Supporting information for

'Stereocontrolled Access to an Optically-enriched Oxabispidines'

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General information

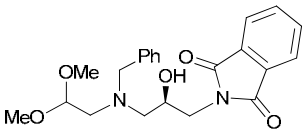
Reactions were carried out in oven-dried glassware under a nitrogen atmosphere. NMR spectra were recorded using a 300 MHz Varian, 400 MHz Varian or 500 MHz Bruker spectrometer (as specified). Chemical shifts are reported in ppm, and coupling constants in Hertz. $CDCl_3$ was referenced at δ 7.26 and 77.16 ppm.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea.

(*S*)-(-)-2,3-Epoxypropylphthalimide was purchased from DAISO Chemical Company, Japan.

Preparation of Oxazine 11

(*R*)-2-{3-[Benzyl-(2,2-dimethoxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione



A stirred solution of *N*-benzyl-2,2-dimethoxyethanamine **7**[i] (48 g, 0.25 mol) and (*S*)-(-)-*N*,*N*-(2,3,-epoxypropyl)phthalimide **6** (50 g, 0.25 mol) in ethanol (1 L) was heated at reflux for 20 h. Removal of solvent by evaporation under reduced pressure yielded (*R*)-2-{3-[benzyl-(2,2-dimethoxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione as a yellow oil (98 g, 100**%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55-2.78 (4H, m, BnN*CH*$_2$CHOH and BnN*CH*$_2$CH(OMe)$_2$), 3.26 (3H, s, OC*H*$_3$), 3.28 (3H, s, OC*H*$_3$), 3.61-3.82 (4H, m, PhC*H*$_2$ and PhthNC*H*$_2$), 3.87-3.98 (1H, m, C*H*OH), 4.29 (1H, dd, *J* 6.2, 4.9, C*H*(OMe)$_2$), 7.19-7.33 (5H, m, Ar-*H*), 7.71 (2H, dd, *J* 5.4, 3.0, Ar-*H*), 7.84 (2H, dd, *J* 5.4, 3.0, Ar-*H*);

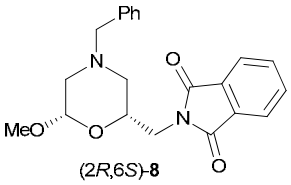
^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.7, 53.7, 53.9, 56.0, 60.7, 67.0, 103.7, 123.5, 127.3, 128.5, 129.1, 132.0, 134.2, 138.5, 168.5;

HRMS *m/z* Calculated for $C_{22}H_{27}N_2O_5$ (M^++H): 399.1914. Found: 399.1909;

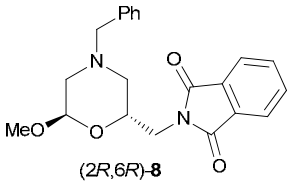
IR (neat) ν_{max}: 3434, 2937, 1767, 1707, 1395, 1069 cm^{-1};

$[\alpha]_D^{20}$ +18.2 (*c* 1.0 in $CHCl_3$).

(2*R*,6*S*)- and (2*R*,6*R*)-2-[(4-Benzyl-6-methoxymorpholin-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione 8



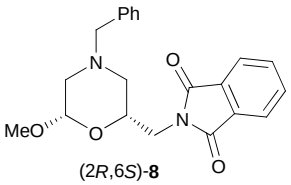
(2*R*,6*S*)-**8**



(2*R*,6*R*)-**8**

A stirred solution of (*R*)-2-{3-[benzyl-(2,2-dimethoxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione (98 g, 0.25 mol), prepared as above, and *para*-toluenesulfonic acid monohydrate (4.76 g, 25 mmol) in toluene (2 L) was heated at reflux for 18 h. The cooled reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5% w/v), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a 65:35 mixture of (2*R*,6*S*)- and (2*R*,6*R*)-**8** as a yellow-brown solid (75 g, 100%).

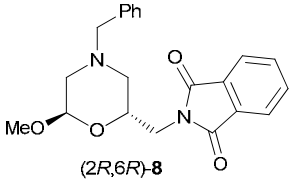
For analytical purposes separation of the two diastereomers was carried out by flash column chromatography on silica gel, eluting with ethyl acetate–*iso*-hexane. However, the (2*R*,6*R*)-isomer proved to be unstable in contact with silica, and could not be obtained in an analytically pure state. Comparison of spectra for pure (2*R*,6*S*) and the diastereomeric mixture enabled a full spectral assignment to be made.



(2*R*,6*S*)-**8**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.91 (1H, dd, *J* 11.0, 8.5, 5-H_{ax}), 2.02 (1H, dd, *J* 11.0, 10.1, 3-H_{ax}), 2.74 (1H, d, *J* 11.1, 3-H_{eq}), 2.80 (1H, d, *J* 10.6, 5-H_{eq}), 3.39 (3H, s, OCH_3), 3.44 (1H, d, *J* 13.0, CH_2Ph), 3.57 (1H, d, *J* 13.0, CH_2Ph), 3.77 (1H, dd, *J* 13.5, 6.0, CH_2NPhth), 3.89 (1H, dd, *J* 13.5, 6.4, CH_2NPhth), 3.93-3.99 (1H, m, 2-*H*); 4.44 (1H, dd, *J* 8.5, 2.4, 6-*H*), 7.21-7.32 (5H, m, Ar-*H*), 7.72 (2H, dd, *J* 5.5, 3.0, Ar-*H*), 7.86 (2H, dd, *J* 5.5, 3.0, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.0, 55.5, 56.0, 56.1, 62.5, 71.4, 100.2, 123.3, 127.2, 128.3, 129.1, 132.0, 134.0, 137.3, 168.1.



