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An approach to chiral amino acids via reductive amination of ketones: hydride reduction of 1-(*S*)-phenethyl amine derived Schiff bases of C-protected α-keto acids

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ABSTRACT

Various 1-acyl-2,4,10-trioxaadamantanes were prepared from the corresponding 1-methoxycarbonyl derivatives, via conversion to the *N*-acylpiperidine derivatives followed by reaction with a Grignard reagent in refluxing THF. These α-keto orthoformates were converted to the corresponding imines with 1-(*S*)-phenethyl amine ($TiCl_4$/Et_3N/toluene/reflux), with the Schiff bases being reduced further with $NaBH_4$ (MeOH/0 °C) into the corresponding 1-(*S*)-phenethyl amines (diastereomeric excess 91:9 by NMR). Hydrogenolysis of the phenethyl group (Pd-C/MeOH) finally led to the 1-(aminoalkyl)trioxaadamantanes, which are chiral C-protected α-amino acids, in excellent overall yields.

1. Introduction

The synthesis of chiral α-amino acids in high enantiomeric purity is of great interest in chemistry and chemical biology. Currently, chirality at the C_2 position may be induced in several ways depending on the synthetic route employed. Catalytic methods apparently dominate the scene, with a variety of approaches having been employed for the selective introduction of groups around the stereogenic center.[1–6]

Resolution of synthetic racemates also remains of continuing interest as it leads to both enantiomeric forms; note that amino acids can be transformed into a variety of final products, and that access to both forms is advantageous to biological activity studies. Catalytic kinetic resolution strategies, particularly enzymatic ones, have often been employed; however, conventional derivatization to diastereomers that are resolved by various chromatographic methods is also being pursued.[7–10]

Herein we report an interesting new approach based on the sodium borohydride reduction of a chiral Schiff base, which was derived from a carboxyl-protected α-keto acid. We have previously reported on the synthetic utility of the 2,4,10-trioxaadamantane unit,[11] a tricyclic orthoester proven to be a robust carboxyl protecting group. This has now been extended to the above synthesis of amino acids.

2. Results and discussion

The carboxyl-protected α-keto acids **3** were prepared from the known[11] trioxaadamantyl carboxylic ester **1** via the corresponding pyrrolidine amide **2** (Scheme 1). The reaction of ester **1** with piperidine in THF was promoted by anhydrous $MgCl_2$ and occurred in excellent yields.[12] The resulting amide **2** was reacted with a variety of Grignard reagents, thus effecting the delivery of the alkyl group in ketones **3** in very high yields (Table 1).[13] These were then condensed with a chiral auxiliary, 1-(*S*)-phenethyl amine, to form the corresponding imines (Schiff bases) **4.** These were not isolated in purified form, but were reduced further as described below.

The reduction of the chiral Schiff bases **4,** with sodium borohydride in MeOH at 0 °C, occurred in excellent yields and diastereoselectivity (91:1, Table 1). The *like* (*l*) and *unlike* (*u*) diastereomeric products **5** were separated by chromatography,[14] and the configuration of the major diastereomer was established as (1*S*) by X-ray crystallography (Fig. 1).[15] The observed diastereoselectivity can be best explained by assuming the formation of the *Z* geometrical isomer of the imines **4**; this apparently adopts a conformation around the N–C single bond with the relatively bulky phenyl ring away from the trioxaadamantyl moiety (Scheme 2). Hydride delivery to the C=N group from the less hindered *Re* face (*syn* to the H rather than the Me at the benzylic center) thus leads to the observed (*S*)-configuration at the newly created stereogenic center.[15]

Thus, the observed stereochemistry is predicated on the preferential formation of the *Z* imine, which also preferentially adopts the above conformation around the C–N bond. The formation of the *Z*-imine may be driven by the lone pair repulsions between the N and O centers in the alternative *E*-isomer; the conformational preference around C–N is presumably driven by steric factors as mentioned above. Explanations for the observed stereoselectivity based on the formation of the *E*-imine are less plausible, and would require a U-shaped arrangement in which R and Ph would clash.

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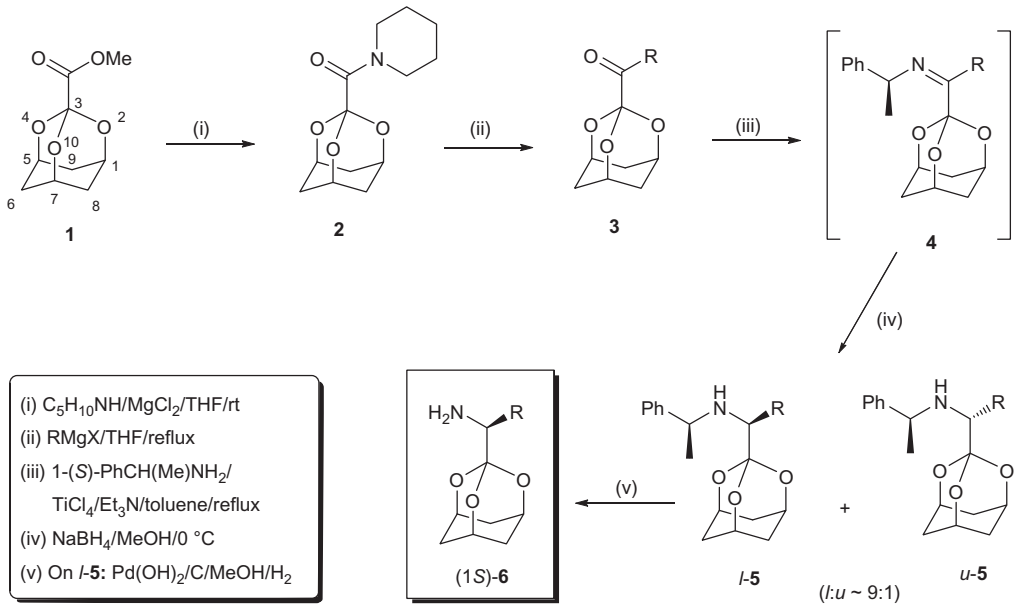


