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Samarium Diiodide Mediated Alkylation of Saturated Heterocycles *alpha* to Nitrogen

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Abstract: A method for α -alkylation of saturated 5-, 6-, 7- and 8-membered aza-heterocycles is described. The auxiliary is an *o*-iodobenzyl group attached at the nitrogen. A radical introduced in the *o*-position is transferred to the amine α -position which subsequently leads to an addition reaction with pentan-3-one.

Introduction

The construction of new carbon-carbon bonds *alpha* to a basic nitrogen represents a versatile process for the synthesis of nitrogen-containing compounds. Usually this transformation has been carried out by lithiation *alpha* to the nitrogen after prior activation by an electron-withdrawing group on the nitrogen.¹ A powerful method to functionalise molecules is to generate carbon-centred radicals at a remote site and translocate the radical by a 1,5-hydrogen atom transfer prior to a subsequent desired reaction.² This strategy has been employed to achieve alkylation *alpha* to nitrogen in good yields.³ Very recently we have reported on the use of tin radicals to effect α -alkylation reactions in cyclic amines.⁴

We report here studies on the samarium diiodide mediated α -alkylation^{3b} of saturated aza-heterocycles. The tin and the samarium approach are complementary in that the intermediate in the latter adds to carbonyl compounds, whereas the former adds to alkenes.

Results and Discussion

Tertiary aza-heterocycles **1a-i** are available by treatment of the parent secondary aza-heterocycle with 2-iodobenzyl chloride. Conversion to the α -alkylated products **2a-h** was achieved by successive addition of the substrate (1 mole eq.), pentan-3-one (1 mole eq.) and hexamethylphosphoric triamide (HMPA) (3 mole eq.) to a solution of samarium diiodide (3 mole eq.) in tetrahydropyran (THP) (Scheme 1).





In the case of five-, seven- and eight-membered cyclic amines (1a, 1c and 1d) the reaction proceeded smoothly to afford 2a, 2c and 2d in high yields (Table 1). Interestingly, in the case of the six-membered cyclic amine, the piperazine 1b, conversion to 2b was achieved in only 35 % yield at best. A lower yield was also observed in the reaction of the benzo[b]piperidine 1f to 2f compared to conversion of the benzo[b]pyrrolidine 1e to 2e.

When THF was substituted for THP as solvent, **2a** was obtained in slightly lower yield. In the case of THF, some intermolecular hydrogen abstraction by the aryl radical took place resulting in an increased yield of reduction product. A similar observation has been reported.⁵ N,N'-Dimethylpropylurea (DMPU) has been used as a substitute for the carcinogenic HMPA in some samarium reactions.⁶ Attempts to use DMPU in the reaction of the pyrrolidine **1a** was unsuccessful, mainly unreacted starting material being recovered. The use of excess pentan-3-one diminished rather than increased the yield of the alkylated pyrrolidine **2a**. Substituting acetophenone or acetone for the electrophile was also unsuccessful and afforded the products of pinacol coupling reactions, the product of simple reduction of the aryl-I bond in the substrate and unreacted starting material.

Fable 1: Samarium()	II) iodide	mediated alk	vlation of secondar	y amines 1 with	pentan-3-one
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No	∩1	Yield of 2 (%)	No I Yield of 2 (%)
а	⟨N 	85	f () 40
b		35	Me N 26
c	(N)	81	
d		72	$ \begin{array}{c} h \\ N \\$
e		68	

Reaction of the piperazines **1g** and **1h** with samarium diiodide and pentan-3-one afforded the alkylated products **2g** and **2h** in low yields (Table 1). In the case of the morpholine derivative **1i**, none of the desired α -alkylated product was obtained, the product of simple reduction of the aryl-I bond being isolated in 71 % yield.

Despite the synthetic advances in the use of samarium diiodide, there is still a hazy picture of most samarium diiodide mediated transformations. In this case, evidence points towards the formation of a transient α -amino organosamarium species.^{3b} The aryl radical formed by deiodination of the *o*-benzyl group by samarium diiodide abstracts the hydrogen *alpha* to nitrogen *via* an intramolecular 1,5-hydrogen atom transfer. One-electron transfer from samarium diiodide to the α -amino radical may afford an organosamarium species like 3 (Scheme 2). The intermediacy of such organosamarium species has been demonstrated in a number of samarium diiodide promoted reactions.⁷ The organosamarium species has also been formed prior to addition of the electrophile.⁷ When this technique was applied to our systems, the electrophile being added at intervals ranging from 2 minutes to 1 hour, the major product in all cases was that of simple reduction of the aryl-I bond. In an attempt to stabilise the organosamarium species, the reaction was performed on 1-(2iodobenzoyl)piperidine (4) (Scheme 2). Since TLC revealed several products being formed isolation was not attempted.



