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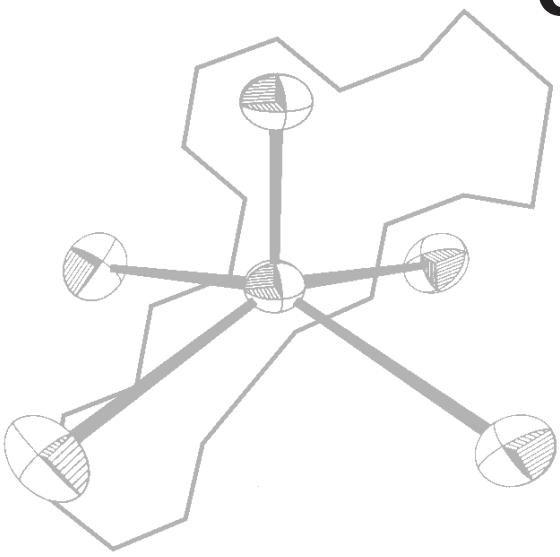

Volume 52, 1999

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Aust. J. Chem., 1999, **52**, 1131–1138

A Hydroformylation Route to Diazabicycloalkanes and Oxazabicycloalkanes Containing Medium and Large Rings[1]

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Diazabicycloalkanes and oxazabicycloalkanes containing medium and large rings can be prepared by rhodium-catalysed reactions of *N*-alkenylpropane-1,3-diamines and 2-(alkenylamino)ethanols with H_2/CO in excellent yields without the need for high dilution. Selective ring opening of these compounds can lead to large heterocycles.

Introduction

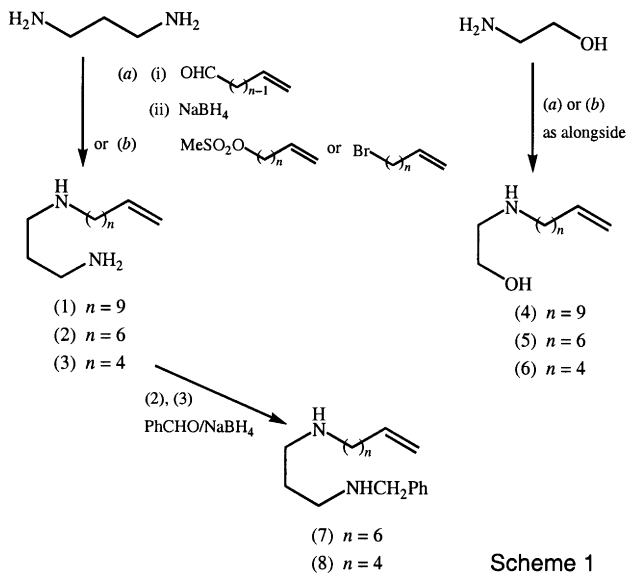
Medium and large heterocycles are of interest in medicinal chemistry.[2] We have previously attempted to synthesize such compounds by hydroformylation reactions of some *o*-alkenyloxybenzylamines.[3] It was argued that an initially formed amino aldehyde, still coordinated to the rhodium catalyst, would cyclize without the need for high dilution conditions. In the event, only polymeric material was obtained and it was realized that the intermediate cyclic imines, if formed, were prone to polymerization. This problem has been surmounted[4] by the use of secondary amines which form more readily hydrogenated enamines or iminium salts[5] and ligands such as BIPHEPHOS[6] which promote hydrogenation. An alternative method of preventing polymerization of the initially formed unsaturated nitrogen heterocycle is to react it with a suitable nucleophile. If this nucleophilic substitution is intramolecular then the formation of heterobicyclic compounds (heterobicycles) eventuates. We have established this methodology for the formation of 5,5 and 5,6-bicyclic systems[7] and it appeared possible that the same technique could be applied to the formation of larger ring systems. Problems of chemoselectivity were encountered in the preparation of 5,5 and 5,6 bicyclic systems due to intramolecular carbonylation reactions (leading to lactams) competing with hydroformylation. This problem was overcome by the use of BIPHEPHOS as ligand.[7] In addition, it appears that intramolecular carbonylation is no longer a problem when the formation of larger rings is involved.[4]

In this paper the application of the above methodology to the synthesis of heterobicycles containing a medium or large ring is described.

Results and Discussion

Preparation of N*-Alkenylpropane-1,3-diamines (1)–(3) and 2-(Alkenylamino)ethanols (4)–(6)*

In general, the title compounds were prepared by reductive amination[8] of the appropriate unsaturated aldehyde with either propane-1,3-diamine or 2-aminoethanol and subsequent borohydride reduction or by reaction of the appropriate unsaturated bromide or mesylate with a large excess of propane-1,3-diamine or 2-aminoethanol (Scheme 1). *N*-Benzyl-substituted diamines (7) and (8) were prepared by reductive alkylation of the diamines (2) and (3) with PhCHO/$NaBH_4$.



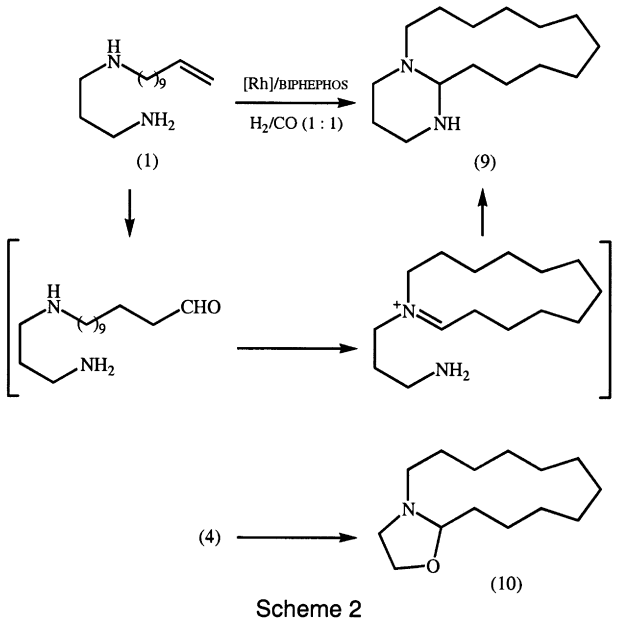
Scheme 1

Manuscript received 6 August 1999 10.1071/CH99097 0004-9425/99/121131

Preparation of Heterobicycles Containing 13-Membered Rings

Reaction of *N*-undec-10-enylpropane-1,3-diamine (1) using BIPHEPHOS as ligand at 80° with H_2/CO, 1 : 1 (initial pressure 400 psi, 2.76 MPa), and a substrate/ligand/catalyst ratio of 200 : 4 : 1 gave the diazabicycloheptadecane (9) in 80% yield (see Table, entry 1). The proposed reaction sequence is shown in Scheme 2 though the cyclic iminium ion could rearrange to the corresponding enamine which is not shown.

Reaction of the ethanol derivative (4) gave the analogous oxazabicyclohexadecane (10) again containing a 13-membered ring (entry 2). The high regioselectivity for products arising from terminal hydroformylation, associated with the use of BIPHEPHOS as ligand,[6,7,9] was maintained. The initial products from these reactions appeared to be pure by ^{1}H and ^{13}C n.m.r. spectroscopy and detailed 2D-correlations were used to establish the structures unambiguously. However, analytically pure samples could not be obtained as distillation, chromatography (on a range of adsorbents) and isolation as salts failed. The lability of the N–C–N bond in aminals and of the corresponding N–C–O bond in hemiaminals is well known.[10]



Scheme 2

Heterobicycles Containing 10-Membered Rings

Reaction of *N*-oct-7-enylpropane-1,3-diamine (2) using BIPHEPHOS as ligand gave the bicycle (11) in poor yield (28%) even when the reaction temperature was reduced to 40° (entry 3). A reaction at 80° only gave polymeric material. The difficulty of forming 10-membered carbocyclic rings is well established but the ease of formation of heterocycles is dependent on the pattern of heteroatom substitution.[11] Reaction of the related secondary amine (7) using PPh_3 as ligand gave an excellent yield of bicyclic material, predominantly (12) but containing *c.* 10% of material originating from branched chain aldehyde (entry 4). Reactions using BIPHEPHOS as ligand at either 40 or 80° gave low yields of cyclic product and significant amounts of hydrogenated material, tentatively identified as hydrogenated starting material and monocyclic material arising from hydrogenation of the intermediate iminium species. Reaction using a H_2/CO gas ratio of 1:5 overcame the problem of this hydrogenation[12] and an excellent yield of (12) was obtained (entry 5).