Scheme 1. The conversion of the trioxaadamantyl methyl ester **1** to the diastereomeric phenethyl amine derivatives **5**, via amide **2,** ketone **3**, and imine **4,** under the indicated reaction conditions.

Table 1
Yields (%) of **3, 5**, and **6,** and the diastereomeric ratio (*l*:*u*) of **5** (*cf.* Scheme 1)

Item	RMgX	**3a–3f**	**5a–5f**		**6a–6f**
		Yield (%)	Yield (%)	*l*:*u*	Yield (%)
1	EtMgBr	92 **3a**	84 **5a**	91:9	96 **6a**
2	Pr^nMgBr	92 **3b**	78 **5b**	89:11	94 **6b**
3	n-$C_6H_{13}MgBr$	93 **3c**	76 **5c**	87:13	95 **6c**
4	Bu^iMgBr	89 **3d**	71 **5d**	83:17	93 **6d**
5	Bu^iCH_2MgBr	94 **3e**	82 **5e**	91:9	93 **6e**
6	$PhCH_2MgCl$	94 **3f**	79 **5f**	88:12	97 **6f**

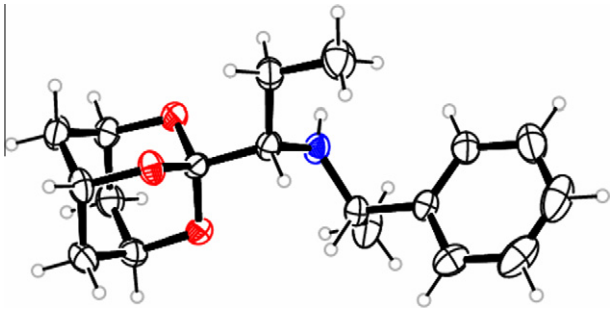
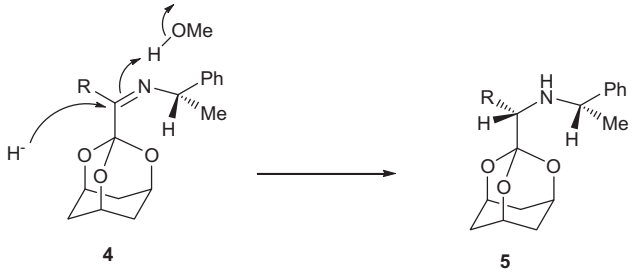


Figure 1. Crystallographic ORTEP diagram of the 1-(*S*)-phenethyl amine derivative *l*-**5a,** obtained via borohydride reduction of imine **4a.** The displayed configuration of the newly created stereogenic center relative to the known absolute stereochemistry of the phenethyl moiety establishes the former as (*S*).

The reduction of imines **4** to the amines **5** was investigated under various other conditions and reagents. With $NaBH_4$ in MeOH, the stereoselectivity was unaltered in the range 0 → −78 °C. DIBAL-H afforded moderate selectivity (72:28) in CH_2Cl_2 and negligible selectivity in THF, both at −78 °C. Lithium aluminum hydride also afforded moderate selectivity (80:20) in THF at −78 °C. The diastereomer ratios are based on the ^1H NMR integration of the proton at the newly-created stereocenter adjacent to 'R' in **5.**

The cleavage of the *N*-phenethyl group in amines **5** was accomplished by hydrogenation in the presence of $Pd(OH)_2/C$, in MeOH at room temperature, to afford the *C*-protected chiral amino acids **6** in high yields. These are enantiomerically pure, since the hydrogenolysis should occur without disturbing the newly-created stereocenter in **5.**



Scheme 2. Explanation for the observed stereoselectivity in the reduction of **4** to **5,** based on the formation of the *Z*-imine **4** and subsequent hydride delivery from the top *Re* face as shown, to form **5.**

Furthermore, although the reductive amination strategy has matured in recent decades, its application to amino acid synthesis is still evolving. The reductive amination of carbonyl compounds has generally been carried out by hydrogenation or borohydride reduction of the intermediate imine species.[16,17] The reductive amination of α-keto acids with enzymes or metal catalysts has also been reported.[18,19] It would thus be useful to extend this strategy to include relatively inexpensive chiral auxiliaries and reducing agents, hence the present studies.

It is noteworthy that chiral-auxiliary based approaches lead to homochiral products upon cleavage of the auxiliary, a level of enantiopurity rarely achieved with chiral catalysis. These approaches apparently define a 'middle ground' in between the catalytic asymmetric synthesis and the resolution of the racemate. The auxiliary-based approach thus possesses the advantages of both: the preferential formation of one of the enantiomers (as in catalytic synthesis) and access to homochiral products (as in resolution).