Scheme 2

It is not obvious why reduced yields are seen in the six-membered ring systems of the piperidine 1b and its fused benzo-homologue 1f. It seems unlikely that the conformation of the six-membered ring should inhibit the 1,5-hydrogen atom transfer step especially as the related reaction of 1b with *n*-tributyltin hydride affords the Michael adduct 5 in 66 % yield (Scheme 2).⁴

In the cases of the azines **1g-h**, where the ring contains more than one heteroatom, it is unclear whether the lower yields obtained are due to interference by the second heteroatom or are due to the effect of a six-membered ring.

Experimental

Samarium metal was purchased from Aldrich and was handled in a glove box under an argon atmosphere. Dry tetrahydropyran (THP) was freshly distilled from calcium hydride. Pentan-3-one and HMPA were distilled from calcium hydride and stored under argon.

TLC was performed on Merck aluminium sheets coated with silica gel 60 F254 (Art 5735); the chromatograms were initially examined under u.v. light and then developed either with iodine vapour or an aqueous potassium permanganate solution containing sodium carbonate. Preparative chromatography was carried out on columns of Merck Kieselgel 60 (230-400 mesh).

¹H spectra and ¹³C spectra were recorded at 200 MHz and 50 MHz respectively on a Gemini 200 n.m.r. spectrometer. Both ¹H and ¹³C spectra were recorded using CDCl₃ and CHCl₃ as internal standards respectively. Electron impact (e.i.) (70 e.v.) and chemical ionisation (c.i.) spectra were recorded with a Prospec VG analytical spectrometer.

Samarium diiodide was prepared according to the method of Kagan.⁸ Samarium metal (432 mg, 2.87 mmol) and 1,2-diiodoethane (540 mg, 1.92 mmol) were stirred at room temperature for 2 h in dry, deoxygenated tetrahydropyran (THP) (19 ml). An exothermic reaction was observed and once formed the samarium diiodide was a deep blue colour in solution.

Starting material available by literature methods:

 $\begin{array}{ll} 1-(2-Iodobenzyl)pyrrolidine & (1a)^{4a}; 1-(2-iodobenzyl)piperidine & (1b)^{4a}; 1-(2-iodobenzyl)-hexahydroazepine & (1c)^{4a}; 1-(2-iodobenzyl)-4-methylpiperazine & (1g)^{4a}; 4-(2-iodobenzyl)-morpholine & (1i)^{4a}. \end{array}$

1-(2-Iodobenzyl)heptamethyleneimine (1d)^{4a}: Heptamethyleneimine (0.90 g, 7.96 mmol), 2iodobenzyl chloride (0.50 g, 1.98 mmol) and anhydous potassium carbonate (3.00 g, 21.70 mmol) were heated at reflux temperature in acetone (20 ml) for 2 h. Water was added, the aqueous phase separated and extracted with diethyl ether. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. Chromatography on silica gel with an eluent gradient of hexane to ethyl acetate-hexane (1:10, v/v) afforded **1d** as a clear, colourless oil (0.54 g, 83 %); R_f (acetone-hexane, 1:19, v/v) 0.58; v_{max} (film)/cm⁻¹ 3060 w, 2910 s, 2850 s, 2800 s, 1450 m; $\delta_{\rm H}$ (200 MHz, CDCl₃) 1.50-1.68 (10 H, complex m, H-3, H-4, H-5, H-6 and H-7), 2.63 (4 H, t, J 5.7, H-2 and H-8), 3.65 (2 H, s, ArCH₂), 6.94 (1 H, ddd, J 7.9, 7.2, 1.8, H-4'), 7.32 (1 H, ddd, J 7.6, 1.2, H-5'), 7.47 (1 H, dd, H-6'), 7.84 (1 H, dd, H-3') ppm; $\delta_{\rm C}$ (50 MHz, CDCl₃) 27.1 (C-4 and C-6), 28.9 (C-5), 29.1 (C-3 and C-7), 55.2 (C-2 and C-8), 68.4 (ArCH₂), 101.3 (C-2'), 128.2 (C-5'), 128.8 (C-4'), 131.0 (C-6'), 139.7 (C-3'), 142.8 (C-1') ppm; *m*/z (EI) 328 (M, 5), 314 (1), 300 (10), 286 (13), 272 (4), 260 (4), 246 (8), 217 (53), 202 (5), 146 (6), 132 (7), 112 (100), 98 (10), 91 (24); (Found: M, 329.0635. C14H₂0IN requires M, 329.0641).