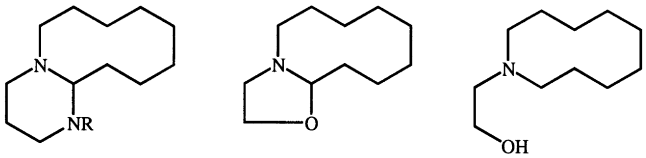


Table 1. Rhodium-catalysed reactions of *N*-alkenylpropane-1,3-diamines and *N*-alkenylaminoethanols with H_2/CO[A]

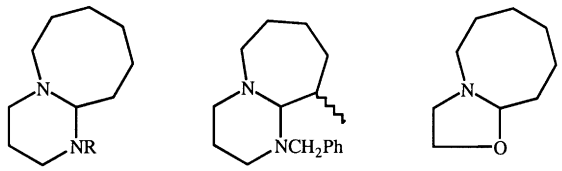
Entry	Reactant amine	Temp (°C)	Ligand	Ratio H_2/CO	Bicyclo product	Ring sizes	Yield[B] (%)
1	(1)	80	BIPHEPHOS	1 : 1	(9)	6/13	80
2	(4)	80	BIPHEPHOS	1 : 1	(10)	5/13	80
3	(2)	40	BIPHEPHOS	1 : 1	(11)	6/10	28
4	(7)	80	PPh_3	1 : 1	(12)	6/10	95[C]
5	(7)	80	BIPHEPHOS	1 : 5	(12)	6/10	95
6	(5)	80	PPh_3	1 : 1	(13)	5/10	93[C]
7	(5)	80	BIPHEPHOS	1 : 5	(13)	5/10	93
8	(3)	50	BIPHEPHOS	1 : 1	(15)	6/8	74
9	(8)	80	BIPHEPHOS	1 : 5	(16)	6/8	95
10	(8)	80	PPh_3	1 : 1	(16)	6/8	14[D]
11	(6)	80	PPh_3	1 : 1	(18)	5/8	92[C]
12	(6)	80	BIPHEPHOS	1 : 5	(18)	5/8	92

[A] Reaction conditions: substrate 0.5–1 mmol with substrate/$[Rh(OAc)_2]_2$/ligand 200 : 1 : 4 in benzene (5–10 ml) for 20 h with an initial gas pressure, H_2+CO, 2.76 MPa (400 psi).
[B] Isolated yields; products from reactions with BIPHEPHOS as ligand contained >95% of linear derived material.
[C] Containing *c.* 10% branch-chain derived product.
[D] The 6,7 bicyclo compound (17) arising from initial internal hydroformylation was the major product (38%).

The related alkenylaminoethanol (5) also gave excellent yields (*c.* 93%) of the bicyclic compound (13) by using either PPh_3 and H_2/CO, 1 : 1, or BIPHEPHOS and H_2/CO, 1 : 5 (entries 6 and 7). The former reaction contained *c.* 10% of material arising from branched chain aldehyde whereas the BIPHEPHOS reaction was regiospecific. A reaction using BIPHEPHOS as ligand with H_2/CO, 1 : 1, at 40° again showed a preference for hydrogenation leading to the monocyclic alcohol (14) (75% yield).

Heterocycles Containing Eight-Membered Rings

Reaction of *N*-hex-5-enylpropane-1,3-diamine (3) using BIPHEPHOS as ligand with H_2/CO, 1 : 1, at 80° gave polymeric material but a reaction at 50° gave the diazabicyclododecane (15) in good yield (74%, entry 8). Reaction of the *N*-benzyl compound (8) with H_2/CO, 1 : 1, and BIPHEPHOS as ligand at either 40 or 80° gave a mixture of products but use of a H_2/CO, 1:5, gas mixture gave the bicyclic compound (16) in excellent yield (95%, entry 9). A reaction using PPh_3 as ligand and H_2/CO, 1 : 1, surprisingly gave a mixture of bicyclic compounds in which the 6-methyl-1,8-diazabicycloundecane (17) predominated (entry 10). This result was obtained from repeat reactions and could be explained by preferential chelation of a nitrogen atom in a seven- rather than an eight-membered ring in the transition state leading to the initial hydroformylation product.



(15) R = H
(16) R = CH_2Ph

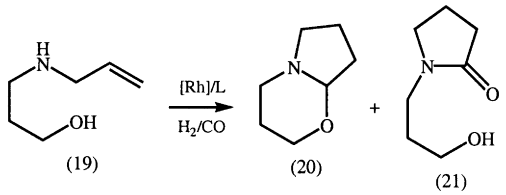
(17)

(18)

Reaction of the aminoethanol (6) with PPh_3 under these conditions gave the oxazabicycloundecane (18) with only *c.* 10% branched material (entry 11). The major changes in regioselectivity of the initial alkene hydroformylation that occur on changing groups remote from the reaction site are difficult to understand. Reaction using BIPHEPHOS and H_2/CO, 1 : 5, gave only (18) in high yield (entry 12). A reaction using BIPHEPHOS but with a H_2/CO gas ratio of 1 : 1 gave a mixture from which monocyclic alcohols arising from hydrogenation of the iminium intermediates were isolated.

Reaction of 3-(Prop-2-enylamino)propan-1-ol (19)

A variation of the above trapping procedure was carried out using the propenylaminopropanol (19). Reaction with H_2/CO, 1 : 1, using PPh_3 as ligand gave a mixture of the oxazabicyclononane (20) and the lactam (21) (Scheme 3). The loss of chemoselectivity parallels that observed previously when the possibility of forming five- or six-membered ring lactams existed.[7] The use of BIPHEPHOS as ligand appeared to suppress lactam formation but other products were formed and pure (20) was obtained in 33% yield.



(19) (20) (21)

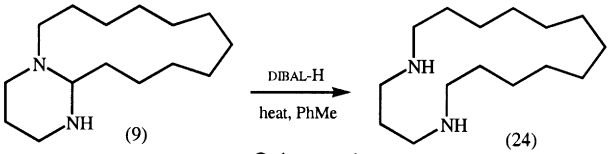
Scheme 3

Ring Opening Reactions

The selective cleavage of the bridging bond in some heterobicycles has been reported.[13–15] Cleavage of the bridging bond in the heterobicycles described in this paper to give large ring compounds would further increase their usefulness. Selective ring opening reactions were thus attempted with the bicyclic compound (9) containing a 13-membered ring, the oxazabicyclononane (20) and the related (6,6) compounds (22) and (23).

Cleavage with DIBAL-*H*

Reactions of compound (9) with DIBAL-H under conditions similar to those described by Yamamoto[13] gave *c.* 60% of 1,5-diazacycloheptadecane comparable with the yield of cyclic amine obtained from 1,5-diazabicyclo[4.4.0]decane (22) by ourselves and by Alder[14] (Scheme 4).



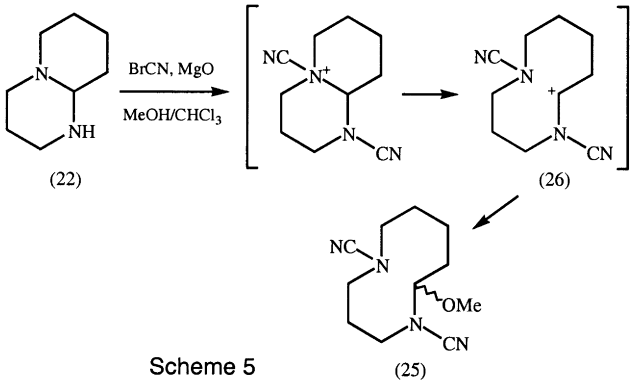
(9) (24)

Scheme 4

Cleavage of the oxazabicyclononane (20) with DIBAL-H was less successful leading to cleavage of the C–O bond and formation of 3-(pyrrolidin-1-yl)propan-1-ol.

Cleavage with Cyanogen Bromide

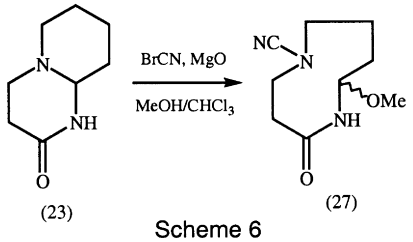
Use of BrCN to cleave benzylic C–N bonds in annelated tetrahydroisoquinoline derivatives has been extensively developed as a route to medium ring heterocycles.[16] Application of these reaction conditions (BrCN with MgO in $MeOH/CHCl_3$) to the bicyclic aminal (22) gave the 10-membered heterocycle (25) in excellent yield (84%) (Scheme 5). Presumably the selectivity arises from stabilization of the carbocation (26) by the adjacent nitrogen atom.



(22) (26) (25)

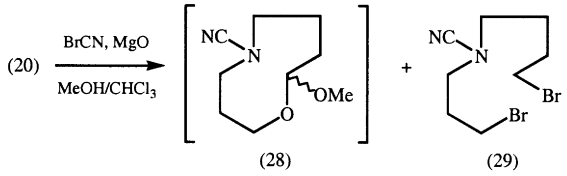
Scheme 5

Reaction of the related lactam (23) under the same conditions led to formation of the nine-membered amino lactam (27) in 47% yield (Scheme 6).



Scheme 6

However, in contrast, reaction of the oxazabicyclononane (20) under these conditions gave a product whose n.m.r. spectra suggested that the oxazanonane (28) and the cyanamide (29) were both present. Only the cyanamide (29) was isolated (26%) after chromatography on silica (Scheme 7); it was presumed that the oxazanonane (28) hydrolysed on the column.



Scheme 7

Experimental

General conditions were as described previously.[17] All n.m.r. spectra were recorded for solutions in $CDCl_3$ unless otherwise stated.

Microanalyses were carried out by the Chemistry Department, University of Otago, Dunedin, New Zealand. Attempts were made to obtain analytically pure samples of the amino starting materials and products by chromatography and/or distillation. Generally, combustion analysis gave errors >±0.4% even though ^{1}H and ^{13}C n.m.r. spectra suggested analytically pure material.