3. Conclusion

We have developed an auxiliary-based approach to chiral amino acids by the reductive amination of the chiral imine of carboxyl pro-

tected α-keto acids. The chirality is induced by a 1-(*S*)-phenethyl unit on the imine nitrogen atom. Our strategy is characterized by high yields and diastereoselectivity in the reductive amination step. Chromatographic separation of the diastereomers and cleavage of the auxiliary in a straightforward fashion give carboxyl-protected amino acids, which are essentially enantiomerically homogeneous. It is noteworthy that an auxiliary-based approach generally possesses certain characteristic advantages, in particular the preferential formation of an essentially homochiral end-product.

4. Experimental

4.1. General comments

Instruments employed: JASCO 410 (FTIR); Bruker AV-400 (NMR); Micromass Q-TOF AMPS MAX 10/6A (HRMS); Stuart SMP10 (melting point); Büchi Rotavapor R-200 (rotary evaporator). The methyl ester **1** was prepared as reported previously.[11] Upon aqueous work-up and extraction, extracts were generally dried over $MgSO_4$ prior to evaporation of the solvent in vacuo on a rotary evaporator. Melting points (mps) are uncorrected. IR spectra were recorded neat and the values are quoted in cm^{-1}. NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal standard at either 400 MHz (δ_H) or 100 MHz (δ_C); the coupling constants (*J*) are in Hz. The NMR assignments indicate atom connectivity only, with the assigned atom or group in italics; substituents (including H) are generally now shown and subscripts (C_2 etc.) indicate chain length (not skeletal numbering).

4.2. 2,4,10-Trioxaadamantan-3-carboxylic acid piperidine amide 2[12,13]

Methyl ester **1** (5 mmol) in dry THF (10 mL) was treated with $MgCl_2$ (5.5 mmol) at 25 °C. The resulting slurry was stirred for 5 min, and treated with piperidine (20 mmol), dropwise over 5 min., with stirring which was continued for 12 h. Water was then added to the reaction mixture which was extracted with EtOAc (3×25 mL). The extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded amide **2** as a pale yellow solid (94%); mp 209–211 °C (lit. [5] 211–212 °C); υ_{max} 2972, 2952, 2936, 2856 (all C–H stretch), 1660 (amide *C*=O), 1203, 1123, 1030, 990; δ_H 4.55 (3H, br s, OC*H*), 3.86–3.84 (2H, m) and 3.56–3.54 (2H, m) (distinct NCH_2 due to partial double bond of CO–N by amide resonance), 2.77–2.74 (3H, d, *J* 12.8, OCCH_{eq}), 1.78–1.75 (3H, d, *J* 12.8, OCCH_{ax}), 1.63–1.54 (6H, m, NCC*H* + NCCC*H*); δ_C 161.53 (*C*=O), 105.60 (OC_3), 69.00 ($OC_{1,5,7}$), 47.57 and 44.22 (distinct N*C*), 32.64 ($OCC_{6,8,9}$), 26.37 and 25.60 (distinct NC*C*), 24.54 (NCC*C*); HRMS *m/z* calcd for $C_{13}H_{19}NO_4$+Na 276.1212, found 276.1210.

4.3. Ketones 3[13]

The Grignard reagents were generally prepared from Mg turnings (15 mmol) in dry THF (7 ml) under N_2, with reaction being initiated with a speck of I_2. This stirred suspension was treated dropwise with the alkyl halide (10 mmol) over 10 min, thus achieving gentle reflux, and stirring was continued for a further 30 min. This was added to amide **2** (0.100 g, 0.4 mmol) in a ratio of 0.6:0.4 in refluxing THF (5 mL) over 5 min., with the reflux being continued for 3 h. The mixture was cooled to room temperature and quenched cautiously with saturated NH_4Cl. The crude product was extracted into EtOAc, and finally purified by column chromatography (SiO_2) to afford the C-protected-α-keto acids **3**.

General spectroscopic features: The δ_H and δ_C of the trioxaadamantyl moiety occur at similar values to those in **2** as assigned above, and are not assigned again. The other resonances are assigned. Similarly, the IR C–H stretch occurs at ~2900 cm^{-1} and is not assigned.

4.4. Ethyl 2,4,10-trioxaadamant-3-yl ketone 3a

White solid, mp 122–123 °C; υ_{max} 2980, 2943, 1747 (C=O), 1318, 1131, 1086, 979, 964; δ_H 4.51 (3H, br s), 2.74–2.68 (5H, m, OCCH_{eq} + –CO–CH_2), 1.80–1.77 (3H, d, *J* 12.8), 1.60 (3H, t, *J* 7.2, *Me*); δ_C 199.89 (*C*=O), 105.56, 68.83, 32.86, 28.82 (–CO–*C*), 7.01 (C_{Me}); HRMS: *m/z* calcd for $C_{10}H_{14}O_4$ + Na 221.0790, found 221.0793.