I-(2-Iodobenzyl)indoline (1e): Prepared as for 1d using indoline (0.50 g, 4.19 mmol), 2-iodobenzyl chloride (0.88 g, 3.49 mmol) and anhydrous potassium carbonate (3.00 g, 21.74 mmol). Chromatography on silica gel with dichloromethane-hexane (1:5, v/v) as eluent afforded 1e (1.01 g, 86 %) as a clear, colourless oil; R_f (diethyl ether-hexane, 1:4, v/v) 0.65; v_{max} (film)/cm⁻¹ 3050 s, 3030 s, 2940 s, 2920 s, 2820 s, 1600 s, 1490 s; $\delta_{\rm H}$ (200 MHz, CDCl₃) 3.07 (2 H, t, J 8.4, H-2), 3.46 (2 H, t, H-3), 4.28 (2 H, s, ArCH₂), 6.49 (1 H, d, J 7.7, H-7), 6.74 (1 H, td, J 7.4, 1.0, H-5), 7.00-7.19 (3 H, complex, H-4', H-4 and H-6), 7.36 (1 H, ddd, J 7.7, 7.3, 1.2, H-5'), 7.46 (1 H, dd, J 1.8, H-6'), 7.92 (1 H, dd, J 7.8, H-3') ppm; $\delta_{\rm C}$ (50 MHz, CDCl₃) 29.2 (C-3), 54.6 (C-2), 59.5 (ArCH₂), 99.4 (C-2'), 107.6 (C-7), 118.4 (C-5), 125.0 (C-6), 127.8 (C-4), 128.8 (C-5'), 129.4 (C-4'), 129.5 (C-6'), 130.3 (C-3a), 140.0 (C-3'), 140.7 (C-1'), 152.7 (C-7a) ppm; m/z (EI) 335 (M, 100), 217 (15), 208 (8), 204 (3), 132 (41), 118 (18), 91 (30), 77 (12).

I-(2-Iodobenzyl)tetrahydroquinoline (**1**f): A solution of tetrahydroquinoline (0.50 g, 3.75 mmol) and 2iodobenzyl chloride (0.63 g, 2.50 mmol) in THF (5 ml) was vigorously stirred with aqueous potassium carbonate (5.00 g in 5 ml water) for 2 days at room temperature. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The organic extracts were dried (MgSO4) and evaporated under reduced pressure to afford **2f** as a yellow oil (0.79 g, 91 %); R_f (ethyl acetate-hexane, 1:9, v/v) 0.40; v_{max} (film)/cm⁻¹ 3050 s, 3030 s, 2940 s, 2920 s, 2820 s, 1600 s, 1490 s; $\delta_{\rm H}$ (200 MHz, CDCl3) 2.07 (2 H, tt, H-3), 2.87 (2 H, t, *J* 6.2, H-4), 3.42 (2 H, t, *J* 5.6, H-2), 4.37 (2 H, s, ArCH₂), 6.29 (1 H, d, *J* 8.0, H-8), 6.61 (1 H, t, *J* 7.3, H-6), 6.94-7.07 (3 H, complex, H-4', H-5 and H-7), 7.25 (1 H, dd, *J* 7.6, 7.3, H-5'), 7.50 (1 H, dd, *J* 1.7, H-6'), 7.88 (1 H, d, *J* 7.7, H-3') ppm; $\delta_{\rm C}$ (50 MHz, CDCl3) 23.3 (C-3), 29.0 (C-4), 50.9 (C-2), 62.0 (ArCH₂), 98.4 (C-2'), 111.4 (C-8), 116.6 (C-6), 127.7 (C-7), 127.9 (C-5), 128.8 (C-5'), 129.1 (C-4'), 129.4 (C-6'), 130.7 (C-4a), 139.8 (C-3'), 140.2 (C-1'), 152.8 (C-8a) ppm; *m/z* (EI) 349 (M, 100), 222 (11), 217 (31), 204 (4), 194 (28), 146 (47), 132 (20), 91 (32), 77 (11); (Found: M, 349.0339. C1₆H₁6NI requires M, 349.0328).