Materials

BIPHEPHOS: *6,6′-{[3,3′-Bis(1,1-dimethylethyl)-5,5′-dimethoxy-1,1′-biphenyl]-2,2′-diyl}bis(oxy)bis(dibenzo*[d,f]*[1,3,2]dioxaphosphepin)*

BIPHEPHOS was prepared according to a literature procedure.[6]

N-*(Undec-10-enyl)propane-1,3-diamine (1)*

Undec-10-enal[18] (1.00 g, 5.94 mmol) in MeOH (5 ml) was added dropwise to a solution of propane-1,3-diamine (2.20 g, 29.7 mmol) in MeOH (10 ml) and the mixture allowed to stir at ambient temperature for 2 days. The reaction mixture was cooled to 0° and $NaBH_4$ (0.45 g, 11.9 mmol) was added portionwise. The mixture was allowed to warm to ambient temperature, stirred for a further 2 h, again cooled to 0°, followed by the addition of conc. HCl (to pH 2). The mixture was diluted with water (30 ml), made basic (pH 11–12) by the addition of NaOH pellets and extracted with ether (2×50 ml). The combined organic extracts were washed with water (2×50 ml), dried (Na_2SO_4), filtered and concentrated to give N-*(undec-10-enyl)propane-1,3-diamine* (1) as a clear oil (0.83 g, 62%). Kugelrohr distillation b.p.(oven) 90°/0.1 mm (Found: *m/z* 227.2477. $(C_{14}H_{30}N_2+H)^+$ requires *m/z* 227.2487). ν_{max} (neat) 3332s, 3261s, 3073s, 2916s, 2876s, 2853s, 2812s, 2774m, 1639m, 1482m, 1471s, 1374m, 1134m, 1056m, 992m, 913s, 720m, 675m, 637m cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.28–1.51, m, 14H, H 2′, 3′, 4′, 5′, 6′, 7′, 8′; 1.64, p, 2H, *J* 7.0 Hz, H 2; 1.90, br s, 3H, NH_2, NH; 1.99–2.08, m, 2H, H 9′; 2.58, t, 2H, *J* 7.4 Hz, 2.66, t, 2H, *J* 7.0 Hz, and 2.76, t, 2H, *J* 6.9 Hz, H 1, 3, 1′; 4.89–5.04, m, 2H, H 11′; 5.81, ddt, 1H, *J* 16.9, 10.1, 6.6 Hz, H 10′. ^{13}C n.m.r. δ (50 MHz) 27.30, 28.83, 29.02, 29.35, 29.45, 29.97 (C 2′, 3′, 4′, 5′, 6′, 7′, 8′); 33.59, 33.71 (C 2′, 9′); 40.36 (C 3); 47.73 (C 1′); 50.06 (C 1); 114.02 (C 11′); 139.13 (C 10′). Mass spectrum (ESI$^+$): *m/z* 226.9 $(M+H)^+$.

N-*(Oct-7-enyl)propane-1,3-diamine (2)*

8-Bromooct-1-ene (1.50 g, 7.85 mmol) was added dropwise to propane-1,3-diamine (5.82 g, 78.5 mmol) at 60° and the mixture was stirred overnight at 60°. After cooling to ambient temperature, CH_2Cl_2 (100 ml) was added and washed with water (4×50ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give N-*(oct-7-enyl)propane-1,3-diamine* (2) as a clear oil (1.10 g, 76%) (Found: *m/z* 185.2014. $(C_{11}H_{24}N_2+H)^+$ requires *m/z* 185.2018). ν_{max} (neat) 3360s, 3077s, 2930s, 2854s, 1640m, 1574s, 1466s, 1318s, 1123m, 994m, 909s cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.33–1.51, m, 8H, H 2′, 3′, 4′, 5′; 1.64, p, 2H, *J* 7.0 Hz, H 2; 1.86, br s, 3H, NH, NH_2; 1.99–2.09, m, 2H, H 6′; 2.58, t, 2H, *J* 7.4 Hz, 2.65, t, 2H, *J* 7.0 Hz, and 2.75, t, 2H, *J* 6.9 Hz, H 1, 3, 1′; 4.89–5.04, m, 2H, H 8′; 5.80, ddt, 1H, *J* 16.9, 10.1, 6.7 Hz, H 7′. ^{13}C n.m.r. δ (50 MHz) 27.03, 28.63, 28.82, 29.82 (C 2′, 3′, 4′, 5′); 33.53 (C 2, 6′); 40.22 (C 3); 47.60 (C 1′); 49.91 (C1); 114.01 (C 8′); 138.85 (C 7′). Mass spectrum (ESI$^+$): *m/z* 184.8 $(M+H)^+$.

N-*Benzyl*-N′*-(oct-7-enyl)propane-1,3-diamine (7)*

Benzaldehyde (0.32 g, 2.99 mmol) in MeOH (2 ml) was added dropwise to a stirred solution of *N*-(oct-7-enyl)propane-1,3-diamine (2) (0.50 g, 2.72 mmol) in MeOH (5 ml). The mixture was stirred for 3 h before the addition of $NaBH_4$ (0.15 g, 4.08 mmol). After a further 2 h, conc. HCl was added cautiously to the mixture (pH 2), which was diluted with water (30 ml), made basic (pH 11–12) by the addition of NaOH pellets and extracted with ether (2×50 ml). The combined organic extracts were washed with water (2×50 ml), dried (Na_2SO_4), filtered and concentrated to give N-*benzyl*-N′*-(oct-7-enyl)propane-1,3-diamine* (7) as a clear oil (0.56 g, 75%) (Found: *m/z* 275.2484. $(C_{18}H_{30}N_2+H)^+$ requires *m/z* 275.2487). ν_{max} (neat) 3063m, 3028m, 2927s, 2854s, 1453s, 1122m, 909m, 734s, 698s cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.27–1.49, m, 8H, H 2′, 3′, 4′, 5′; 1.68, p, 2H, *J* 6.9 Hz, H 2; 2.38, br s, 2H, NH, NH; 2.54, t, 2H, *J* 7.0 Hz, 2.62, t, 2H, *J* 6.9 Hz, and 2.66, t, 2H, *J* 6.9 Hz, H 1, 3, 1′; 3.75, s, 2H, PhC**H**$_2$N; 4.89–5.04, m, 2H, H 8′; 5.80, ddt, 1H, *J* 16.9, 10.1, 6.7 Hz, H 7′; 7.09–7.37, m, 5H, Ph. ^{13}C n.m.r. δ (50 MHz) 27.16, 28.77, 28.96, 29.83, 29.92 (C 2′, 3′, 4′, 5′); 47.74, 48.33, 49.93 (C 1, 3, 1′); 53.92 (Ph**C**H$_2$N); 114.18 (C 8′); 126.90, 128.07, 128.35 (Ar CH); 139.03 (C 7′); 140.11 (C 1′′). Mass spectrum (ESI$^+$): *m/z* 275.2 $(M+H)^+$.

N-*(Hex-5-enyl)propane-1,3-diamine (3)*

Hex-5-enyl mesylate (1.48 g, 8.31 mmol) was added dropwise to stirred propane-1,3-diamine (6.16 g, 83.1 mmol) at 60° and the mixture stirred overnight at 60°. The mixture was cooled to ambient temperature, CH_2Cl_2 (100 ml) was added and washed with water (4×50 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give N-*(hex-5-enyl)propane-1,3-diamine* (3) as a clear oil (0.89 g, 69%), b.p. (oven) 90–95°/12 mm (Found: *m/z* 157.1701. $(C_9H_{20}N_2+H)^+$ requires *m/z* 157.1705). ν_{max} (neat) 3286s(br), 3076m, 2929s, 2856s, 1640m, 1458m, 1126m, 994m, 909s cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.21, br s, 3H, NH, NH_2; 1.28–1.35, m, 2H, H 3′; 1.37–1.44, m, 2H, H 2′; 1.49–1.57, m, 2H, H 2; 1.94–1.99, m, 2H, H 4′; 2.50, t, 2H, *J* 7.0 Hz, H 3; 2.57, t, 2H, *J* 7.0 Hz, H 1′; 2.66, t, 2H, *J* 6.8 Hz, H 1; 4.82–4.93, m, 2H, H 6′; 5.65–5.75, m, 1H, H 5′. ^{13}C n.m.r. δ (100 MHz) 26.55 (C 3′); 29.49 (C 2′); 33.50, 33.77 (C 2, 4′); 40.45 (C 3); 47.79 (C 1′); 49.83 (C 1); 114.30 (C 6′); 138.61 (C 5′). Mass spectrum (ESI$^+$): *m/z* 156.7 $(M+H)^+$.