4.5. *n*-Propyl 2,4,10-trioxaadamant-3-yl ketone 3b

White solid, mp 101–103 °C; υ_{max} 2968, 2940, 1747 (C=O), 1311, 1125, 1117, 1087, 1044, 1007, 983; δ_H 4.51 (3H, br s), 2.74–2.71 (3H, d, *J* 12.8), 2.65 (2H, t, *J* 7.2, –CO–CH_2), 1.80–1.77 (3H, d, *J* 12.8), 1.66–1.57 (2H, m, –CO–C–CH_2), 0.92 (3H, t, *J* 7.2, *Me*); δ_C 199.16 (*C*=O), 105.49, 68.86, 37.39 (–CO–*C*), 32.89, 16.37 (–CO–C*C*), 13.59 (C_{Me}); HRMS: *m/z* calcd for $C_{11}H_{16}O_4$+Na 235.0946, found 235.0943.

4.6. *n*-Hexyl 2,4,10-trioxaadamant-3-yl ketone 3c

White solid, mp 94–95 °C; υ_{max} 2962, 2934, 1744 (C=O), 1314, 1127, 1087, 989, 975; δ_H 4.51 (3H, br s), 2.74–2.71 (3H, d, *J* 12.8), 2.66 (2H, t, *J* 7.6, –CO–CH_2), 1.80–1.76 (3H, d, *J* 12.8), 1.61–1.54 (2H, m, –CO–C–CH_2), 1.34–1.24 (6H, m, remaining CH_2 of the hexyl moiety), 0.87 (3H, t, *J* 7.2, *Me*); δ_C 199.31 (*C*=O), 105.52, 68.86, 35.52 (–CO–*C*), 32.89, 31.50 (–CO–C*C*), 28.70 (–CO–C_2*C*), 22.83 (–CO–C_3*C*), 22.44 (–CO–C_4*C*), 13.98 (C_{Me}); HRMS: *m/z* calcd for $C_{14}H_{22}O_4$+Na 277.1416, found 277.1415.

4.7. *iso*-Butyl 2,4,10-trioxaadamant-3-yl ketone 3d

White solid, mp 102–103 °C; υ_{max} 2979, 2958, 2936, 1747 (*C*=O), 1311, 1124, 1086, 1010, 991; δ_H 4.51 (3H, br s), 2.74–2.71 (3H, d, *J* 12.8), 2.56–2.55 (2H, d, *J* 6.8, –CO–CH_2), 2.23–2.13 (1H, m, Me_2C*H*), 1.79–1.76 (3H, d, *J* 12.8), 0.93–0.91 (6H, d, *J* 6.8, 2 x *Me*); δ_C 198.62 (*C*=O), 105.40, 68.87, 44.30 (–CO–*C*), 32.90, 23.41 (Me_2*C*), 22.49 (C_{Me}); HRMS: *m/z* calcd for $C_{12}H_{18}O_4$ + Na 249.1103, found 249.1104.

4.8. 3-Methylbutyl 2,4,10-trioxaadamant-3-yl ketone 3e

White solid, mp 100–101 °C; υ_{max} 2963, 2957, 2931, 1745 (C=O), 1310, 1124, 1118, 1086, 1044, 994; δ_H 4.52 (3H, br s), 2.74–2.71 (3H, d, *J* 12.8), 2.67 (2H, t, *J* 7.6, –CO–CH_2), 1.80–1.77 (3H, d, *J* 12.8), 1.61–1.45 (3H, m, –CO–CCH_2 + Me_2C*H*), 0.90–0.88 (6H d, *J* 6.4, $2 \times$ *Me*); δ_C 199.47 (*C*=O), 105.57, 68.87, 33.54 (–CO–*C*), 32.89, 31.64 (–CO–C*C*), 27.59 (Me_2*C*), 22.32 (C_{Me}); HRMS: *m/z* calcd for $C_{13}H_{20}O_4$+Na 263.1259, found 263.1257.

4.9. Benzyl 2,4,10-trioxaadamant-3-yl ketone 3f

White solid, mp 181–184 °C; υ_{max} 2969, 2939, 1749 (C=O), 1312, 1118, 1084, 1010, 992; δ_H 7.32–7.18 (5H, m, Ar*H*), 4.54 (3H, br s), 3.99 (2H, s, PhCH_2), 2.76–2.73 (3H, d, *J* 12.8), 1.80–1.77 (3H, d, *J* 12.8); δ_C 196.04 (*C*=O), 133.63 (C_{Ar}), 129.89 (C_{Ar}), 128.26 (C_{Ar}), 126.71 (C_{Ar}), 105.74, 68.98, 41.94 (–CO–*C*), 32.87; HRMS: *m/z* calcd for $C_{15}H_{16}O_4$+Na 283.0946, found 283.0945.

4.10. Reductive amination of ketones 3 to amines 5

The ketone (0.25 mmol) in toluene (5 mL) was treated with (*S*)-(−)-α-methylbenzylamine (39 μL, 0.3 mmol) and triethylamine

(87 μL, 0.625 mmol) with stirring. The mixture was cooled to 0 °C and treated dropwise with titanium(IV) chloride (15 μL, 0.13 mmol). The stirred reaction mixture was refluxed for 12 h. Upon cooling to room temperature, the mixture was filtered to remove the precipitated TiO_2 and $Et_3N{\cdot}HCl$. The filter cake was washed with toluene and the combined organic layers were concentrated under reduced pressure. The resulting crude imine product **4** was used for the following step. The crude imine was taken into dry methanol at 0 °C and treated with $NaBH_4$ (10 mg, 0.25 mmol). The mixture was stirred for 1 h and cautiously quenched by the addition of water (2 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the extracts washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified chromatographically over neutral Al_2O_3 to obtain the diastereomerically pure phenethyl amines *l*-**5.**

General spectroscopic features: The δ_H and δ_C of the trioxaadamantyl moiety occur at similar values to those in **2** as assigned above, and are not assigned again (*cf.* **3**). The other resonances are assigned. Similarly, the IR C–H stretch occurs at ~2900 cm^{-1} and is not assigned; the N–H stretch occurs at ~3345 cm^{-1} and is assigned.