I-Carbobenzyloxy-4-(2-iodobenzyl)piperazine (**1h**): Prepared as for **1d** using 1-carbobenzyloxypiperazine (2.00 g, 9.08 mmol), 2-iodobenzyl chloride (2.29 g, 9.08 mmol) and anhydrous potassium carbonate (3.14 g, 22.71 mmol). Chromatography on silica gel with ethyl acetate-hexane (2:3, v/v) as eluent afforded **1h** (3.69 g, 93 %) as a clear, colourless oil; Rf (ethyl acetate-hexane, 1:1, v/v) 0.51; v_{max} (film)/cm⁻¹ 3070 w, 3050 w, 2945 m, 2805 m, 1705 s, 1430 m, 1240 m; $\delta_{\rm H}$ (200 MHz, CDCl3) 2.49 (4 H, t, *J* 4.5, H-2 and H-6), 3.45 (2 H, s, ArCH₂N), 3.54 (4 H, t, H-3 and H-5), 5.15 (2 H, s, PhCH₂O), 6.97 (1 H, ddd, H-4'), 7.26-7.47 (7 H, complex, C6H5, H-5' and H-6'), 7.85 (1 H, d, *J* 7.9, H-3') ppm; $\delta_{\rm C}$ (50 MHz, CDCl3) 44.4 (C-3 and C-5), 53.1 (C-2 and C-6), 66.9 (ArCH₂N), 67.6 (PhCH₂O), 101.2 (C-2'), 128.4 (C-5), 128.5 (C-4'), 128.9, 129.4 (C6H5), 130.8 (C-6'), 137.3 (C'), 140.1 (C-3'), 140.6 (C-1'), 155.7 (C=O) ppm; *m*/z (EI) 436 (M⁺, 50), 392 (5), 301 (12), 272 (17), 260 (13), 217 (52), 175 (8), 149 (7), 105 (9), 91 (100); (Found: MH⁺, 437.0691. C19H₂1IN₂O₂ requires MH, 437.0681).

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1-Benzyl-2-(3-hydroxypentan-3-yl)pyrrolidine (2a): A solution of samarium diiodide (606 mg, 1.50 mmol) in tetrahydropyran (14 ml) was cooled to -10 °C. 1-(2-Iodobenzyl)pyrrolidine (1) (146 mg, 0.50 mmol) in THP (2 ml), pentan-3-one (41 mg, 0.48 mmol) and HMPA (0.74 ml) were added successively. Stirring was continued at -10 °C for 4 h. The reaction mixture was quenched with saturated potassium carbonate solution and the product extracted into dichloromethane. The organic phase was dried (MgSO4) and evaporated under reduced pressure. The residue was passed down a short column of silica using diethyl ether as the eluent to remove HMPA. Chromatography on silica gel with ethyl acetate-hexane (4:1, v/v) as eluent afforded 2a (101 mg, 85 %) as a clear, colourless oil; Rf (diethyl ether) 0.44; v_{max} (film)/cm⁻¹ 3445 br. (OH), 3020 w, 3010 w, 2965 s, 2930 s, 2880 m, 2780 w; 5H (200 MHz, CDCl3) 0.89 (3 H, t, J 7.5, CH3), 0.90 (3 H, t, J 7.4, CH3),1.39 (1 H, dq, J 14.2, 7.2, H-3a), 1.49-1.92 (7 H, complex m, H-3b, H-4, CH2CH3), 2.50 (1 H, br. m, H-2), 2.70-2.95 (3 H, m, H-5 and OH), 3.62 (1 H, d, J 13.9, PhCHaHb), 4.04 (1 H, d, PhHaHb), 7.19-7.40 (5 H, complex m, C6H5) ppm; & (50 MHz, CDCl3) 8.9 (CH3), 9.1 (CH3), 26.0 (CH2CH3), 27.0 (CH₂CH₃), 28.2 (C-3 or C-4), 30.2 (C-3 or C-4), 55.8 (C-5), 63.8 (C-2), 70.5 (ArCH₂), 76.6 (C-OH), 127.3 (Cp), 128.5 (Co), 128.8 (Cm), 139.9 (C') ppm; m/z (EI) 229 (M-H₂O, 8), 218 (6), 183 (5), 167 (9), 160 (95), 149 (24), 105 (16), 97 (22), 91 (100), 83 (25), 69 (36), 57 (56), 43 (44), 29 (18); (Found: M-H₂O, 229.1833. C16H25NO requires M-H2O, 229.1831)