N-*Benzyl*-N′*-(hex-5-enyl)propane-1,3-diamine (8)*

Benzaldehyde (0.61 g, 5.71 mmol) in MeOH (2 ml) was added dropwise to a stirred solution of *N*-(hex-5-enyl)propane-1,3-diamine (3) (0.89 g, 5.71 mmol) in MeOH (5 ml) and the mixture stirred for 3 h. $NaBH_4$ (0.32 g, 8.56 mmol) was added and stirring continued for 2 h. Conc. HCl was added cautiously to the mixture (pH 2), which was diluted with water (30 ml), made basic (pH 11–12) with NaOH pellets,

and extracted with CH_2Cl_2 (2×50 ml). The combined organic extracts were washed with water (2×50 ml), dried (Na_2SO_4), filtered and concentrated to give a cloudy oil (1.66 g). Kugelrohr distillation gave *N-benzyl-N′-(hex-5-enyl)propane-1,3-diamine* (8) as a clear oil (0.95 g, 68%), b.p.(oven) 150°/0.5 mm (Found: C, 77.7; H, 10.6; N, 11.2. $C_{16}H_{26}N_2$ requires C, 78.0; H, 10.6; N, 11.4%.) ν_{max} (neat) 3290m(br), 3063m, 3027m, 2928s, 2855s, 2813s, 1640m, 1494m, 1454s, 1126s, 994m, 910s, 734s, 698s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.37–1.44, m, 2H, H 3′; 1.46–1.53, m, 2H, H 2′; 1.61, br s, 2H, NH, NH; 1.70, p, 2H, *J* 6.8 Hz, H 2; 2.06, q, 2H, *J* 7.1 Hz, H 4′; 2.59, t, 2H, *J* 7.0 Hz, H 1′; 2.67, t, 2H, *J* 7.2 Hz, and 2.69, t, 2H, *J* 7.4 Hz, H 1, 3; 3.78, s, 2H, PhC**H**$_2$N; 4.91–4.96, m, 1H, H 6′$_E$; 5.00, dq, 1H, *J* 17.1, 1.6 Hz, H 6′$_Z$; 5.80, ddt, 1H, *J* 16.9, 10.2, 6.7 Hz, H 5′; 7.22–7.33, m, 5H, Ph. ^{13}C n.m.r. δ (100 MHz) 26.62 (C 3′); 29.52 (C 2′); 30.18 (C 2); 33.62 (C 4′); 47.94 (C 1′); 48.55 (C 3); 49.89 (C 1); 54.03 (Ph**C**H$_2$N); 114.44 (C 6′); 126.84, 128.04, 128.34 (Ar CH); 138.74 (C 5′); 140.39 (C 1′′). Mass spectrum (ESI$^+$): *m/z* 246.9 $(M+H)^+$.

2-(Undec-10-enylamino)ethanol (4)

Undec-10-enal (1.00 g, 5.94 mmol) in MeOH (5 ml) was added dropwise to a solution of 2-aminoethanol (0.36 g, 5.94 mmol) in MeOH (10 ml) and the mixture allowed to stir at ambient temperature for 1 h. The mixture was cooled to 0° and $NaBH_4$ (0.45 g, 11.9 mmol) was added portionwise. The reaction mixture was allowed to warm to ambient temperature, stirred for a further 2 h, again cooled to 0°, followed by the addition of conc. HCl (to pH 2). The mixture was diluted with water (30 ml), made basic (pH 11–12) by the addition of NaOH pellets and extracted with ether (2×50 ml). The combined organic extracts were washed with water (2×50 ml), dried (Na_2SO_4), filtered and concentrated to give *2-(undec-10-enylamino)ethanol* (4) as a clear oil (0.45 g, 36%). b.p.(oven) 110°/0.2 mm (Found: *m/z* 214.2165. $(C_{13}H_{27}NO+H)^+$ requires *m/z* 214.2171). ν_{max} (neat) 3271s, 3075s, 2917s, 2853s, 1642m, 1463s, 1438m, 1128m, 1077s, 994m, 955m, 936m, 917m, 862m cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.28, br s, 10H, and 1.36–1.39, m, 2H, H 3′, 4′, 5′, 6′, 7′, 8′; 1.49, p, 2H, *J* 7.0 Hz, H 2′; 2.04, m, 2H, H 9′; 2.40, br s, 1H, OH; 2.61, t, 2H, *J* 7.2 Hz, H 1′; 2.77, t, 2H, *J* 5.2 Hz, H 2; 3.64, t, 2H, *J* 5.2 Hz, H 1; 4.93, dq, 1H, *J* 10.2, 1.1 Hz, H 11′$_E$; 4.99, dq, 1H, *J* 17.1, 2.1 Hz, H 11′$_Z$; 5.81, ddt, 1H, *J* 16.9, 10.2, 6.7 Hz, H 10′. ^{13}C n.m.r. δ (100 MHz) 27.29, 28.94, 29.12, 29.44, 29.53, 29.54, 30.06 (C 2′, 3′, 4′, 5′, 6′, 7′, 8′); 33.79 (C 9′); 49.55 (C 1′); 51.15 (C 2); 60.79 (C 1); 114.10 (C 11′); 139.20 (C 10′). Mass spectrum (ESI$^+$): *m/z* 213.9 $(M+H)^+$.

2-(Oct-7-enylamino)ethanol (5)

8-Bromooct-1-ene (1.00 g, 5.23 mmol) was added dropwise to stirred 2-aminoethanol (1.60 g, 26.2 mmol) at 60° and the mixture stirred overnight at 60°. The mixture was cooled to ambient temperature, CH_2Cl_2 (100 ml) was added and washed with water (4×50 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give *2-(oct-7-enylamino)ethanol* (5) as a clear oil (0.84 g, 94%) (Found: *m/z* 172.1693. $(C_{10}H_{21}NO+H)^+$ requires *m/z* 172.1701). ν_{max} (neat) 3302s(br), 3076s, 2926s, 2855s, 1641m, 1459s, 1122m, 1062s, 995m, 909s cm^{-1}. ^1H n.m.r. δ (200 MHz) 1.33–1.52, m, 8H, H 2′, 3′, 4′, 5′; 1.99–2.09, m, 2H, H 6′; 2.06, t, 2H, *J* 7.4 Hz, H 1′; 2.73, t, 2H, *J* 5.2 Hz, H 2; 3.06, br s, 2H, NH, OH; 3.65, t, 2H, *J* 5.3 Hz, H 1; 4.89–5.05, m, 2H, H 8′; 5.08, ddt, 1H, *J* 16.9, 10.1, 6.7 Hz, H 7′. ^{13}C n.m.r. δ (50 MHz) 27.09, 28.76, 28.92, 29.84 (C 2′, 3′, 4′, 5′); 33.64 (C 6′); 49.59 (C 1′); 51.28 (C 2); 60.60 (C 1); 114.18 (C 8′); 138.94 (C 7′). Mass spectrum (ESI$^+$): *m/z* 172.0 ((M+H)$^+$.

2-(Hex-5-enylamino)ethanol (6)

Hex-5-enyl mesylate (1.0 g, 5.62 mmol) was added dropwise to stirred 2-aminoethanol (3.43 g, 56.2 mmol) at 60° and the mixture stirred overnight before being cooled to ambient temperature. CH_2Cl_2 (100 ml) was added and the solution washed with water (4×50 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to give *2-(hex-5-enylamino)ethanol* (6) as a clear oil (0.44 g, 55%), b.p.(oven) 110°/20 mm (Found: *m/z* 144.1383. $(C_8H_{17}NO+H)^+$ requires *m/z* 144.1388). ν_{max} (neat) 3299s(br), 3077s, 2929s, 2857s, 1641m, 1456s, 1122m, 1062s, 994m, 910s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.31–1.39, m, 2H, H 3′; 1.41–1.48, m, 2H, H 2′; 2.00 (apparent q), 2H, *J* 7.1 Hz, H 4′; 2.55, t, 2H, *J* 7.1 Hz, H 1′; 2.67, t, 2H, *J* 5.2 Hz, H 2; 2.84, br s, 1H, NH or OH; 3.58, t, 2H, *J* 5.2 Hz, H 1; 4.63, br s, 1H, OH or NH; 4.88, ddt, 1H, *J* 10.2, 2.4, 1.2 Hz, H 6′$_E$; 4.93, ddt, 1H, *J* 17.1, 3.2, 1.6 Hz, H 6′$_Z$; 5.73, ddt, 1H, *J* 16.9, 10.2, 6.7 Hz, H 5′. ^{13}C n.m.r. δ (100 MHz) 26.49 (C 3′); 29.34 (C 2′); 33.49 (C 4′); 49.39 (C 1′); 51.26 (C 2); 60.64 (C 1); 114.47 (C 6′); 138.55 (C 5′). Mass spectrum (ESI$^+$): *m/z* 143.6 $(M+H)^+$.

3-(Prop-2-enylamino)propanol (19)[19]

A sample of the alcohol (19) was prepared by addition of allylamine to ethyl acrylate followed by $LiAlH_4$ reduction of the resulting ester[20] (80%). ν_{max} (neat) 3288s(br), 2934s, 1458m, 1109m, 1069s, 996m cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.71, m, 2H, H 2; 2.82, t, 2H, *J* 6.1 Hz, H 3; 3.24, dt, 2H, *J* 6.0, 1.4 Hz, H 1′; 3.75, t, 2H, *J* 5.6 Hz, H 1; 5.10, ddt (apparent dq), 1H, *J* 10.3, 1.3, 1.3 Hz, H 3′$_E$; 5.17, ddt (apparent dq), 1H, *J* 17.2, 1.6, 1.6 Hz, H 3′$_Z$; 5.88, ddt, 1H, *J* 17.2, 10.3, 6.0 Hz, H 2′. ^{13}C n.m.r. δ (100 MHz) 31.11 (C 2); 48.17 (C 3); 52.07 (C 1′); 62.89 (C 1); 116.13 (C 3′); 136.10 (C 2′). Mass spectrum (EI): *m/z* 114 (M^+, 4%), 98 (3), 84 (10), 70 (100), 56 (25).

Reactions with H_2/CO

General Conditions

Reactions were carried out in a 100 ml Parr autoclave with a glass sleeve containing a stirrer bead. The substrate (0.1–0.3 g, *c*. 1 mmol), the rhodium catalyst precursor, and the ligand (in ratio 200 : 1 : 4) were placed in the autoclave under N_2 followed by deoxygenated benzene (10 ml).