(2*R*,6*R*)-**8**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.91 (1H, dd, *J* 11.0, 8.5, 5-H_{ax}), 2.02 (1H, dd, *J* 11.0, 10.1, 3-H_{ax}), 2.74 (1H, d, *J* 11.1, 3-H_{eq}), 2.80 (1H, d, *J* 10.6, 5-H_{eq}), 3.24 (3H, s, OCH_3), 3.48 (1H, d, *J* 13.0, CH_2Ph), 3.54 (1H, d, *J* 13.0, CH_2Ph), 3.63 (1H, dd, *J* 13.9, 4.9, CH_2NPhth), 3.89-3.95 (2H, m, CH_2NPhth and 2-*H*), 4.69 (1H, t, *J* 2.3, 6-*H*), 7.23-7.31 (5H, m, Ar-*H*), 7.72 (2H, ddd, *J* 5.5, 3.1, 1.1, Ar-*H*), 7.86 (2H, ddd, *J* 5.5, 3.1, 0.8, Ar-*H*);

^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.1, 55.0, 55.3, 56.1, 63.1, 66.6, 97.0, 123.5, 127.3, 128.3, 129.3, 132.0, 134.2, 136.8, 168.2;

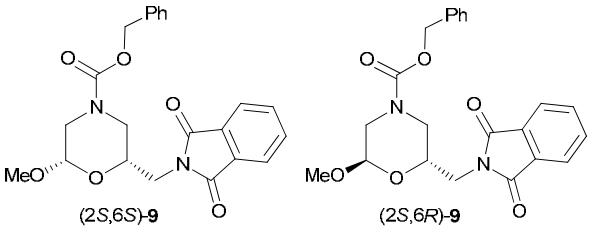
Analysis of (2*R*,6*S*)- and (2*R*,6*R*)-**8** ***mixture***

Mp: 128-130 °C;

IR (neat) ν_{max}: 2925, 2853, 1774, 1715, 1396 cm^{-1};

HRMS *m/z* Calculated for $C_{21}H_{23}N_2O_4$ (M^++H): 367.1652. Found: 367.1647.

(2*S*,6*S*)- and (2*S*,6*R*)-Benzyl 2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-6-methoxymorpholine-4-carboxylate 9



Benzyl chloroformate (37 mL, 0.25 mol) was added to a stirred solution of **8** (75 g, 0.25 mol), prepared as above, in dichloromethane (0.75 L) and stirring continued at room temperature overnight. The solvent was evaporated under reduced pressure to yield a 65:35 mixture of (2*S*,6*S*)- and (2*S*,6*R*)-**9** as a brown oil contaminated with benzyl chloride (110 g). The crude mixture was used without further purification in the subsequent step.

Analysis of purified sample of (2*S*,6*S*)- and (2*S*,6*R*)-**9**:

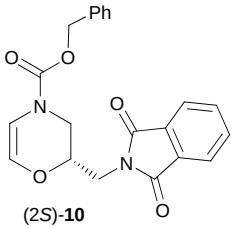
^{1}H NMR (300 MHz, $CDCl_3$) δ: δ: 2.69-2.95 (1H, m, 5-H_{ax}), 3.13 (1H, dd, *J* 13.5, 2.7, 3-H_{ax}), 3.24 (3H, s, OCH_3, minor isomer), 3.41 (3H, s, OCH_3, major isomer), 3.64-4.11 (5H, m, CH_2Phth, 3-H_{eq}, 5-H_{eq} and 2-*H*, minor isomer), 4.16-4.29 (1H, m, 2-*H*, major isomer), 4.37 (1H, dd, *J* 8.6, 2.6, 6-*H*, major isomer), 4.64 (1H, s, 6-*H*, minor isomer), 5.12 (2H, d, *J* 4.8, CH_2Ph), 7.15-7.43 (5H, m, Ar-*H*), 7.66-7.90 (4H, m, Ar-*H*);

^{13}C NMR (75 MHz, $CDCl_3$) δ: 39.6, 42.2, 46.1, 46.3, 54.6, 56.1, 64.9, 67.4, 71.1, 95.6, 99.1, 123.5, 128.0, 128.4, 128.5, 128.6, 128.7, 131.9, 134.1, 137.5, 168.0, 168.1;

IR (neat) ν_{max}: 2939, 1774, 1710, 1393, 1239 cm^{-1};

HRMS *m/z* Calculated for $C_{22}H_{23}N_2O_6$ (M^++H): 411.1551. Found: 411.1552.

(*S*)-Benzyl 2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2,3-dihydro-4*H*-1,4-oxazine-4-carboxylate 10



(2*S*)-**10**

A stirred solution of **9** (110 g, 0.25 mol), prepared as above, and *p*-toluenesulfonic acid monohydrate (4.76 g, 25 mmol) in toluene (2 L) was heated at reflux overnight. The cooled solution was washed with aqueous sodium hydrogen carbonate solution (5 %w/v), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel, eluting with *iso*-hexane:ethyl acetate (60:40) to yield **10** as a pale yellow gum (63.4 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.38 (1H, dd, *J* 13.2, 7.3, 3-H_2, major rotamer), 3.45 (1H, dd, *J* 13.1, 7.0, 3-H_2, minor rotamer), 3.73-3.81 (1H, m, CH_2NPhth), 3.92-4.05 (2H, m, 3-H_2 and CH_2NPhth), 4.27-4.36 (1H, m, 2-*H*), 5.18 (2H, s, CH_2Ph), 5.85 (1H, d, *J* 5.0, 5-*H*, major rotamer), 5.97 (1H, d, *J* 5.0, 5-*H*, minor rotamer), 6.24 (1H, d, *J* 5.0, 6-*H*, major rotamer), 6.37 (1H, d, *J* 5.0, 6-*H*, minor rotamer), 7.28-7.46 (5H, m, Ar-*H*), 7.73 (2H, dd, *J* 5.4, 3.0, Ar-*H*), 7.87 (2H, dd, *J* 5.4, 3.0, Ar-*H*);

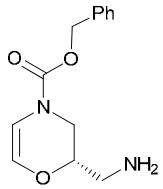
^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.8, 43.3, 43.9, 67.8, 67.9, 70.5, 71.0, 105.6, 106.1, 123.5, 128.0, 128.2, 128.3, 128.4, 128.7, 129.0, 132.0, 134.3, 136.1, 151.9, 152.3, 168.1;

HRMS *m/z* Calculated for $C_{21}H_{19}N_2O_5$ (M^++H): 379.1288. Found: 379.1282;

IR (neat) ν_{max}: 3035, 1777, 1699, 1656, 1400;

$[\alpha]_D^{21}$ -7.9 (*c* 1.0 in $CHCl_3$).