1-Benzyl-2-(3-hydroxypentan-3-yl)piperidine (2b): As for the preparation of 2a, 1-(2iodobenzyl)piperidine (1b) (157 mg, 0.52 mmol), pentan-3-one (35 mg, 0.40 mmol) and HMPA (0.80 ml) were added successively to a solution of samarium diiodide (606 mg, 1.50 mmol) in tetrahydropyran (15 ml) cooled to -10 °C. Stirring was continued at -10 °C for 4 h. The reaction mixture was quenched with saturated potassium carbonate solution, the product extracted into dichloromethane and the organic phase dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-hexane (1:1, v/v) as eluent afforded 2b (37 mg, 35 %) as a clear, colourless oil. R_f (diethyl ether-hexane, 1:1, v/v) 0.33; v_{max} (film)/cm⁻¹ 3330 br., 2930 m, 2920 s, 2850 m; δ H (200 MHz, CDCl3) 0.83 (3 H, t, J 7.5, CH3), 0.89 (3 H, t, J 7.4, CH3), 1.37-1.95 (10 H, complex, CH₂CH₃, H-3, H-4 and H-5), 2.65 (2 H, m, H-6), 2.80 (1 H, m, H-1), 3.05 (1 H, br. s, OH), 3.83 (1 H, d, J 13.6, PhCHaCHb), 4.00 (1 H, d, PhCHaCHb), 7.23-7.34 (5 H, m, C6H5) ppm; δ C (50 MHz, CDCl3) 9.2 (CH3), 9.4 (CH3), 19.4 (CH₂CH₃), 21.4 (CH₂CH₃), 22.7 (C-4), 29.3 (C-3 and C-5), 46.8 (C-6), 58.6 (C-2), 65.4 (PhCH₂), 77.2 (C-OH), 127.3 (Cp), 128.7 (Co), 128.9 (Cm), 140.4 (C') ppm; m/z (EI) 243 (M-H₂O, 5), 232 (8), 214 (2), 200 (3), 174 (100), 152 (1), 133 (2), 91 (80), 82 (4), 65 (7), 55 (9); (Found: M-H₂O, 243.1981. C₁₇H₂₇NO requires M-H₂O, 243.1987).

1-Benzyl-2-(3-hydroxypentan-3-yl)hexahydroazepine (2c): As for the preparation of 2a, 1-(2iodobenzyl)hexahydroazepine (1c) (194 mg, 0.61 mmol), pentan-3-one (55 mg, 0.64 mmol) and HMPA (0.99 ml) were added successively to a solution of samarium diiodide (739 mg, 1.83 mmol) in tetrahydropyran (19 ml) cooled to -10 °C. Stirring was continued at -10 °C for 4 h. Saturated sodium carbonate solution was added and the product extracted into ethyl acetate. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with ethyl acetate as eluent afforded 2c as a clear, colourless oil (136 mg, 4.95 mmol, 81 %). R_f (ethyl acetate) 0.75; v_{max} (film)/cm⁻¹ 3420 b (OH), 3090 w, 3060 w, 3030 w, 2950 s, 2920 s, 1460 m; δ_H (200 MHz, CDCl₃) 0.90 (3 H, t, J 7.4, CH₃), 0.93 (3 H, t, J 7.4, CH₃), 1.27-1.95 (12 H, complex m, H-3, H-4, H-5, H-6 and CH₂CH₃), 2.81 (3 H, m, H-2 and H-7), 3.85 (1 H, d, J 13.9, PhCH_aH_b), 4.23 (1 H, d, PhCH_aH_b), 7.25-7.36 (5 H, complex m, C₆H₅) ppm; $\delta_{\rm C}$ (50 MHz, CDCl₃) 9.3 (CH₃), 24.9 (CH₂CH₃), 28.2 (CH₂CH₃), 29.1 (C-5 or C-4), 29.2 (C-5 or C-4), 30.4 (C-6 or C-3), 30.7 (C-6 or C-3), 48.7 (C-7), 60.2 (C-2), 70.4 (PhCH₂), 76.9 (C-OH), 128.8 (Cp), 128.9 (Co and Cm), 138.8 (C') ppm; m/z (EI) 257 (M-H₂O, 2), 246 (M-C₂H₅, 6), 242 (3), 228 (2), 200 (3), 188 (100), 172 (11), 166 (2); (Found: M-C₂H₅, 246.1857. C₁₈H₂9NO requires M-C₂H₅, 246.1858).