4.11. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)propyl amine 5a

White solid, mp 101–103 °C; $[\alpha]_D^{24} = -98.1$ (*c* 1, $CHCl_3$); υ_{max} 3358 (N–H), 2963, 2931, 2872, 1598 (C=C), 1315, 1136, 1027, 971; δ_H 7.36–7.34 (2H, m, Ar*H*), 7.29–7.26 (2H, m, Ar*H*), 7.20–7.17 (1H, m, Ar*H*), 4.40 (3H, br s), 4.26–4.21 (1H, q, *J* 6.4, PhC*H*), 2.60–2.57 (3H, d, *J* 12.8), 2.27–2.24 (1H, dd, *J* 3.2 and 9.2, NC*H*), 1.72–1.68 (3H, d, *J* 12.8), 1.65–1.55 (2H, m, N*H* + diastereotopic MeC*H*), 1.33–1.32 (3H, d, *J* 6.4, PhC*Me*), 1.20–1.11 (1H, m, diastereotopic MeC*H*), 0.69 (3H, t, *J* 7.2, CH_2Me); δ_C 146.52 (C_{Ar}), 127.86 (C_{Ar}), 127.47 (C_{Ar}), 126.40 (C_{Ar}), 112.19, 67.75, 62.07 (NCPh), 56.80 (NCEt), 33.17, 24.83 (PhC*Me*), 22.98 (Me*C*), 10.93 (C_{Me}); HRMS: *m/z* calcd for $C_{18}H_{25}NO_3$+H 304.1913, found 304.1912.

4.12. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)butyl amine 5b

Colorless liquid; $[\alpha]_D^{24} = -110.9$ (*c* 1.38, $CHCl_3$); υ_{max} 3349 (N–H), 2958, 2931, 2870, 1595 (C=C), 1314, 1135, 988; δ_H 7.35–7.30 (2H, m, Ar*H*), 7.29–7.25 (2H, m, Ar*H*), 7.21–7.16 (1H, m, Ar*H*), 4.40 (3H, br s), 4.27–4.22 (1H, q, *J* 6.8, PhC*H*), 2.61–2.58 (3H, d, *J* 12.8), 2.33–2.30 (1H, dd, *J* 3.2 and 9.8, NC*H*), 1.71–1.68 (3H, d, *J* 12.8), 1.62 (1H, br s, N*H*), 1.53–1.45 (1H, m, diastereotopic MeCC*H*), 1.39–1.25 (4H, m, PhC*Me* + diastereotopic MeCC*H*), 1.17–1.07 (1H, m, diastereotopic MeC*H*), 0.99–0.88 (1H, m, diastereotopic MeC*H*), 0.65 (3H, t, *J* 7.2, CH_2Me); δ_C 146.45 (C_{Ar}), 127.90 (C_{Ar}), 127.51 (C_{Ar}), 126.44 (C_{Ar}), 112.26, 67.78, 60.20 (NCPh), 56.74 (NCPr), 33.18, 32.35 (MeCC), 24.84 (PhC*Me*), 19.34 (Me*C*), 14.06 (C_{Me}); HRMS: *m/z* calcd for $C_{19}H_{27}NO_3$+H 318.2069, found 318.2068.

4.13. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)heptyl amine *l*-5c

Colorless liquid; $[\alpha]_D^{24} = -73.2$ (*c* 2.2, $CHCl_3$); υ_{max} 3344 (N–H), 2956, 2928, 2857, 1598 (C=C), 1314, 1136, 1006; δ_H 7.34–7.32 (2H, m, Ar*H*), 7.28–7.24 (2H, m, Ar*H*), 7.19–7.16 (1H, m, Ar*H*), 4.39 (3H, br s), 4.26–4.21 (1H, q, *J* 6.4, PhC*H*), 2.59–2.56 (3H, d, *J* 12.8), 2.32–2.29 (1H, dd, *J* 2.8 and 9.2, NC*H*), 1.70–1.65 (4H, m, N*H* + OCCH_{ax}), 1.55–1.47 (1H, m, diastereotopic NCC*H*), 1.32–1.31 (3H, d, *J* 6.4, PhC*Me*), 1.28–1.22 (1H, m, diastereotopic NCC*H*), 1.20–1.06 [5H, m, $(CH_2)_2$ + diastereotopic C*H*], 1.04–0.88 [3H, m, (CH_2) + diastereotopic C*H*], 0.82 (3H, t, *J* 7.2, CH_2Me); δ_C 146.48 (C_{Ar}), 127.85 (C_{Ar}), 127.49 (C_{Ar}), 126.41 (C_{Ar}), 112.26, 67.75, 60.41 (NCPh), 56.83 (NCC_6H_{13}), 33.17, 30.08 (NCC), 31.85 (NC$_2$C), 29.27 (NC$_3$C), 26.09 (NC$_4$C), 24.80 (PhC*Me*), 22.56 (NC$_5$C), 14.07 (NC$_6$C); HRMS: *m/z* calcd for $C_{22}H_{33}NO_3$+H 360.2539, found 360.2538.