(*S*)-Benzyl 2-(aminomethyl)-2,3-dihydro-4*H*-1,4-oxazine-4-carboxylate 11



(2*S*)-**11**

Method 1 – Use of hydrazine

A stirred solution of **10** (18.9 g, 50 mmol) in hydrazine (0.5M in tetrahydrofuran, 0.4 L) was stirred at room temperature for 3 days. The reaction mixture was quenched with water (1 L) and extracted with 2-methyltetrahydrofuran (2 x 1 L). The organic extract was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to yield **11** as a light coloured gum (8.8 g, 70%).

Method 2 – Use of methylamine[ii]

To a solution of **10** (2.0 g, 5.3 mmol) in EtOH (53 mL) was added $MeNH_2$ (33% in EtOH, 2.0 mL, 15.9 mmol). The mixture was heated at 70°C for 4 h. After allowing the reaction to cool to ambient temperature, water was added (50 mL) and the mixture was then acidified with 2M HCl (pH 2) and washed with diethyl ether. The organic layer was discarded and the aqueous layer was basified with solid KOH (pH >10) then extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to yield **11** as a light coloured waxy solid (1.15 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (2H, brs, N*H*$_2$), 2.88 (2H, dd, *J* 11.4, 5.7, C*H*$_2$NH$_2$), 3.21 (1H, dd, *J* 12.8, 8.5, 3-*H*$_2$, major rotamer), 3.28 (1H, dd, *J* 12.5, 8.7, 3-*H*$_2$, minor rotamer), 3.80-3.90 (1H, m, 2-*H*), 3.95 (1H, d, *J* 12.9, 3-*H*$_2$, minor rotamer), 4.04 (1H, d, *J* 13.0, 3-*H*$_2$, major rotamer), 5.19 (2H, s, C*H*$_2$Ph), 5.92 (1H, d, *J* 4.7, 5-*H*, major rotamer), 6.05 (1H, d, *J* 4.5, 5-*H*, minor rotamer), 6.21 (1H, d, *J* 4.6, 6-*H*, major rotamer), 6.34 (1H, d, *J* 4.5, 6-*H*, minor rotamer), 7.32-7.42 (5H, m, Ar-*H*);

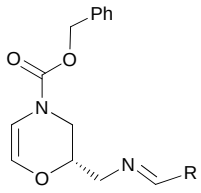
^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.6, 44.3, 67.9, 67.9, 74.7, 75.2, 105.6, 106.1, 128.3, 128.4, 128.5, 128.6, 128.8, 129.6, 136.2, 136.3, 152.2, 152.5;

IR (neat) ν_{max}: 2924, 1698, 1662, 1413, 1211;

HRMS *m/z* Calculated for $C_{13}H_{17}N_2O_3$ (M^++H) 249.1234. Found 249.1236;

$[\alpha]_D^{21}$ +6.2 (*c* 1.0 in $CHCl_3$).

General procedure for preparation of Imines 12

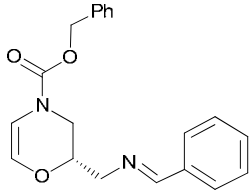


(2*S*)-**12**

A suspension of **11** and magnesium sulfate in dichloromethane was stirred at r.t. for 10 min and aldehyde was added. After an additional 10 min stirring time the magnesium sulfate was removed from the reaction mixture by filtration, giving a solution of **12** suitable for use in the subsequent transformation. For analytical purposes, a sample was removed and the solvent removed under reduced pressure.

Following the general procedure, the data are reported as follows: (a) quantity of **11**; (b) quantity of $MgSO_4$; (c) volume of dichloromethane; (d) aldehyde; and (e) quantity of aldehyde.

(*S*,*E*)-Benzyl 2-((benzylideneamino)methyl)-2*H*-1,4-oxazine-4(3*H*)-carboxylate, 12a (R = Ph)



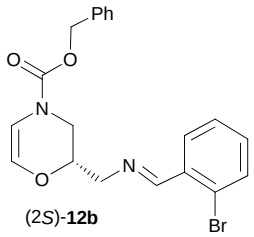
(2*S*)-**12a**

(a) 1 g, 4.03 mmol; (b) 4.85 g, 40.3 mmol; (c) 20 mL; (d) PhCHO; and (e) 0.43 g, 4.03 mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.35 (1H, dd, *J* 13.0, 8.2, 3-H_2, major rotamer), 3.51 (1H, dd, *J* 13.0, 7.6, 3-H_2, minor rotamer), 3.75-3.87 (2H, m, CH_2N=CHPh), 4.03 (1H, d, *J* 10.9, 3-H_2, minor rotamer), 4.16 (1H, d, *J* 13.0, 3-H_2, major rotamer), 4.20-4.30 (1H, m, 2-*H*), 5.16 (2H, s, CH_2Ph, minor rotamer), 5.19 (2H, s, CH_2Ph, major rotamer), 5.91 (1H, d, *J* 5.0, 5-*H*, major rotamer), 6.04 (1H, d, *J* 5.0, 5-*H*, minor rotamer), 6.23 (1H, d, *J* 4.6, 6-*H*, major rotamer), 6.35 (1H, d, *J* 4.8, 6-*H*, minor rotamer), 7.25-7.45 (8H, m, Ar-*H*), 7.70-7.80 (m, 2H, Ar-*H*), 8.29 (s, 1H, PhC*H*=N).

Irradiation of the signal at 8.29 ppm resulted in nOe enhancement of the multiplet at 3.75-3.87 ppm (as well as the aryl multiplet at 7.70-7.80 ppm), confirming the *E*-geometry of the imine.