1-Benzyl-2-(3-hydroxypentan-3-yl)heptamethyleneimine (2d): As for the preparation of 2a, 1-(2iodobenzyl)heptamethyleneimine (1d) (211 mg, 0.64 mmol), pentan-3-one (55 mg, 0.64 mmol) and HMPA (0.99 ml) were added successively to a solution of samarium diiodide (739 mg, 1.83 mmol) in tetrahydropyran (19 ml) cooled to -10 °C. The reaction mixture was stirred at -10 °C for 3 h and then at room temperature for 48 h. A saturated solution of sodium carbonate was added and the aqueous mixture extracted with ethyl acetate. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with ethyl acetate-hexane (1:4, v/v) as eluent afforded 2d as a clear, colourless oil (133 mg, 72 %). R_f (ethyl acetate-hexane, 1:4, v/v) 0.61; v_{max} (film)/cm⁻¹ 3420 b (OH), 3090 w, 3060 w, 3030 w, 2950 s, 2920 s, 1460 m; $\delta_{\rm H}$ (200 MHz, CDCl₃) 0.90 (6 H, t, *J* 7.4, CH₃), 1.26-1.86 (14 H, complex m, H-3, H-4, H-5, H-6, H-7 and CH₂CH₃), 2.75 (1 H, br. m, H-2), 3.00 (2 H, br. m, H-8), 3.89 (1 H, d, *J* 14.7, ArCH_aH_b), 4.11 (1 H, d, *J* 14.7, ArCH_aH_b), 7.24-7.36 (5 H, m, C6H₅) ppm; $\delta_{\rm C}$ (50 MHz, CDCl₃) 8.37 (CH₃), 24.0 (CH₂CH₃), 26.1 (CH₂CH₃), 27.2 (C-6), 27.7 (C-4), 28.0 (C-5), 28.6 (C-7), 28.9 (C-3), 53.8-56.0 (broad, C-2 and C-8), 67.2 (broad, PhCH₂), 76.6 (C-OH), 127.3 (Cp), 128.5 (Co), 129.0 (Cm), 140.8 (C') ppm; m/z (EI) 271 (M-H₂O, 2), 260 (M-C₂H₅, 7), 256 (4), 242 (2), 228 (2), 202 (100), 188 (22), 180 (4), 172 (21), 166 (2); (Found: M-C₂H₅, 260.2023. C19H₃1NO requires M-C₂H₅, 260.2014).

1-Benzyl-2-(3-hydroxypentan-3-yl)indoline (2e): As for the preparation of 2a, 1-(2iodobenzyl)indoline (1e) (300 mg, 0.90 mmol), pentan-3-one (77mg, 0.90 mmol) and HMPA (0.99 ml) were added successively to a solution of samarium diiodide (1.09 g, 2.70 mmol) in tetrahydropyran (20 ml) cooled to -10 °C. Stirring was continued at -10 °C for 2 h and then warmed to room temperature overnight. A saturated solution of sodium carbonate was added and the aqueous mixture extracted with dichloromethane. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-hexane (1:9, v/v) as eluent afforded 2e (179 mg, 68 %) as a clear, colourless oil; Rf (diethyl-etherhexane, 1:9, v/v) 0.17; v_{max} (film)/cm⁻¹ 3560-3480 br., 3040 m, 3020 m, 2970 s, 2930 s, 2880 s, 1610 s, 1480 s, 1460 s; δH (200 MHz, CDCl₃) 0.88 (3 H, t, J 7.5, CH₃), 0.95 (3 H, t, J 7.4, CH₃), 1.44-1.79 (4 H, m, CH₂CH₃), 3.05 (1 H, dd, J 16.5, 7.9, H-3a), 3.21 (1 H, dd, J10.2, H-3b), 3.88 (1 H, dd, H-2), 4.41 (1 H, d, J 16.5, PhCH_aH_b), 4.61 (1 H, d, PhCH_aH_b), 6.50 (1 H, dd, J 7.7, 1.1, H-7), 6.76 (1 H, ddd, J 7.7. 7.0, H-5), 7.02-7.11 (2 H, m, H-4 and H-6), 7.28-7.38 (5 H, m, PhCH₂) ppm; δ_C (50 MHz, CDCl₃) 8.1 (CH3), 8.3 (CH3), 26.9 (CH2CH3), 29.4 (CH2CH3), 31.7 (C-3), 58.2 (C-2), 71.2 (ArCH2), 77.5 (C-OH), 109.7 (C-7), 119.2 (C-5), 124.5 (C-6), 127.4 (Cp), 127.5 (Co), 127.9 (C-4), 129.2 (Cm), 129.8 (C-3a), 140.3 (C'), 154.9 (C-7a) ppm; m/z (EI) 295 (M, 13), 277 (4), 266 (8), 208 (100), 130 (8), 118 (18), 91 (93), 77 (4); (Found: M, 295.1930. C20H25NO requires M, 295.1936).