The vessel was flushed, and evacuated, three times with 200 psi (1.38 MPa) of H_2/CO (1 : 1 molar mixture) and then pressurized to 400 psi (2.76 MPa). Alternatively it was flushed with H_2, and then pressurized to an initial pressure of 400 psi (2.76 MPa) with an H_2/CO (1 : 5) gas mixture. The reaction was kept at the reported temperature for 20 h, the autoclave cooled, the gases were released and the contents analysed as reported. In general, ratios of products including regioisomers were determined by relative peak areas of appropriate hydrogens in ^1H n.m.r. spectra and/or relative signal intensities of comparable carbons in ^{13}C n.m.r. spectra. Selective extraction of the total product with light petroleum gave in most cases n.m.r. pure material in higher yields than chromatography on silica or alumina.

Reactions involving the use of $[Rh(OAc)_2]_2$ and PPh_3 as the catalyst system at 80° for 20 h are referred to as 'the usual conditions'.

Reactions leading to cyclized products were repeated at least once and gave product ratios within ±5% reproducibility.

1,14-Diazabicyclo[11.4.0]heptadecane (9)

N-(Undec-10-enyl)propane-1,3-diamine (1) (0.20 g, 0.89 mmol), BIPHEPHOS (13.9 mg, 17.6 μmol) and rhodium(II) acetate dimer (2.0 mg, 4.4 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave *1,14-diazabicyclo[11.4.0]heptadecane* (9) as a yellow viscous oil (0.19 g, 80%) (Found: *m/z* 239.2480. $(C_{15}H_{30}N_2+H)^+$ requires *m/z* 239.2487). ν_{max} (neat) 3285m, 2922s, 2852s, 1464s, 1368m, 1250m, 1182m, 1128m, 1096m, 900m, 734s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.20, m, 12H, H 5, 6, 7, 8, 9, 10; 1.25–1.37, m, 7H, H 3, 4, 11, 16$_A$; 1.53–1.60, m, 3H, H 16$_B$, 12; 2.17–2.24, m, 1H, H 2$_A$; 2.34, dt, 1H, *J* 9.1, 2.4 Hz, H 17$_A$; 2.48–2.53, m, 1H, H 2$_B$; 2.58, t, 1H, *J* 11.0 Hz, H 15$_A$; 2.97, m, 1H, H 17$_B$; 3.00, m, 1H, H 15$_B$; 3.07–3.09, m, 1H, H 13. ^{13}C n.m.r. δ (100 MHz) 25.02 (C 11); 25.76, 26.50, 27.53, 29.40, 29.42, 29.76 (C 3, 4, 5, 6, 7, 8, 9, 10, 16); 32.91 (C 12); 44.90 (C 15); 51.13, 51.16 (C 2, 17); 75.99 (C 13). Mass spectrum (ESI$^+$): *m/z* 239.0 $(M+H)^+$.

Dry HCl(g) was bubbled through a solution of 1,14-diazabicyclo[11.4.0]heptadecane (9) (0.05 g) in $CHCl_3$ (10 ml) for 1 h. Evaporation of the solvent gave a highly viscous oil. ^1H and ^{13}C n.m.r. spectroscopy indicated a complex mixture of products (0.06 g).

14-Oxa-1-azabicyclo[11.3.0]hexadecane (10)

2-(Undec-10-enylamino)ethanol (4) (0.10 g, 0.47 mmol), BIPHEPHOS (7.3 mg, 9.4 μmol) and rhodium(II) acetate dimer (1.0 mg, 2.4 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave *14-oxa-1-azabicyclo[11.3.0]hexadecane* (10) as a yellow viscous oil (0.10 g, 80%) (Found: *m/z* 226.2166. $(C_{14}H_{27}NO+H)^+$ requires *m/z* 226.2171). ν_{max} (neat) 2925s, 2853s, 1466m, 1182m, 1060m cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.20, br s, 14H, H 4, 5, 6, 7, 8, 9, 10; 1.33–1.50, m, 6H, H 3, 11, 12; 2.13–2.20, m, 1H, $H 2_A$; 2.39–2.46, m, 1H, $H 16_A$; 2.48–2.55, m, 1H, $H 2_B$; 3.15, (apparent p), 1H, *J* 6.1 Hz, $H 16_B$; 3.74–3.78, m, 2H, H 15; 3.90, dd, 1H, *J* 6.1, 3.6 Hz, H 13. ^{13}C n.m.r. δ (100MHz) 25.03 (C 11); 27.40 (C 3); 29.12, 29.48, 29.52, 29.55, 29.70 (C 4, 5, 6, 7, 8, 9, 10); 34.11 (C 12); 52.13 (C 16); 53.28 (C 2); 64.15 (C 15); 96.71 (C 13). Mass spectrum (ESI$^+$): *m/z* 226.9 $(M+H)^+$.

1,11-Diazabicyclo[8.4.0]tetradecane (11)

N-(Oct-7-enyl)propane-1,3-diamine (2) (0.10 g, 0.54 mmol), BIPHEPHOS (8.5 mg, 10.9 μmol) and rhodium(II) acetate dimer (1.2 mg, 2.7 μmol) were reacted under the standard conditions with H_2/CO (1 : 1) at 40° for 44 h. A significant amount of benzene-insoluble polymer lined the autoclave glass sleeve. Concentration of the benzene-soluble fraction gave *1,11-diazabicyclo[8.4.0]tetradecane* (11) as a yellow oil (0.03 g, 28%) (Found: *m/z* 197.2008. $(C_{12}H_{24}N_2+H)^+$ requires *m/z* 197.2018). ν_{max} (neat) 3288m(br), 2926s, 2854s, 1638s, 1462s, 1369m, 1306m, 1250m, 1173m, 1064m, 731s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.28, m, 8H, H 4, 5, 6, 7; 1.44, m, 5H, H 3, 8, 13_A; 1.56–1.67, m, 3H, H 9, 13_B; 2.29, m, 1H, $H 2_A$; 2.41, t, 1H, *J* 10.4 Hz, $H 14_A$; 2.56, m, 1H, $H 2_B$; 2.65, t, 1H, *J* 11.1 Hz, $H 12_A$; 3.04, m, 1H, $H 14_B$; 3.07, m, 1H, $H 12_B$; 3.14, m, 1H, H 10. ^{13}C n.m.r. δ (100 MHz) 25.26 (C 3); 25.87 (C 9); 27.01 (C 4); 29.24, 29.42, 29.52, 29.83 (C 5, 6, 7, 8); 33.10 (C 13); 45.03 (C 12); 51.28 (C 2); 51.61 (C 14); 76.11 (C 10). Mass spectrum (ESI$^+$): *m/z* 196.9 ($(M+H)^+$, 54%), 393.1 ($(2M+H)^+$, 100).

11-Benzyl-1,11-diazabicyclo[8.4.0]tetradecane (12)

The diamine (7) (0.10 g, 0.37 mmol), PPh_3 (1.9 mg, 7.3 μmmol) and rhodium(II) acetate dimer (0.8 mg, 1.8 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave *11-benzyl-1,11-diazabicyclo[8.4.0]tetradecane* (12) as a yellow oil (0.10 g, 95%) (Found: *m/z* 287.2486. $(C_{19}H_{30}N_2+H)^+$ requires *m/z* 287.2487). ν_{max} (neat) 3062m, 3027m, 2929s, 2853s, 2805s, 1494m, 1453s, 1356m, 1117m, 1071m, 1027m, 733s, 698s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.31–1.45, m, 13H, H 3, 4, 5, 6, 7, 8, 13_A; 1.47–1.59, m, 1H, $H 9_A$; 1.60–1.71, m, 1H, $H 9_B$; 1.82–1.98, m, 1H, $H 13_B$; 2.39–2.45, m, 1H, $H 2_A$; 2.52–2.56, m, 1H, $H 2_B$; 2.60–2.62, m, 2H, $H 12_A$, 14_A; 2.79–2.87, m, $H 12_B$, 14_B; 3.31, m, 1H, H 10; 3.71, d, 1H, *J* 13.5 Hz, PhC$\mathbf{H}_A$N; 3.80, d, 1H, *J* 13.6 Hz, PhC$\mathbf{H}_B$N; 7.19–7.22, m, 1H, and 7.25–7.35, m, 4H, ArH. ^{13}C n.m.r. δ (100 MHz) 20.37 (C 13); 22.90 (C 9); 26.60 (C 8); 27.55, 28.00 (C 3, 4); 29.67, 29.71, 29.79 (C 5, 6, 7); 45.14 (C 12); 46.18 (C 14); 52.94 (C 2); 56.76 (Ph$\mathbf{C}H_2$N); 76.56 (C 10); 126.56 (C 4′); 128.02, 128.29 (C 2′, 3′, 5′, 6′); 140.59 (C 1′). Mass spectrum (ESI$^+$): *m/z* 287.1 ($(M+H)^+$, 60%); 573.5 ($(2M+Na)^+$, 100). N.m.r. spectroscopy indicated less than 10% of the internal product, 10-benzyl-8-methyl-1,10-diazabicyclo[7.4.0]tridecane. ^1H n.m.r. δ (400 MHz) 1.07, d, *J* 7.0 Hz, CH_3. ^{13}C n.m.r. δ (100 MHz) 13.25 (CH_3); 55.70 (C 8); 75.18 (C 9).