(*S*)-Benzyl 2-({[(1*E*)-(2-bromophenyl)methylene]amino}methyl)-2,3-dihydro-4*H*-1,4-oxazine-4-carboxylate, 12b (R = *o*-BrC_6H_4)

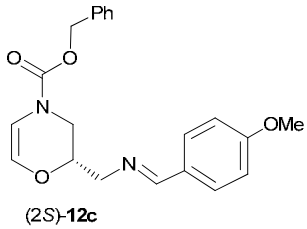


(2*S*)-**12b**

(a) 1 g, 4.03 mmol; (b) 4.85 g, 40.3 mmol; (c) 20 mL; (d) 2-BrC_6H_4CHO; and (e) 0.75 g, 4.03 mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37 (1H, dd, *J* 13.0, 8.2, 3-H_2, major rotamer), 3.51 (1H, dd, *J* 13.0, 7.7, 3-H_2, minor rotamer), 3.75-3.85 (2H, m, CH_2N=CHAr), 4.02 (1H, d, *J* 11.7, 3-H_2, minor rotamer), 4.17 (1H, d, *J* 13.1, 3-H_2, major rotamer), 4.24-4.26 (1H, m, 2-*H*), 5.17 (2H, s, CH_2Ph, minor rotamer), 5.19 (2H, s, CH_2Ph, major rotamer), 5.92 (1H, d, *J* 5.0, 5-*H*, major rotamer), 6.04 (1H, d, *J* 4.9, 5-*H*, minor rotamer), 6.24 (1H, d, *J* 4.9, 6-*H*, major rotamer), 6.36 (1H, d, *J* 4.8, 6-*H*, minor rotamer), 7.25-7.45 (6H, m, Ar-*H*), 7.55 (1H, d, *J* 7.8, Ar-*H*), 7.63-7.65 (1H, m, Ar-*H*, major rotamer), 7.90-7.92 (1H, m, Ar-*H*, minor rotamer), 7.98 (1H, d, *J* 8.0, Ar-*H*, minor rotamer); 8.03 (1H, d, *J* 7.7, Ar-*H*, major rotamer); 8.66 (1H, s, ArC*H*=N).

(*S*,*E*)-Benzyl 2-((4-methoxybenzylideneamino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate, 12c (R = *p*-$MeOC_6H_4$)



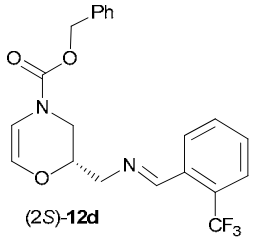
(2*S*)-**12c**

(a) 1 g, 4.03 mmol; (b) 4.85 g, 40.3 mmol; (c) 20 mL; (d) 4-$MeOC_6H_4CHO$; and (e) 0.55 g, 4.03 mmol.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.33 (1H, dd, *J* 13.0, 8.3, 3-H_2, major rotamer), 3.49 (1H, dd, *J* 13.0, 7.7, 3-H_2, minor rotamer), 3.74-3.81 (2H, m, CH_2N=CHAr), 3.84 (3H, s, $ArOCH_3$, major rotamer), 3.89 (3H, s, $ArOCH_3$, minor rotamer), 4.02 (1H, d, *J* 13.2, 3-H_2, minor rotamer), 4.16 (1H, d, *J* 14.3, 3-H_2, major rotamer), 4.20-4.24 (1H, m, 2-*H*), 5.16 (2H, s, CH_2Ph, minor

rotamer), 5.19 (2H, s, C*H*$_2$Ph, major rotamer), 5.92 (1H, d, *J* 5.0, 5-*H*, major rotamer), 6.04 (1H, d, *J* 5.0, 5-*H*, minor rotamer), 6.23 (1H, d, *J* 4.9, 6-*H*, major rotamer), 6.34 (1H, d, *J* 4.9, 6-*H*, minor rotamer), 6.92 (2H, d, *J* 8.7, Ar-*H*, major rotamer), 7.01 (2H, d, *J* 8.7, Ar-*H*, minor rotamer), 7.26-7.38 (5H, m, Ar-*H*), 7.67 (2H, d, *J* 8.5, Ar-*H*, major rotamer), 7.85 (2H, d, *J* 8.8, Ar-*H*, minor rotamer); 8.21 (1H, s, ArC*H*=N).

(*S*,*E*)-Benzyl 2-(((2-(trifluoromethyl)benzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate, 12d (R = *o*-$CF_3C_6H_4$)

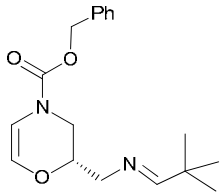


(2*S*)-**12d**

(a) 0.22 g, 0.9 mmol; (b) 1.08 g, 9.0 mmol; (c) 4.5 mL; (d) 2-$CF_3C_6H_4CHO$; and (e) 0.16 g, 0.9 mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (1H, dd, *J* 12.9, 8.0, 3-*H*$_2$, major rotamer), 3.49-3.53 (1H, 3-*H*$_2$, minor rotamer), 3.81-3.92 (2H, m, C*H*$_2$N=CHAr), 4.05-4.08 (1H, d, 3-*H*$_2$, minor rotamer), 4.19 (1H, d, *J* 13.2, 3-*H*$_2$, major rotamer), 4.27-4.32 (1H, m, 2-*H*), 5.18 (2H, s, C*H*$_2$Ph, minor rotamer), 5.20 (2H, s, C*H*$_2$Ph, major rotamer), 5.94 (1H, d, *J* 4.9, 5-*H*, major rotamer), 6.07 (1H, d, *J* 4.9, 5-*H*, minor rotamer), 6.27 (1H, d, *J* 4.9, 6-*H*, major rotamer), 6.39 (1H, d, *J* 4.9, 6-*H*, minor rotamer), 7.36-7.41 (5H, m, Ar-*H*), 7.55-7.61 (2H, m, Ar-*H*), 7.70-7.76 (1H, m, Ar-*H*), 8.15-8.20 (1H, m, Ar-*H*, minor rotamer), 8.25 (1H, d, *J* 7.5, Ar-*H*, major rotamer); 8.68 (1H, s, ArC*H*=N).