4.14. *N*-[(1*S*)-Phenethyl] (1*R*)-(2,4,10-trioxaadamant-3-yl)heptyl amine *u*-5c

Colorless liquid; $[\alpha]_D^{24} = -2.9$ (*c* 0.46, $CHCl_3$); υ_{max} 3343 (N–H), 2955, 2927, 2856, 1601 (C=C), 1450, 1314, 1136, 1006; δ_H 7.33–7.26 (4H, m, Ar*H*), 7.22–7.19 (1H, m, Ar*H*), 4.38 (3H, br s), 4.07–4.02 (1H, q, *J* 6.4, PhC*H*), 2.59–2.55 (3H, d, *J* 13.6), 2.48–2.46 (1H, dd, *J* 4.4 and 6.0, NC*H*), 1.78 (1H, br s, N*H*), 1.69–1.62 (4H, m, diastereotopic NCC*H* + OCCH_{ax}), 1.45–1.42 (1H, m, diastereotopic NCC*H*), 1.33–1.25 [11H, m, PhC*Me* + (CH_2)$_4$], 0.87 (3H, t, *J* 6.4, CH_2Me); δ_C 146.49 (C_{Ar}), 128.21 (C_{Ar}), 126.74 (C_{Ar}), 126.45 (C_{Ar}), 111.73, 67.86, 60.39 (NCPh), 55.19 (NCC_6H_{13}), 33.11, 31.89 (NCC), 29.79 (NC$_2$C), 29.14 (NC$_3$C), 26.60 (NC$_4$C), 23.98 (PhC*Me*), 22.69 (NC$_5$C), 14.14 (NC$_6$C); HRMS: *m/z* calcd for $C_{22}H_{33}NO_3$+H 360.2539, found 360.2538.

4.15. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)-3-methylbutylamine 5d

White solid, mp 84–86 °C; $[\alpha]_D^{24} = -90.2$ (*c* 1.8, $CHCl_3$); υ_{max} 3346 (N–H), 2955, 2866, 1597 (C=C), 1314, 1135, 1063, 998; δ_H 7.35–7.33 (2H, m, Ar*H*), 7.28–7.25 (2H, m, Ar*H*), 7.20–7.16 (1H, m, Ar*H*), 4.40 (3H, br s), 4.32–4.27 (1H, q, *J* 6.4, PhC*H*), 2.61–2.58 (3H, d, *J* 12.8), 2.38–2.34 (1H, dd, *J* 2.4 and 10.4, NC*H*), 1.71–1.68 (3H, d, *J* 12.8), 1.60–1.53 (2H, m, N*H* + diastereotopic NCC*H*), 1.32–1.31 (3H, d, *J* 6.4, PhC*Me*), 1.27–1.24 (1H, m, diastereotopic NCC*H*), 1.14–1.07 (1H, m, Me$_2$C*H*), 0.79–0.78 (3H, d, *J* 6.4, diastereotopic MeC*Me*), 0.31–0.29 (3H, d, *J* 6.4, diastereotopic *Me*CMe); δ_C 146.51 (C_{Ar}), 127.92 (C_{Ar}), 127.63 (C_{Ar}), 126.48 (C_{Ar}), 112.48, 67.78, 58.15 (NCPh), 56.54 (NCBu^i), 39.43 (NCC), 33.24, 24.76 (PhC*Me*), 24.18 (Me$_2$C), 23.83 (diastereotopic C_{Me}), 20.87 (diastereotopic C_{Me}); HRMS: *m/z* calcd for $C_{20}H_{29}NO_3$+H 332.2226, found 332.2226.

4.16. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)-4-methylpentylamine 5e

Colorless liquid; $[\alpha]_D^{24} = -72.3$ (*c* 2.15, $CHCl_3$); υ_{max} 3346 (N–H), 2955, 2868, 1601 (C=C), 1314, 1135, 1005; δ_H 7.34–7.32 (2H, m, Ar*H*), 7.28–7.25 (2H, m, Ar*H*), 7.20–7.16 (1H, m, Ar*H*), 4.39 (3H, br s), 4.24–4.19 (1H, q, *J* 6.8, PhC*H*), 2.60–2.56 (3H, d, *J* 12.8), 2.30–2.27 (1H, dd, *J* 2.8 and 8.8, NC*H*), 1.70–1.67 (4H, m, N*H* + OCCH_{ax}), 1.60–1.52 (1H, m, diastereotopic NCC*H*), 1.32–1.31 (3H, d, *J* 6.8, PhC*Me*), 1.28–1.19 (1H, m, diastereotopic NCC*H*), 1.17–1.05 (2H, m, NCCC*H*), 0.88–0.80 (1H, m, Me$_2$C*H*), 0.76–0.74 (3H, d, *J* 6.4, diastereotopic *Me*), 0.73–0.71 (3H, d, *J* 6.4, diastereotopic *Me*); δ_C 146.51 (C_{Ar}), 127.86 (C_{Ar}), 127.50 (C_{Ar}), 126.40 (C_{Ar}), 112.24, 67.75, 60.82 (NCPh), 56.90 (NCCBu^i), 35.34 (NCC), 33.18, 27.82 (NC$_2$C), 27.79 (Me$_2$C), 24.81 (PhC*Me*), 22.87 (diastereotopic C_{Me}), 22.21 (diastereotopic C_{Me}); HRMS: *m/z* calcd for $C_{21}H_{31}NO_3$ + H 346.2382, found 346.2382.

