an authentic sample, generated by reduction of **5** with Ph_3P/H_2O; see: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.
(5) Red-Al® has previously been used for the reductive cyclisation of azido-oxindoles: Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465.
(6) Thorsett et al. (ref.[1]) report a coupling constant of 7 Hz between the ring junction protons in a *cis*-fused octahydro[2,3-*b*]pyrrole.
(7) Coates, B.; Montgomery, D. J.; Stevenson, P. J. *Tetrahedron* **1994**, *50*, 4025.
(8) Abdel-Baky, S.; Giese, R. W. *J. Org. Chem.* **1986**, *51*, 3390.
(9) The relative stereochemistry of this compound is assigned by analogy to reactions in ref.[7]