(*S*,*E*)-Benzyl 2-((2,2-dimethylpropylideneamino)methyl)-2*H*-1,4-oxazine-4(3*H*)-carboxylate, 12e (R = ^{t}Bu)

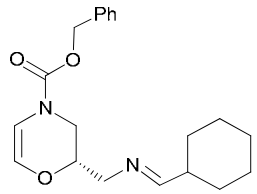


(2*S*)-**12e**

(a) 1 g, 4.03 mmol; (b) 4.85 g, 40.3 mmol; (c) 20 mL; (d) ^{t}BuCHO; and (e) 0.35 g, 4.03 mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (9H, s, ^{t}Bu, minor rotamer), 1.06 (9H, s, ^{t}Bu, major rotamer), 3.25 (1H, dd, *J* 13.1, 8.0, 3-*H*$_2$, major rotamer), 3.33 (1H, dd, *J* 12.6, 7.5, 3-*H*$_2$, minor rotamer), 3.45-3.67 (2H, m, C*H*$_2$N=CH^{t}Bu), 3.92-4.07 (1H, m, 3-*H*$_2$), 4.05 - 4.17 (1H, m, 2-*H*), 5.17 (2H, s, C*H*$_2$Ph, minor rotamer), 5.19 (2H, s, C*H*$_2$Ph, major rotamer), 5.89 (1H, d, *J* 5.0, 5-*H*, major rotamer), 6.01 (1H, d, *J* 4.9, 5-*H*, minor rotamer), 6.21 (1H, d, *J* 5.0, 6-*H*, major rotamer), 6.32 (1H, d, *J* 6.3, 6-*H*, minor rotamer), 7.26-7.38 (5H, m, Ar-*H*), 7.53 (s, 1H, ^{t}BuC*H*=N).

(*S*,*E*)-Benzyl 2-((cyclohexylmethyleneamino)methyl)-2*H*-1,4-oxazine-4(3*H*)-carboxylate, 12f
(R = ^{c}Hex)



(2*S*)-**12f**

(a) 1 g, 4.03 mmol; (b) 4.85 g, 40.3 mmol; (c) 20 mL; (d) ^{c}HexCHO; and (e) 0.45 g, 4.03 mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08-1.40 (5H, m, ^{c}HexC*H*$_2$), 1.59-1.94 (5H, m, ^{c}HexC*H*$_2$), 2.10-2.28 (1H, m, ^{c}HexC*H*), 3.24 (1H, dd, *J* 13.1, 8.2, 3-*H*$_2$, major rotamer), 3.34 (1H, dd, *J* 12.9, 7.8, 3-*H*$_2$, minor rotamer), 3.46 (2H, dd, *J* 12.1, 5.5, C*H*$_2$NCH^{c}Hex, minor rotamer), 3.50 (2H, dd, *J* 12.4, 5.5, C*H*$_2$NCH^{c}Hex, major rotamer), 3.95 (1H, dd, *J* 12.9, 1.9, 3-*H*$_2$, minor rotamer), 4.03 (1H, dd, *J* 13.1, 1.7, 3-*H*$_2$, major rotamer), 4.07-4.16 (1H, m, 2-*H*), 5.16 (2H, s, C*H*$_2$Ph, minor rotamer), 5.18 (2H, s, C*H*$_2$Ph, major rotamer), 5.92 (1H, d, *J* 5.0, 5-*H*, major rotamer), 6.04 (1H, d, *J* 4.9, 5-*H*, minor rotamer), 6.24 (1H, d, *J* 4.9, 6-*H*, major rotamer), 6.36 (1H, d, *J* 4.8, 6-*H*, minor rotamer), 7.42-7.28 (5H, m, Ar-*H*), 7.52 (1H, d, *J* 5.0, ^{c}HexC*H*=N).

General procedure for the preparation of oxabispidine hemiaminal ethers 13

Method A

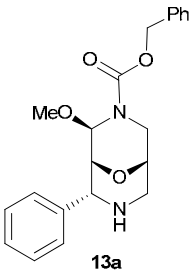
A stirred solution of the imine **12** in dichloromethane was cooled to -20 ^{o}C. Trifluoromethanesulfonic acid and methanol were added and the solution allowed to slowly warm to room temperature. The solution was then washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to yield **13**.

Method B

A stirred solution of **12** and *p*-toluenesulfonic acid monohydrate in methanol was stirred at 65 ^{o}C for 48 h. The solution was then evaporated under reduced pressure and the crude product dissolved in dichloromethane, washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to yield **13**.

Following either of these general procedures, the data are reported as follows: (a) imine (quantity); (b) method; (c) volume of dichloromethane; (d) quantity of acid; (e) quantity of methanol; (f) yield; and (g) rotamer ratio.

(1*R*,2*R*,5*S*,8*R*)-Benzyl 2-methoxy-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate, 13a (R = Ph)



13a

(a) **12a** (4.03 mmol); (b) method A; (c) 20 mL; (d) 640 mg, 4.03 mmol; (e) 120 mg, 4.03 mmol; and (f) white amorphous solid, 1.37 g, 92%; and (g) 65:35.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.13 (3H, s, OC*H*$_3$, major rotamer), 3.20 (1H, d, *J* 11.7, 6-*H*$_{eq}$, minor rotamer), 3.20 (3H, s, OC*H*$_3$, minor rotamer), 3.29 (1H, d, *J* 11.8, 6-*H*$_{eq}$, major rotamer), 3.47-3.77 (2H, m, 4-*H*$_{ax}$ + 6-*H*$_{ax}$), 3.86-3.96 (2H, m, 1-*H* + 5-*H*), 4.05 (1H, d, *J* 13.6, 4-*H*$_{eq}$, minor rotamer), 4.13 (1H, d, *J* 13.6, 4-*H*$_{eq}$, major rotamer), 4.37-4.44 (1H, m, 8-*H*), 4.83 (1H, s, 2-*H*, major rotamer), 4.99 (1H, s, 2-*H*, minor rotamer), 5.10-5.40 (2H, m, C*H*$_2$Ph), 7.04-7.50 (10H, m, Ar-*H*);