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1-Benzyl-2-(3-hydroxypentan-3-yl)tetrahydroquinoline (2f): As for the preparation of 2a, 1-(2iodobenzyl)tetrahydroquinoline (1f) (200 mg, 0.57 mmol), pentan-3-one (49 mg, 0.57 mmol) and HMPA (0.99 ml) were added successively to a solution of samarium diiodide (691 mg, 1.71 mmol) in tetrahydropyran (19 ml) cooled to -10 °C. The reaction mixture was stirred at -10 °C for 2 h and then warmed to room temperature overnight. A saturated solution of sodium carbonate was added and the aqueous mixture extracted with dichloromethane. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-hexane (1:4, v/v) as eluent afforded 2f (72 mg, 40 %) as a clear, colourless oil; Rf (diethyl ether-hexane, 1:4, v/v) 0.31; vmax (film) 3426 br. (OH), 3070 m, 3040 m, 2960 s, 2935 s, 2880 m, 2830 m, 1615 s, 1492 s; δH (200 MHz, CDCl₃) 0.85 (3 H, t, J 7.5, CH₃), 0.89 (3 H, t, J 7.3, CH3), 1.42-2.12 (5 H, complex, H-3ax and CH2CH3), 2.13 (1 H, dddt, J 14, 6, 3, H-3eq), 2.63 (1 H, m, H-4eq), 3.09 (1 H, ddd, J 15, 14, H-4ax), 3.37 (1 H, dd, J 5, H-2), 4.46 (1 H, d, J 16.5, PhCHaCHb), 4.94 (1 H, d, PhCHaCHb), 6.64 (1 H, dd, J 7.3, 6.2, H-8), 6.79 (1 H, d, J 8, H-6), 6.96-7.05 (2 H, m, H-5 and H-7), 7.21-7.36 (5 H, complex, PhCH₂) ppm; δ_C (50 MHz, CDCl₃) 8.3 (CH₃), 22.3 (CH2CH3), 25.3 (CH2CH3), 26.4 (C-3), 30.1 (C-4), 59.2 (C-2), 62.0 (PhCH2), 79.9 (C-OH), 115.3 (C-8), 117.4 (C-6), 124.8 (C-7), 127.2 (C-5 or Cp), 127.4 (C-5 or Cp), 127.9 (Co), 128.0 (Cm), 129.9 (C-4a), 139.3 (C'), 146.0 (C-8a) ppm; m/z (EI) 309 (M, 2), 291 (4), 222 (89), 208 (2), 130 (8), 91 (100), 77 (3); (Found: M, 309.2093 C21H27NO requires M, 309.2079).