Column chromatography (basic alumina) resulted in product decomposition giving still impure bicyclic amine (12) in poor yield (0.04 g, 38%).

A reaction of the diamine (7) (0.10 g, 0.37 mmol), BIPHEPHOS (5.7 mg, 7.3 μmol) and rhodium(II) acetate dimer (0.8 mg, 1.8 μmol) with H_2/CO (1 : 5) gave the bicyclic compound (12) as a yellow oil (0.10 g, 95%).

Reactions of (7) using BIPHEPHOS as ligand and H_2/CO (1 : 1) for 40 h at 40° or 20 h at 80° gave a mixture of products. Mass spectroscopy (ESI$^+$) suggested the presence of starting material (7) (*m/z* 275.2), hydrogenated starting material (*m/z* 277.1) and hydrogenated intermediate iminium cation (*m/z* 289.1).

11-Oxa-1-azabicyclo[8.3.0]tridecane (13)

2-(Oct-7-enylamino)ethanol (5) (0.20 g, 1.17 mmol), PPh_3 (6.1 mg, 23.4 μmol) and rhodium(II) acetate dimer (2.6 mg, 5.8 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave *11-oxa-1-azabicyclo[8.3.0]tridecane* (13) as a yellow oil (0.20 g, 93%) (Found: *m/z* 184.1696. $(C_{11}H_{23}NO+H)^+$ requires *m/z* 184.1701). ν_{max} (neat) 2926s, 2853s, 1731m, 1651m, 1464s, 1368m, 1157s, 1120s, 1071s, 920m, 726s cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.22–1.38, m, 8H, H 4, 5, 6, 7; 1.42–1.59, m, 6H, H 3, 8, 9; 2.21, dt, 1H, *J* 11.6, 7.1 Hz, $H 2_A$; 2.43–2.55, m, 1H, $H 13_A$; 2.56–2.62, m, 1H, $H 2_B$; 3.22, ddd, 1H, *J* 10.0, 6.1, 4.8 Hz, $H 13_B$; 3.76–3.88, m, 2H, H 12; 3.95, dd, 1H, *J* 6.4, 3.3 Hz, H 10. ^{13}C n.m.r. δ (100 MHz) 25.00 (C 8); 27.36 (C 3); 29.06, 29.37, 29.49, 29.62 (C 4, 5, 6, 7); 34.04 (C 9); 52.21 (C 13); 53.09 (C 2); 64.14 (C 12); 96.61 (C 10). Mass spectrum (ESI$^+$): *m/z* 183.6 $(M+H)^+$. N.m.r. spectroscopy indicated less than 10% of the internal product, 8-methyl-10-oxa-1-azabicyclo[7.3.0]dodecane. ^1H n.m.r. δ (400 MHz) 1.08, d, *J* 7.0 Hz, CH_3. ^{13}C n.m.r. δ (100 MHz) 13.05 (CH_3); 46.16 (C 8); 95.95 (C 9).

Column chromatography (basic alumina: 1% MeOH/CH_2Cl_2) resulted in product decompostion with 11-oxa-1-azabicyclo-[8.3.0]tridecane (13) being recovered in low yield (0.03 g, 28%) and without any improvement in the purity.

A reaction of (5) (0.10 g, 0.59 mmol), BIPHEPHOS (9.2 mg, 11.7 μmol) and rhodium(II) acetate dimer (1.3 mg, 2.9 μmol) with H_2/CO (1 : 1) at 80° gave a reasonably pure sample of the tridecane (13) (0.10 g, 93%).

A reaction of (5) under the above conditions but with H_2/CO (1 : 1) at 40° for 44 h gave *2-(decahydroazecin-1-yl)ethanol* (14) as a yellow oil (0.08 g, 75%) (Found: *m/z* 186.1856. $(C_{11}H_{23}NO+H)^+$ requires *m/z* 186.1858). ν_{max} (neat) 3385s(br), 2926s, 2854s, 1465s, 1368m, 1172m, 1053s, 732m cm^{-1}. ^1H n.m.r. δ (400 MHz) 1.43–1.57, m, 14H, H 3′, 4′, 5′, 6′, 7′, 8′, 9′; 2.44, t, 4H, *J* 7.3 Hz, H 2′, 10′; 2.57, t, 2H, *J* 5.1 Hz, H 2; 3.53, t, 2H, *J* 4.9 Hz, H 1. ^{13}C n.m.r. δ (100 MHz) 26.90, 27.31, 29.69, 29.76 (C 3′, 4′, 5′, 6′, 7′, 8′, 9′); 53.80 (C 2′, 10′); 55.45 (C 2); 58.32 (C 1). Mass spectrum (ESI$^+$): *m/z* 186.0 ($(M+H)^+$, 16%), 371.3 ($(2M+H)^+$, 100).

1,9-Diazabicyclo[6.4.0]dodecane (15)

N-(Hex-5-enyl)propane-1,3-diamine (3) (0.10 g, 0.64 mmol), BIPHEPHOS (10.0 mg, 12.8 μmol) and rhodium(II) acetate dimer (1.4 mg, 3.2 μmol) were reacted with H_2/CO (1 : 1) at 50° for 44 h. Concentration of the solvent gave *1,9-diazabicyclo[6.4.0]dodecane* (15) as a yellow oil (0.80 g, 74%) (Found: *m/z* 169.1700. $(C_{10}H_{20}N_2+H)^+$ requires *m/z* 169.1705). ν_{max} (neat) 3286m(br), 2931s, 2857s, 1640s, 1459s, 1376m, 1074m, 910s, 754s, 732s cm^{-1}. ^1H n.m.r. δ (200 MHz) 1.20–1.50, m, 9H, H 3, 4, 5, 6, 11_A; 1.59–1.75, m, 3H, $H 11_B$,7; 2.14–2.42, m, 2H, $H 2_A$, 12_A; 2.48–2.71, m, 2H, $H 2_B$, 10_A; 3.03, m, 1H, $H 12_B$; 3.09, m, 1H, $H 10_B$; 3.16, m, 1H, H 8. ^{13}C n.m.r. δ (50 MHz) 25.20, 25.78, 26.53, 27.67, 29.89 (C 3, 4, 5, 6, 11); 32.99 (C 7); 44.96 (C 10); 51.19 (C 2, 12); 75.96 (C 8). Mass spectrum (ESI$^+$): *m/z* 168.8 $(M+H)^+$.

9-Benzyl-1,9-diazabicyclo[6.4.0]dodecane (16) and 8-Benzyl-6-methyl-1,8-diazabicyclo[5.4.0]undecane (17)

The diamine (8) (0.20 g, 0.81 mmol), PPh_3 (4.3 mg, 16.3 μmol) and rhodium(II) acetate dimer (1.8 mg, 4.1 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave a yellow oil (0.24 g). The crude ^1H and ^{13}C n.m.r. spectra of the total product indicated a 30 : 70 mixture of linear to branched products. Column chromatography (alumina: 20% EtOAc/light petroleum) gave *8-benzyl-6-methyl-1,8-diazabicyclo[5.4.0]undecane* (17) as a clear oil (0.08 g, 38%) (Found: *m/z* 259.2175. $(C_{17}H_{26}N_2+H)^+$ requires *m/z* 259.2174). ν_{max} (neat) 3026m, 2926s, 2853s, 1494m, 1453s, 1363m, 1148m, 1115s, 1045w, 1027m, 737s, 698s cm^{-1}. ^1H n.m.r. δ (400 MHz) 0.96, d, 3H, *J* 6.7 Hz, CH_3; 1.37–1.44, m, 1H, $H 5_A$; 1.46–1.52, m, 3H, $H 3_A$, 4_A, 10_A; 1.57–1.62, m, 2H, $H 5_B$, 3_B; 1.63–1.70, m, 2H, $H 4_B$, 10_B; 2.17, m, 1H, H 6; 2.52–2.58, m, 1H, $H 9_A$; 2.63, t, 1H, *J* 13.2 Hz, $H 2_A$; 2.70, p, 1H, *J* 5.8 Hz, $H 11_A$; 2.94–3.08, m, 4H, $H 2_B$, 7, 9_B, 11_B; 3.77, d, 1H, *J* 13.7 Hz, and 4.01, d, 1H, *J* 13.7 Hz, PhC$\mathbf{H}_2$N; 7.20, t, 1H, *J* 7.2

Hz, H 4′; 7.28, t, 2H, *J* 7.2 Hz, H 3′,5′; 7.36, d, 2H, *J* 7.4 Hz, H 2′,6′. ^{13}C n.m.r. δ (100 MHz) 18.66 (C 10); 21.11 (CH_3); 25.23 (C 3); 26.98 (C 4); 33.33 (C 5); 35.08 (C 6); 46.33 (C 9); 50.39 (C 11); 53.48 (C 2); 55.09 (Ph**C**H_2N); 85.59 (C 7); 126.52 (C 4′); 128.07 (C 3′, 5′); 128.75 (C 2′, 6′); 141.02 (C 1′). Mass spectrum (ESI$^+$): *m/z* 259.0 $(M+H)^+$. Further elution (20–50% EtOAc/light petroleum) gave an impure sample of *9-benzyl-1,9-diazabicyclo[6.4.0]dodecane* (16) (0.03 g, 14%) (Found: *m/z* 259.2173. $C_{17}H_{26}N_2$ requires *m/z* 259.2174). ν_{max} (neat) 2930s, 2854m, 1453m, 1356m, 734m, 698s cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.06–1.51, m, 9H, H 3, 4, 5, 6, 11$_A$; 1.58–1.66, m, 2H, H 7; 1.80–2.11, m, 1H, H 11$_B$; 2.19–2.35, m, 1H, H 2$_A$; 2.49–2.51, m, 1H, H 2$_B$; 2.60–2.75, m, 2H, H 10$_A$, 12$_A$; 2.82–2.94, m, 2H, H 10$_B$, 12$_B$; 3.26–3.40, m, 1H, H 8; 3.71–3.84, m, 2H, PhC**H**$_2$N; 7.20–7.42, m, 5H, ArH. ^{13}C n.m.r. δ (100 MHz) 20.31, 22.68, 26.57, 27.55, 27.97, 29.32 (C 3, 4, 5, 6, 7, 11); 45.03 (C 10); 46.06 (C 12); 52.91 (C 2); 56.74 (Ph**C**H_2N); 76.45 (C 8); 126.53, 127.98, 128.55 (Ar CH); 140.51 (C 1′). Mass spectrum (ESI$^+$): *m/z* 258.9 $(M+H)^+$.