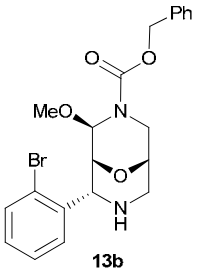
^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.7, 43.2, 50.6, 54.5, 54.7, 61.7, 62.4, 66.2, 66.5, 67.5, 67.7, 75.0, 75.4, 78.8, 78.9, 126.8, 127.2, 127.7, 127.9, 128.0, 128.3, 128.4, 128.7, 128.8, 136.3, 137.0, 139.4, 139.6, 155.3, 155.4;

IR (neat) ν_{max}: 2933, 1698, 1646, 1419;

HRMS *m/z* Calculated for $C_{21}H_{25}N_2O_4$ (M^++H) 369.1809. Found 369.1815;

$[\alpha]_D^{20}$ -104.3 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Benzyl 8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 13b (R = 2-BrC_6H_4)



13b

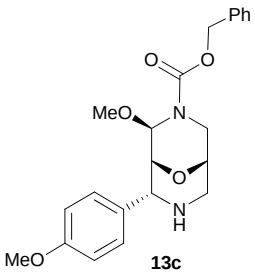
(a) **12b** (4.03 mmol); (b) method A; (c) 20 mL; (d) 640 mg, 4.03 mmol; (e) 120 mg, 4.03 mmol; (f) white amorphous solid, 2.08 g, 96%; and (g) 65:35.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.11 (3H, s, OC*H*$_3$, major rotamer), 3.16 (3H, s, OC*H*$_3$, minor rotamer), 3.17 (1H, d, *J* 11.5, 6-*H*$_{eq}$, minor rotamer), 3.26 (1H, d, *J* 11.6, 6-*H*$_{eq}$, major rotamer), 3.50-3.55 (1H, m, 6-*H*$_{ax}$), 3.62 (1H, ddd, *J* 13.4, 4.2, 2.0, 4-*H*$_{ax}$, major rotamer), 3.67 (1H, ddd, *J* 13.5, 4.2, 2.0, 4-*H*$_{ax}$, minor rotamer), 3.78 (1H, t, *J* 3.8, 1-*H*, minor rotamer), 3.87 (1H, t, *J* 3.9, 1-*H*, major rotamer), 4.04 (1H, d, *J* 13.4, 4-*H*$_{eq}$, minor rotamer), 4.12 (1H, d, *J* 13.2, 4-*H*$_{eq}$, major rotamer), 4.13-4.15 (m, 1H, 5-*H*), 4.67 (1H, d, *J* 3.7, 8-*H* major rotamer), 4.69 (1H, d, *J* 3.7, 8-*H* minor rotamer), 4.77 (1H, s, 2-*H*, major rotamer), 4.90 (1H, s, 2-*H*, minor rotamer), 5.08-5.38 (2H, m, C*H*$_2$Ph), 6.74 (1H, t, *J* 7.6, Ar-*H*, major rotamer), 7.01 (1H, t, *J* 7.6, Ar-*H*, minor rotamer), 7.12 - 7.60 (8H, m, Ar-*H*);

IR (neat) ν_{max}: 1699, 1419, 1114;

HRMS *m/z* Calculated for $C_{21}H_{24}BrN_2O_4$ (M^++H) 447.0914. Found 447.0913.

(1*R*,2*R*,5*S*,8*R*)-Benzyl 2-methoxy-8-(4-methoxyphenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 13c (R = 4-$MeOC_6H_4$)



13c

(a) **12c** (4.03 mmol); (b) method B; (c) -; (d) 77 mg, 0.403 mmol; (e) 20 mL; (f) white amorphous solid, 1.49 g, 93%; and (g) 60:40.

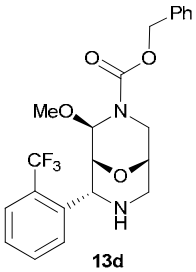
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.13 (3H, s, 2-OC*H*$_3$, major rotamer), 3.15 (1H, d, *J* 12.0, 6-*H*$_{eq}$, minor rotamer), 3.18 (3H, s, 2-OC*H*$_3$, minor rotamer), 3.24 (1H, d, *J* 11.9, 6-*H*$_{eq}$, major rotamer), 3.48-3.50 (1H, m, 6-*H*$_{ax}$), 3.59 (1H, ddd, *J* 13.4, 3.9, 1.7, 4-*H*$_{ax}$, major rotamer), 3.66 (1H, ddd, *J* 13.5, 3.7, 1.7, 4-*H*$_{ax}$, minor rotamer), 3.70 (3H, s, C*H*$_3$OAr, major rotamer), 3.79 (3H, s, C*H*$_3$OAr, minor rotamer), (1H, t, *J* 3.6, 1-*H*, minor rotamer), 3.81 (1H, d, *J* 3.5, 1-*H*, major rotamer), 3.85 (1H, m, 5-*H*), 4.04 (1H, d, *J* 13.4, 4-*H*$_{eq}$, minor rotamer), 4.12 (1H, d, *J* 13.4, 4-*H*$_{eq}$, major rotamer), 4.32 (1H, d, *J* 3.5, 8-*H*), 4.86 (1H, s, 2-*H*, major rotamer), 5.02 (1H, s, 2-*H*, minor rotamer), 5.16 - 5.34 (2H, m, C*H*$_2$Ph), 6.61 (2H, d, *J* 8.7, Ar-*H*, major rotamer), 6.88 (2H, d, *J* 8.7, Ar-*H*, minor rotamer), 7.17 (2H, d, *J* 8.5, Ar-*H*, major rotamer), 7.25 (2H, d, *J* 8.6, minor rotamer), 7.25 - 7.45 (5H, m, Ar-*H*);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.5, 43.0, 50.4, 50.5, 54.3, 54.6, 55.2, 55.6, 61.1, 61.6, 65.9, 66.2, 67.2, 67.5, 74.9, 75.3, 78.6, 78.7, 113.8, 114.3, 127.7, 127.8, 128.1, 128.2, 128.4, 128.5, 131.3, 131.4, 136.1, 136.8, 155.1, 155.2, 158.9, 159.0;

IR (neat) ν_{max}: 1697, 1512, 1420, 1247, 1231, 1075;

HRMS *m/z* Calculated for $C_{22}H_{27}N_2O_5$ (M^++H) 399.1914. Found 399.1914.