1-Benzyl-4-methyl-2-(3-hydroxypentan-3-yl)piperazine (2g): As for the preparation of 2a, 4methyl-1-(2-iodobenzyl)piperazine (1g) (202 mg, 0.64 mmol) in THP (2 ml), pentan-3-one (55 mg, 0.64 mmol) and HMPA (1.0 ml) were added successively to a solution of samarium diiodide (774 mg, 1.92 mmol) in tetrahydropyran (19 ml) cooled to -10 °C. Stirring was continued at -10 °C for 2 h followed by further stirring at room temperature overnight. The reaction mixture was quenched with a saturated solution of potassium carbonate and the product extracted into ethyl acetate. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with methanol-ethyl acetate (1:4, v/v) as eluent afforded 2g as a clear, colourless oil (46 mg, 26 %). Rf (methanol-ethyl acetate, 1:4) 0.23; δ H (200 MHz, CDCl3) 0.77 (3 H, t, *J* 7.4, CH3), 0.79 (3 H, t, *J* 7.7, CH3), 1.26-1.84 (4 H, complex m, CH₂CH3), 2.23 (3 H, s, NCH3), 2.32-2.58 (5 H, complex m, H-5, H-6 and H-3a), 2.92 (1 H, d, *J* 11, H-3b), 3.44-3.59 (1 H, m, H-2), 3.74 (1 H, d, *J* 13.6, PhCH_aCH_b), 4.01 (1 H, d, PhCH_aCH_b), 7.20-7.40 (5 H, complex, C6H5) ppm; δ C (50 MHz, CDCl3) 8.7 (CH3), 9.0 (CH3), 27.6 (CH₂CH₃), 30.7 (CH₂CH₃), 46.0 (C-3 or C-5), 47.0 (C-3 or C-5), 49.7 (C-6?), 58.3 (C-2), 60.7 (PhCH₂), 78.0 (C-OH), 127.5 (Cp), 128.7 (Co), 129.2 (Cm), 141.0 (C') ppm; m/z (EI) 247 (7), 190 (19), 189 (100), 146 (14), 134 (6), 91 (49), 70 (24); (Found: M-C₂H₅, 247.1807. C₁7H₂8N₂O requires M-C₂H₅, 247.1810).

4-Benzyl-1-carbobenzyloxy-3-(3-hydroxypentan-3-yl)piperazine (2h): As for the preparation of 2a, 1-carbo-benzyloxy-4-(2-iodobenzyl)piperazine (1h) (400 mg, 0.92 mmol) in THP (2 ml), pentan-3-one (80 mg, 0.92 mmol) and HMPA (1.30 ml) were added successively to a sloution of samarium diiodide (1.10 g, 2.75 mmol) in tetrahydropyran (25 ml) cooled to -10 $^{\circ}$ C. Stirring was continued at -10 $^{\circ}$ C for 4 h. The reaction mixture was quenched with a saturated solution of potassium carbonate and the product extracted into dichloromethane. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-hexane (1:1, v/v) as eluent afforded 2h (81 mg, 22 %) as a

clear, colourless oil. R_f (diethyl ether-hexane, 1:1) 0.28; v_{max} (film)/cm⁻¹ 3463 br. (OH), 3040 w, 3030 w, 2990 s, 2970 s, 1700 s (C=O), 1410 m, 1450 m; δ H (200 MHz, CDCl₃) 0.80-0.98 (6 H, t, CH₃), 1.50-1.70 (4 H, m, CH₂CH₃), 2.55-3.40 (7 H, complex, H-2, H-3, H-5 and H-6), 3.75 (1 H, d, J 13.6, PhCH_aH_bN), 3.80 (1 H, br. s, OH), 3.84 (1 H, d, PhCH_aH_bN), 5.21 (2 H, s, PhCH₂O), 7.15-7.40 (10 H, m, C₆H₅) ppm; δ C (50 MHz, CDCl₃) 9.4 (CH₃), 9.5 (CH₃), 27.2 (CH₂CH₃), 29.4 (CH₂CH₃), 40.1 (C-5?), 44.0 (C-2 and C-6?), 60.8 (C-3?), 65.2 (PhCH₂N), 68.1 (PhCH₂O), 77.9 (C-OH), 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.8 (C₆H₅), 138.9 (C=O) ppm; *m*/z (EI) 378 (M-H₂O, 4), 363 (2), 349 (2), 309 (22), 287 (5), 243 (7), 218 (25), 200 (8), 188 (3), 173 (3), 161 (18), 153 (5), 91 (100), 65 (6); (Found: M-H₂O, 378.2322. C₂4H₃2N₂O₃ requires M-H₂O, 378.2307).

Reaction of 1-(2-iodobenzyl)morpholine with pentan-3-one and samarium diiodide: Samarium diiodide (800 mg, 1.98 mmol) in THP (18.5 ml) was cooled to -10 °C. 1-(2-Iodobenzyl)morpholine (1i) (200 mg, 0.66 mmol) in THP (2 ml), pentan-3-one (55 mg, 0.63 mmol) and HMPA (0.90 ml) were added successively. Stirring was continued at -10 °C for 4 h. The reaction mixture was quenched with saturated potassium carbonate solution and the product extracted into dichloromethane. The organic phase was dried (MgSO4) and evaporated under reduced pressure. Chromatography on silica gel with diethyl ether-hexane (1:1, v/v) as eluent afforded the product of reduction of the Ar-I bond as a clear, colourless oil (79 mg, 71 %).

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