4.17. *N*-[(1*S*)-Phenethyl] (1*S*)-(2,4,10-trioxaadamant-3-yl)-2-phenethylamine 5f

White solid, mp 117–119 °C; $[\alpha]_D^{24} = -72.2$ (*c* 0.49, $CHCl_3$); υ_{max} 3344 (N–H), 2956, 2928, 2857, 1598 (C=C), 1314, 1136, 1006, 972; δ_H 7.18–7.17 (3H, m, Ar*H*), 7.06–6.98 (5H, m, Ar*H*), 6.68–6.66 (2H, d, *J* 7.2, Ar*H*), 4.44 (3H, br s), 4.20–4.15 (1H, q, *J* 6.8, PhC*H*), 3.06–3.02 (1H, dd, *J* 2.8 and 13.6, NC*H*), 2.65–2.57 (4H, m, diastereotopic NCC*H* + OCCH_{eq}), 2.42–2.36 (1H, dd, *J* 11.2 and 13.6, diastereotopic NCC*H*), 1.74–1.71 (3H, d, *J* 12.8), 1.55 (N*H* + H_2O), 1.19–1.17 (3H, d,

J 6.8, diastereotopic PhC*Me*); δ_C 145.63 (C_{Ar}), 139.72 (C_{Ar}), 129.75 (C_{Ar}), 128.00 (C_{Ar}), 127.79 (C_{Ar}), 126.81 (C_{Ar}), 125.93 (C_{Ar}), 125.68 (C_{Ar}), 111.90, 67.91, 61.38 (NCPh), 56.40 (NCBn), 36.13 ($PhCH_2$), 33.22, 24.77 (PhC*Me*); HRMS: *m/z* calcd for $C_{23}H_{27}NO_3$+H 366.2069, found 366.2069.

4.18. Hydrogenolysis of the phenethyl amines 5 to C-protected amino acids 6

A solution of **5** (0.15 mmol) in methanol (5 mL) was treated with $Pd(OH)_2$ (0.01 mmol) under dry argon. The reaction mixture was hydrogenated for 16 h at 4 atmosphere pressure. The mixture was then filtered through a pad of celite, which was washed with methanol. The filtrate was concentrated in vacuo and the residue column chromatographed on basic Al_2O_3 to obtain the C-protected amino acids **6.**

General spectroscopic features: The δ_H and δ_C of the trioxaadamantyl moiety occur at similar values to those in **2** as assigned above, and are not assigned again (*cf.* **3** and **5**). The other resonances are assigned. Similarly, the IR C–H stretch occurs at ~2900 cm^{-1} and is not assigned; the N–H stretch occurs at ~3370–3400 cm^{-1} and the N–H deformation ('def.') at ~1610 cm^{-1} and are assigned.

4.19. (1*S*)-(2,4,10-Trioxaadamant-3-yl)propylamine 6a

White solid, mp 98–100 °C; $[\alpha]_D^{24} = -14.1$ (*c* 0.8, $CHCl_3$); υ_{max} 3382 (N–H), 2954, 1613 (N–H def.), 1313, 1136, 1062, 1007, 949; δ_H 4.40 (3H, br s), 2.59–2.47 (4H, m, OCH_{eq} + NC*H*), 1.81–1.75 (1H, m, diastereotopic MeC*H*), 1.72–1.69 (3H, d, *J* 12.8), 1.41 (2H, br s, NH_2), 1.28–1.17 (1H, m, diastereotopic MeC*H*), 0.99 (3H, t, *J* 7.2, *Me*); δ_C 110.77, 68.01, 59.14 (NC), 33.14, 22.93 (NCC), 11.25 (C_{Me}); HRMS: *m/z* calcd for $C_{10}H_{17}NO_3$+H 200.1287, found 200.1289.

4.20. (1*S*)-(2,4,10-Trioxaadamant-3-yl)butylamine 6b

Colorless liquid; $[\alpha]_D^{24} = -35.7$ (*c* 3.8, $CHCl_3$); υ_{max} 3391 (N–H), 2958, 2929, 2872, 1614 (N–H def.), 1353, 1315, 1133, 1011, 993; δ_H 4.40 (3H, br s), 2.63–2.56 (4H, m, OCH_{eq} + NC*H*), 1.73–1.67 (4H, m, OCH_{ax} + diastereotopic NCC*H*), 1.64 (2H, br s, NH_2), 1.60–1.52 (1H, m, diastereotopic NCC*H*), 1.40–1.29 (1H, m, diastereotopic MeC*H*), 1.27–1.16 (1H, m, diastereotopic MeC*H*), 0.92 (3H, t, *J* 7.2, *Me*); δ_C 110.76, 68.05, 57.36(NC), 33.14, 32.06 (NCC), 19.84 (MeC), 14.17 (C_{Me}); HRMS: *m/z* calcd for $C_{11}H_{19}NO_3$+H 214.1443, found 214.1447.