(1*R*,2*R*,5*S*,8*R*)-Benzyl 2-methoxy-8-(2-(trifluoromethyl)phenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 13d (R = 2-$CF_3C_6H_4$)



13d

(a) **12d** (0.9 mmol); (b) method A; (c) 5 mL; (d) 140 mg, 0.9 mmol; (e) 30 mg, 0.9 mmol; (f) white amorphous solid, 300 mg, 76%; and (g) 60:40.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (3H, s, OC*H*$_3$, major rotamer), 3.17 (3H, s, OC*H*$_3$, minor rotamer), 3.18 (1H, d, *J* 11.8, 6-*H*$_{eq}$, minor rotamer), 3.22 (1H, d, *J* 11.8, 6-*H*$_{eq}$, major rotamer), 3.51-3.54 (1H, m, 6-*H*$_{ax}$), 3.59-3.72 (1H, m, 4-*H*$_{ax}$), 3.79 (1H, m, 5-*H*, minor rotamer), 3.88-3.89 (1H, m, 5-*H*, major rotamer), 3.92 (1H, d, *J* 2.9, 8-*H*, major rotamer), 3.96 (1H, d, *J* 2.9, 8-*H*,

minor rotamer), 4.06 (1H, d, *J* 13.5, 4-H_{eq}, minor rotamer), 4.16 (1H, d, *J* 13.4, 4-H_{eq}, major rotamer), 4.72 (m, 1H, 1-*H*), 5.00 (1H, s, 2-*H*, major rotamer), 5.15 (1H, s, 2-*H*, minor rotamer), 5.19-5.39 (2H, m, CH_2Ph), 6.86 (1H, t, *J* 7.6, Ar-*H*, major rotamer), 7.25 (1H, t, *J* 7.6, Ar-*H*, minor rotamer), 7.28-7.38 (5H, m, Ar-*H*), 7.44-7.46 (1H, m, Ar-*H*), 7.55-7.65 (1H, m, Ar-*H*), 7.74 (1H, d, *J* 7.8, Ar-*H*, major rotamer), 7.89 (1H, d, *J* 7.8, Ar-*H*, minor rotamer);

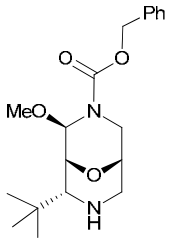
^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.6, 43.0, 50.6, 50.7, 54.4, 54.7, 58.5, 58.7, 65.8, 66.1, 67.4, 67.7, 73.3, 73.7, 78.5, 78.6, 126.0, 126.1, 126.2, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.5, 130.2, 131.8, 132.4, 136.1, 136.8, 137.9, 138.1, 155.0, 155.4

IR ($CHCl_2$) ν_{max}: 3071, 2948, 1701, 1311;

HRMS *m/z* Calculated for $C_{22}H_{24}F_3N_2O_4$ (M^++H) 437.1683. Found 437.1680;

$[\alpha]_D^{20}$ -80.7 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Benzyl 8-*tert*-butyl-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 13e (R = ^{t}Bu)



13e

(a) **12e** (4.03 mmol); (b) method A; (c) 20 mL; (d) 640 mg, 4.03 mmol; (e) 120 mg, 4.03 mmol; (f) white amorphous solid, 1.26 g, 90%; and (g) 60:40.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (9H, s, C(CH_3)$_3$, major rotamer), 0.96 (9H, s, C(CH_3)$_3$, minor rotamer), 2.93 (1H, dd, *J* 10.3, 3.3, 8-*H*), 3.04 (1H, d, *J* 13.1, 6-H_{eq}, minor rotamer), 3.10 (1H, d, *J* 13.1, 6-H_{eq}, major rotamer), 3.27 (3H, s, OCH_3, major rotamer), 3.31 (1H, ddd, *J* 13.2, 4.0, 2.3, 6-H_{ax}), 3.34 (3H, s, OCH_3, minor rotamer), 3.53-3.71 (3H, m, 1-H + 5-H + 4-H_{ax}), 3.84 (1H, d, *J* 12.3, 4-H_{eq}, major rotamer), 3.91 (1H, d, *J* 13.3, 4-H_{eq}, minor rotamer), 5.06 - 5.27 (3H, m, CH_2Ph + 2-*H*, minor rotamer), 5.41 (1H, s, 2-*H*, major rotamer), 7.33-7.41 (m, 5H, Ar-*H*);

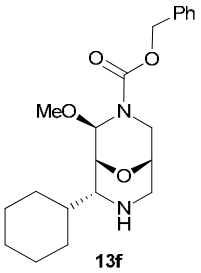
^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.5, 32.4, 32.5, 42.8, 43.2, 51.0, 54.9, 55.4, 65.2, 65.6, 65.9, 66.1, 67.5, 67.9, 70.8, 71.1, 80.4, 80.8, 127.8, 128.2, 128.4, 128.5, 135.7, 136.3, 155.2.