A reaction of the diamine (8) (0.10 g, 0.41 mmol), BIPHEPHOS (6.4 mg, 8.13 μmol) and rhodium(II) acetate dimer (0.9 mg, 2.0 μmol) with H_2/CO (1 : 5) gave a yellow oil (0.10 g, 95%) whose ^{1}H and ^{13}C n.m.r. spectra indicated predominantly 9-benzyl-1,9-diazabicyclo[6.4.0]dodecane (16) with less than 10% internal derived product (17).

9-Oxa-1-azabicyclo[6.3.0]undecane (18)

2-(Hex-5-enylamino)ethanol (6) (0.10 g, 0.70 mmol), PPh_3 (3.7 mg, 14.0 μmol) and rhodium(II) acetate dimer (1.5 mg, 3.5 μmol) were reacted under the standard conditions with H_2/CO (1 : 1). Concentration of the solvent gave a mixture containing some 6-methyl-8-oxa-1-azabicyclo[5.3.0]decane, with ^{13}C n.m.r. δ (50 MHz) 15.03 (CH_3), 39.8 (C 6), 95.57 (C 7), and *9-oxa-1-azabicyclo[6.3.0]undecane* (18) as a yellow oil (0.10 g, 92%) (Found: *m/z* 156.1382. $(C_9H_{17}NO+H)^+$ requires *m/z* 156.1388). ν_{max} (neat) 2933s, 2856s, 2808m, 1459m, 1157m, 1070m cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.22–1.42, m, 6H, H 4, 5, 6; 1.43–1.75, m, 4H, H 3, 7; 2.16–2.32, m, 1H, H 2$_A$; 2.40–2.66, m, 2H, H 2$_B$, 11$_A$; 3.23, m, 1H, H 11$_B$; 3.84, dt, 2H, *J* 7.4, 1.8 Hz, H 10; 3.96, m, 1H, H 8. ^{13}C n.m.r. δ (50 MHz) 25.02 (C 6); 27.42 (C 3); 29.05, 29.61 (C 4, 5); 34.03 (C 7); 52.10 (C 11); 53.23 (C 2); 64.19 (C 10); 96.63 (C 8). Mass spectrum (ESI$^+$): *m/z* 155.8 ($(M+H)^+$, 50%); 311.1 ($(2M+H)^+$, 30); 333.1 ($(2M+Na)^+$, 100). Kugelrohr distillation, b.p.(oven) 100°/16 mm, gave 9-oxa-1-azabicyclo[6.3.0]undecane (18) (0.03 g, 27%). The distillation residue was chloroform-insoluble material, the sample apparently decomposing on heating.

A reaction of (6) (0.10 g, 0.70 mmol), BIPHEPHOS (21.8 mg, 28.0 μmol) and rhodium(II) acetate dimer (1.5 mg, 3.5 μmol) with H_2/CO (1 : 1) gave 9-oxa-1-azabicyclo[6.3.0] undecane (18) (0.10 g, 92%).

2-(Octahydroazocin-1-yl)ethanol

A reaction of (6) (0.10 g, 0.70 mmol), BIPHEPHOS (10.9 mg, 14.0 μmol) and rhodium(II) acetate dimer (1.5 mg, 3.5 μmol) under the standard conditions with H_2/CO (1 : 1) gave a mixture of 2-(octahydroazocin-1-yl)ethanol and 2-(3-methylhexahydroazepin-1-yl)ethanol, estimated in the ratio of 70 : 30, as a yellow oil (0.08 g). Column chromatography (alumina: 10% EtOH/EtOAc) gave only the linear product *2-(octahydroazocin-1-yl)ethanol* as a clear oil (0.04 g, 36%) (Found: *m/z* 158.1541. $(C_9H_{19}NO+H)^+$ requires *m/z* 158.1545). ν_{max} (neat) 3382s(br), 2929s, 2859m, 1637m, 1571s, 1490m, 1450m, 1406s, 1079m, 1050m cm^{-1}. ^{1}H n.m.r. δ (200 MHz) 1.64–1.73, m, 10H, H 3′, 4′, 5′, 6′, 7′; 2.81, t, 2H, *J* 5.1 Hz, 2.84, t, 2H, *J* 6.2 Hz, and 2.87, t, 2H, *J* 5.1 Hz, H2′, 8′, 2; 3.69, t, 2H, *J* 5.1 Hz, H 1; 5.55, br s, 1H, OH. ^{13}C n.m.r. δ (50 MHz) 25.74, 26.22, 26.39 (C 3′, 4′, 5′, 6′, 7′); 52.91 (C 2′, 8′); 57.92 (C 2); 59.57 (C 1). Mass spectrum (ESI$^+$): *m/z* 157.9 $(M+H)^+$.

5-Oxa-1-azabicyclo[4.3.0]nonane (20) and N-(3-Hydroxypropyl)pyrrolidin-2-one (21)

3-(Prop-2-enylamino)propan-1-ol (19) (0.30 g, 2.61 mmol), BIPHEPHOS (40.8 mg, 52.2 μmol) and rhodium(II) acetate dimer (5.8 mg, 13.0 mmol) were reacted with H_2/CO (1 : 1) under standard conditions to give a yellow oil (0.32 g). Kugelrohr distillation, b.p.(oven) 40°/16 mm (lit.[21] 60–61°/14 mm), gave 5-oxa-1-azabicyclo[4.3.0]nonane (20) as a clear oil (0.11 g, 33%). ν_{max} (neat) 2930s, 2852s, 2796m, 1652s, 1453m, 1340m, 1158m, 1065m cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.06, m, 1H, H 3$_A$; 1.60–1.69, m, 1H, H 7$_A$; 1.69–1.77, m, 1H, H 8$_A$; 1.83–1.90, m, 1H, H 8$_B$; 1.91–1.96, m, 1H, H 7$_B$; 1.97–2.05, m, 1H, H 3$_B$; 2.66, dt, 1H, *J* 8.5, 3.6 Hz, H 9$_A$; 3.02–3.09, m, 3H, H 9$_B$, 2; 3.59, dq, 1H, *J* 11.4, 2.4 Hz, H 4$_A$; 3.94–3.98, m, 1H, H 4$_B$; 4.37, dd, 1H, *J* 5.1, 1.8 Hz, H 6. ^{13}C n.m.r. δ (100 MHz) 20.12 (C 3); 21.15 (C 8); 31.68 (C 7); 45.73 (C 2); 47.57 (C 9); 67.06 (C 4); 91.55 (C 6). Mass spectrum (ESI$^+$): *m/z* 127.4 $(M+H)^+$.

A reaction of (19) (0.30 g, 2.61 mmol), PPh_3 (13.7 mg, 52.2 μmol) and rhodium(II) acetate dimer (5.8 mg, 13.0 μmol) with H_2/CO (1 : 1) gave a yellow oil (0.31 g). Kugelrohr distillation as above gave 5-oxa-1-azabicyclo[4.3.0]nonane (20) as a clear oil (0.15 g, 45%). The residue was predominantly *N*-(3-hydroxypropyl)pyrrolidin-2-one (21) (0.13 g, 35%). ν_{max} (neat) 3382s(br), 2948s, 2873s, 1667s, 1497m, 1466s, 1438s, 1292m, 1065s, 753s, 725s cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.68–1.74, m, 2H, H 4; 2.05, p, 2H, *J* 7.7 Hz, H 2′; 2.42, t, 2H, *J* 8.0 Hz, H 3; 3.41, t, 4H, *J* 7.0 Hz, H 5, 3′; 3.54, t, 2H, *J* 5.8 Hz, H 1′. ^{13}C n.m.r. δ (100 MHz) 17.72 (C 4); 29.44, 30.64 (C 2′, 3); 38.84 (C 5); 47.42 (C 3′); 58.88 (C 1′); 175.89 (C 2). Mass spectrum (ESI$^+$): *m/z* 143.9 $(M+H)^+$. Spectroscopic data for (21) were in agreement with the literature.[22]

Ring Opening Reactions

1,5-Diazacycloheptadecane (24)