4.21. (1*S*)-(2,4,10-Trioxaadamant-3-yl)heptylamine 6c

Colorless liquid; $[\alpha]_D^{24} = -14.5°$ (c 1.25, $CHCl_3$); υ_{max} 3390 (N–H), 2954, 2927, 2856, 1612 (N–H def.), 1312, 1136, 1063, 1011, 970; δ_H 4.40 (3H, br s), 2.59–2.56 (4H, m, OCH_{eq} + NC*H*), 1.74–1.69 (4H, m, OCH_{ax} + diastereotopic NCC*H*), 1.59–1.51 (3H, m, NH_2 + diastereotopic NCC*H*), 1.34–1.15 [8H, m, Me(CH_2)$_4$], 0.87 (3H, t, *J* 6.4, *Me*); δ_C 110.78, 68.02, 57.68 (NC), 33.13, 31.79 (NCC), 29.96 (NC_2C), 29.46 (NC_3C), 26.72 (NC_4C), 22.61 (NC_5C), 14.05 (C_{Me}); HRMS: *m/z* calcd for $C_{14}H_{25}NO_3$+H 256.1913, found 256.1913.

4.22. (1*S*)-(2,4,10-Trioxaadamant-3-yl)-3-methylbutylamine 6d

Colorless liquid. $[\alpha]_D^{24} = -17.6$ (*c* 0.64, $CHCl_3$); υ_{max} 3374 (N–H), 2956, 1612 (N–H def.), 1312, 1133, 1064, 1008; δ_H 4.40 (3H, br s), 2.70–2.66 (1H, dd, *J* 2.4 and 14.8, NC*H*), 2.59–2.56 (3H, d, *J* 12.8), 1.86–1.76 (1H, m, diastereotopic NCC*H*), 1.72–1.69 (3H, d, *J* 12.8), 1.60 (2H, br s, NH_2), 1.48–1.41 (1H, m, diastereotopic NCC*H*), 1.25–1.18 (1H, m, Me_2CH), 0.94–0.93 (3H, d, *J* 6.4, diastereotopic *Me*), 0.89–0.88 (3H, d, *J* 6.4, diastereotopic *Me*); δ_C 110.89, 68.07, 55.43 (NC), 38.76 (NCC), 33.16, 24.52 (Me_2C), 24.11 (diastereotopic C_{Me}), 21.19 (diastereotopic C_{Me}); HRMS: *m/z* calcd for $C_{12}H_{21}NO_3$+H 228.1600, found 228.1606.

4.23. (1*S*)-(2,4,10-Trioxaadamant-3-yl)-4-methylpentylamine 6e

Colorless liquid. $[\alpha]_D^{24} = -17.6$ (*c* 1.7, $CHCl_3$); υ_{max} 3383 (N–H), 2956, 2929, 1607 (N–H def.), 1353, 1131, 1315, 1063, 1013; δ_H 4.40 (3H, br s), 2.60–2.54 (4H, m, OCH_{eq} + NC*H*), 1.77–1.69 (4H, m, OCH_{ax} + NCC*H*), 1.57–1.49 (3H, m, NH_2 + diastereotopic NCC*H*), 1.46–1.36 (1H, m, Me_2CH), 1.25–1.12 (2H, m, NC_2CH), 0.90–0.89 (3H, d, *J* 3.2 Hz, diastereotopic *Me*), 0.885–0.877 (3H, d, *J* 3.2 Hz, diastereotopic *Me*); δ_C 110.78, 68.03, 57.99 (NC), 36.06 (NCC), 33.13, 28.25 (NC_2C), 27.77 (Me_2C), 22.89 (diastereotopic C_{Me}), 22.40 (diastereotopic C_{Me}); HRMS: *m/z* for $C_{13}H_{23}NO_3$+H, calcd for 242.1756; found: 242.1756.

4.24. (1*S*)-(2,4,10-Trioxaadamant-3-yl)-2-phenethylamine 6f

White solid, mp 118–120 °C; $[\alpha]_D^{24} = -23.7$ (*c* 2.8, $CHCl_3$); υ_{max} 3407 (N–H), 2956, 2929, 1607 (N–H def.), 1353, 1316, 1131, 1014; δ_H 7.30–7.17 (5H, m, Ar*H*), 4.45 (3H, br s), 3.17–3.13 (1H, dd, *J* 2.0 and 13.6, NC*H*), 2.98–2.95 (1H, dd, *J* 2.0 and 10.8, diastereotopic PhC*H*), 2.64–2.61 (3H, d, *J* 12.4), 2.48–2.42 (1H, dd, *J* 10.8 and 13.6, diastereotopic PhC*H*), 1.75–1.72 (3H, d, *J* 12.8), 1.50 (2H, br s, NH_2); δ_C 139.89 (C_{Ar}), 129.35 (C_{Ar}), 128.26 (C_{Ar}), 125.95 (C_{Ar}), 110.46, 68.13, 58.81 (NC), 36.56 (NCC), 33.11; HRMS: *m/z* calcd for $C_{15}H_{19}NO_3$+H 262.1443, found 262.1445.

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