DIBAL-H (1.5 M in toluene) (0.84 mmol, 0.56 ml) was added to a solution of 1,14-diazabicyclo[11.4.0]heptadecane (9) (0.05 mg, 0.21mmol) in toluene (5 ml) and the solution heated at reflux overnight.[13,14] NaF (0.27 g) was added at ambient temperature, followed by water (0.1 ml) and the mixture allowed to stir for 0.5 h. The mixture was filtered and the solids were washed with ether. Concentration of the filtrate gave *1,5-diazacycloheptadecane* (24) which was dissolved in ether, cooled to 0°C and dry HCl(g) was bubbled through. The ether was decanted to give the HCl salt as a white hygroscopic solid (0.04 g, 61%) (Found: *m/z* 241.2639. $(C_{15}H_{30}N_2+H)^+$ requires *m/z* 241.2644). ν_{max} 3374m(br), 2922s, 2851s, 1646m, 1466s, 731m cm^{-1}. ^{1}H n.m.r. δ (400 MHz, CD_3OD) 1.32–1.57, m, 18H, H 8, 9, 10, 11, 12, 13, 14, 15, 2×NH; 1.72–1.74, m, 4H, H 7, 16; 2.15, m, 2H, H 3; 3.02, m, 4H, H 6, 17; 3.13, m, 4H, H 2, 4. ^{13}C n.m.r. δ (100 MHz, CD_3OD) 23.68 (C 3); 24.19, 27.26 (C 7, 16); 27.55, 30.19, 30.40, 30.45, 30.57, 30.61, 30.66 (C 8, 9, 10, 11, 12, 13, 14, 15); 45.87 (C 2, 4); C 6 and C 17 were obscured by CD_3OD. Mass spectrum (ESI$^+$): *m/z* 241.2 $(M+H)^+$.

3-(Pyrrolidin-1-yl)propan-1-ol

Reaction of 5-oxa-1-azabicyclo[4.3.0]nonane (20) with DIBAL-H as described above gave 3-(pyrrolidin-1-yl)propan-1-ol as an oil (0.04 g, 60%). ν_{max} (neat) 3312s(br), 2958s, 2876s, 2806s, 1460m, 1134m, 1066s, 732m cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.68–1.78, m, 6H, H 2, 3′, 4′; 2.55–2.58, m, 4H, H 2′, 5′; 2.72, t, 2H, *J* 5.9 Hz, H 3; 3.79, t, 2H, *J* 5.4 Hz, H 1. ^{13}C n.m.r. δ (100 MHz) 23.38 (C 3′, 4′); 29.58 (C 2); 54.18 (C 2′, 5′); 56.25 (C 3); 64.49 (C 1). Mass spectrum(ESI$^+$): *m/z* 129.6 $(M+H)^+$. The ^{1}H and ^{13}C n.m.r. spectra were in agreement with the literature.[23]

6-Methoxy-3,4,7,8,9,10-hexahydro-1,5-diazecine-1,5(2H,6H)-dicarbonitrile (25)

Cyanogen bromide (89.5 mg, 0.85 mmol) was added to a stirred suspension of 1,5-diazabicyclo[4.4.0]decane (22) (53 mg, 0.38 mmol) and MgO (32.5 mg, 0.81 mmol) in $CHCl_3$/MeOH (1 : 1) (5 ml) under N_2 following the procedure of Bremner.[16] The reaction was kept at 40° for 14 h and then the mixture was evaporated to dryness. 2 M HCl (15 ml) was added and the mixture extracted with $CHCl_3$ (3×30 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the *diazecinedicarbonitrile* (25) as a yellow oil (0.07 g, 82%) (Found: *m/z* 245.1372. $(C_{11}H_{18}N_4O+Na)^+$ requires *m/z* 245.1378). ν_{max} (neat) 2936m, 2207s, 1451m, 1192m, 1136m, 1089m, 1040m cm^{-1}. ^{1}H n.m.r.

δ (400 MHz) 1.50–1.67, m, 2H, H 8_A, 9_A; 1.74–1.86, m, 3H, H 7_A, 8_B, 9_B; 1.93–2.00, m, 1H, H 7_B; 2.05–2.12, m, 2H, H 3; 3.01–3.06, m, 1H, H 2_A; 3.08–3.13, m, 1H, H 4_A; 3.18, dt, 1H, *J* 6.3, 1.6 Hz, H 10_A; 3.26–3.34, m, 3H, H 2_B, 4_B, 10_B; 3.45, s, 3H, OMe; 4.32, dd, 1H, *J* 10.1, 1.6 Hz, H6. ^{13}C n.m.r. δ (100 MHz) 22.95 (C 3); 23.19 (C 9); 24.25 (C 8); 30.68 (C 7); 40.13 (C 4); 45.33 (C 2); 54.54 (C 10); 56.02 (OMe); 95.94 (C 6); 116.24 (5-CN); 117.18 (1-CN). Mass spectrum (ESI$^+$): *m/z* 223.0 ((M+H)$^+$, 30%), 245.1 ((M+Na)$^+$, 100%).

*6-Methoxy-4-oxooctahydro-1*H*-1,5-diazonin-1-carbonitrile (27)*

Cyanogen bromide (99.9 mg, 0.94 mmol) was added to a stirred suspension of 1,5-diazabicyclo[4.4.0]decan-4-one (23) (60 mg, 0.43 mmol) and MgO (36.3 mg, 0.90 mmol) in $CHCl_3$/MeOH (1 : 1) (5 ml) under N_2. The reaction was kept at 40° for 14 h and the product isolated as above to give a yellow oil. Column chromatography (silica gel: 20% EtOAc/light petroleum) gave the *diazoninecarbonitrile* (27) as a clear oil (0.04 g, 47%) (Found: *m/z* 220.1051. $(C_9H_{15}N_3O_2 + Na)^+$ requires *m/z* 220.1062.). ν_{max} (neat) 3285s, 2939s, 2208s, 1663s, 1448m, 1126m, 1085s cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.69, m, 2H, H 8; 1.77, m, 1H, H 7_A; 2.03, m, 1H, H 7_B; 2.51, dd, 1H, *J* 13.7, 5.9 Hz, H 3_A; 2.87, dt, 1H, *J* 13.6, 1.4 Hz, H 3_B; 3.03, dd, 1H, *J* 14.9, 11.6 Hz, H 2_A; 3.30, m, 2H, H 9; 3.43, s, 3H, OMe; 3.74, ddd, 1H, *J* 15.1, 6.0, 1.7 Hz, H 2_B; 5.05, dt, 1H, *J* 10.7, 3.7 Hz, H 6; 5.94, d, 1H, *J* 10.3 Hz, NH. ^{13}C n.m.r. δ (100 MHz) 22.92 (C 8); 34.82 (C 7); 35.80 (C 3); 48.03 (C 2); 53.47 (C 9); 55.74 (OMe); 85.23 (C 6); 117.51 (CN); 173.32 (C 4). Mass spectrum (ESI$^+$): *m/z* 197.9 ((M+H)$^+$, 5%); 219.9 ((M+Na)$^+$, 100%).

*9-Methoxy-3,4,6,7,8,9-hexahydro-1,5-oxazonine-5(2*H*)-carbonitrile (28) and (4-Bromobutyl)(3′-bromopropyl)cyanamide (29)*

Cyanogen bromide (91.8 mg, 0.87 mmol) was added to a stirred suspension of 5-oxa-1-azabicyclo[4.3.0]nonane (20) (50 mg, 0.39 mmol) and MgO (33.3 mg, 0.83 mmol) in $CHCl_3$/MeOH (1 : 1) (5 ml) under N_2. The reaction was kept at 40° for 14 h and the product isolated as above to give a yellow oil. The ^{1}H and ^{13}C n.m.r. spectra indicated a mixture of products including the oxazoninecarbonitrile (28) as a significant component (^{13}C δ 54.66 (OMe), 104.05 (C 9)). Column chromatography (silica gel: 50% EtOAc/light petroleum) gave only *(4-bromobutyl)(3′-bromopropyl)cyanamide* (29) as a clear oil (0.03 g, 26%) (Found: *m/z* 295.9516, 297.9496, 299.9474. $C_8H_{14}Br_2N_2$ requires *m/z* 295.9524, 297.9504, 299.9484). ν_{max} (neat) 2938m, 2208s, 1447m, 1256m cm^{-1}. ^{1}H n.m.r. δ (400 MHz) 1.80–1.89, m, 2H, H 2; 1.93–2.00, m, 2H, H 3; 2.20, p, 2H, *J* 6.6 Hz, H 2′; 3.09, t, 2H, *J* 6.9 Hz, H 1; 3.20, t, 2H, *J* 6.7 Hz, H 1′; 3.44, t, 2H, *J* 6.3 Hz, H 4; 3.50, t, 2H, *J* 6.2 Hz, H 3′. ^{13}C n.m.r. δ (100 MHz) 26.37 (C 2); 29.43 (C 3); 29.54 (C 3’); 30.29 (C 2′); 32.57 (C 4); 49.46 (C 1′); 51.43 (C 1); 116.81 (CN). Mass spectrum (EI): *m/z* 296 ($C_8H_{14}{}^{79}Br_2N_2$, 1%), 298 ($C_8H_{14}{}^{79}Br^{81}BrN_2$, 2), 300 ($C_8H_{14}{}^{81}Br_2N_2$, 1), 219 (10), 217 (10), 189 (12), 175 (15), 150 (10), 137 (42), 121 (18), 111 (20), 69 (14), 55 (100).

Acknowledgments

We thank the Australian Research Council for support and provision of a postgraduate award (to D.J.B.) and Johnson Matthey Pty Ltd for a loan of rhodium.

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