IR (neat) ν_{max}: 2953, 1700, 1415, 1061;

HRMS *m/z* Calculated for $C_{19}H_{29}N_2O_4$ (M^++H) 349.2122. Found 349.2122;

$[\alpha]_D^{20}$ +2.1 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Benzyl 8-cyclohexyl-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 13f (R = ^{c}Hex)



13f

(a) **14f** (4.03 mmol); (b) method A; (c) 20 mL; (d) 640 mg, 4.03 mmol; (e) 120 mg, 4.03 mmol; (f) white amorphous solid, 1.15 g, 76%; and (g) 60:40.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 - 1.28 (6h, m, ^{c}HexCH_2), 1.65 - 1.72 (4H, m, ^{c}HexCH_2), 1.80-1.88 (1H, m, ^{c}HexC*H*), 2.79 (1H, dd, *J* 9.7, 3.5, 8-*H*), 2.95 (1H, d, *J* 12.8, 6-H_{eq}, minor rotamer), 3.07 (1H, d, *J* 12.7, 6-H_{eq}, major rotamer), 3.25 (3H, s, OCH_3, major rotamer), 3.29 (1H, ddd, *J* 13.2, 3.8, 2.3, 6-H_{ax}), 3.34 (3H, s, OCH_3, minor rotamer), 3.55 (1H, ddd, *J* 13.4, 4.2, 2.2, 4-H_{ax}, minor rotamer), 3.59 (1H, t, *J* 3.8, 5-*H*, minor rotamer), 3.61 (1H, ddd, *J* 13.4, 4.2, 2.2, 4-H_{ax}, major rotamer), 3.67 (1H, t, *J* 3.8, 5-*H*, major rotamer), 3.75 (1H, d, *J* 3.5, 1-*H*, major rotamer), 3.81 (1H, d, *J* 3.5, 1-*H*, minor rotamer), 3.88 (1H, d, *J* 12.3, 4-H_{eq}, major rotamer), 3.99 (1H, d, *J* 13.3, 4-H_{eq}, minor rotamer), 5.09-5.31 (3H, m, CH_2Ph + 2-*H*), 7.29-7.37 (m, 5H, Ar-*H*);

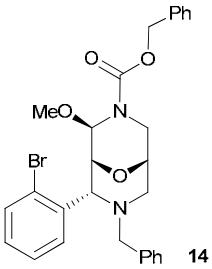
^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 25.8, 25.9, 26.0, 26.4, 26.5, 28.8, 28.8, 30.3, 30.4, 39.3, 39.5, 42.6, 43.3, 50.2, 50.2, 54.8, 55.2, 61.1, 61.3, 65.7, 66.2, 67.6, 67.8, 71.1, 71.3, 79.8, 80.1, 128.2, 128.2, 128.4, 128.5, 128.7, 128.8, 136.4, 136.7, 155.2, 155.6;

IR (neat) ν_{max}: 2925, 2852, 1700, 1420;

HRMS *m/z* Calculated for $C_{21}H_{31}N_2O_4$ (M^++H) 375.2278. Found 375.2280;

$[\alpha]_D^{20}$ -27.5 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Benzyl 7-benzyl-8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 14



14

13b (1 g, 2.24 mmol), prepared as above, was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C. Sodium hydride (98 mg of a 60% suspension in mineral oil, 2.46 mmol) was added portionwise (CAUTION, hydrogen evolution!) with stirring. Following a further 10 min stirring, benzyl bromide (0.42 g, 2.46 mmol) was added in a dropwise fashion, maintaining the temperature below 5 °C. The mixture was stirred for a further 10 min at this temperature, then allowed to warm to room temperature and stirred overnight. The mixture was quenched with water (10 mL) and extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting *i*-hexane – ethyl acetate to give **14** (white amorphous solid, 1.03 g, 80%) as a 50:50 mixture of rotamers. In order to provide material suitable for study by X-ray diffractometry, a sample was recrystallized from ethyl acetate to give colourless needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.63-2.66 (1H, m, NCH_2Ph), 2.67 (1H, d, *J* 13.7, 6-H_{ax}, rotamer 1), 2.73 (1H, d, *J* 14.1, 6-H_{ax}, rotamer 2), 2.97 (1H, d, *J* 11.9, NCH_2Ph, rotamer 1), 3.03 (1H, d, *J* 12.1, NCH_2Ph, rotamer 1), 3.16 (3H, s, CH_3O, rotamer 2), 3.19 (3H, s, CH_3O, rotamer 1), 3.57 (1H, ddd, *J* 13.4, 4.2, 1.7, 4-H_{ax}, rotamer 2), 3.62 (1H, ddd, *J* 13.7, 4.1, 2.1, 4-H_{ax}, rotamer 1), 3.83 (1H, d, *J* 14.1, 6-H_{eq}, rotamer 2), 3.87-3.92 (2H, m, 4-H_{eq}, rotamer 1 + 6-H_{eq}, rotamer 1), 3.96 (1H, t, *J* 3.8, 5-*H*), 4.01 (1H, d, *J* 13.4, 4-H_{eq}, rotamer 2), 4.06 (1H, dd, *J* 3.8, 0.9, 1-*H*, rotamer 2), 4.11 (1H, dd, *J* 3.7, 0.6, 1-*H*, rotamer 1), 4.23 (1H, d, *J* 3.8, 8-*H*, rotamer 2), 4.23 (1H, d, *J* 3.8, 8-*H*, rotamer 1), 4.92 (1H, s, 2-*H*, rotamer 2), 5.12 (1H, s, 2-*H*, rotamer 1), 5.20 (1H, d, *J* 12.1, CO_2CH_2Ph, rotamer 2), 5.25 (1H, d, *J* 12.3, CO_2CH_2Ph, rotamer 1), 5.40 (1H, d, *J* 12.3, CO_2CH_2Ph, rotamer 1), 5.45 (1H, d, *J* 12.1, CO_2CH_2Ph, rotamer 2), 6.60 (1H, td, *J* 7.6, 1.1, Ar-*H*, rotamer 2), 6.99 (1H, td, *J* 7.7, 1.7, Ar-*H*, rotamer 1), 7.15-7.47 (11H, m, Ar-*H* and 1H, m,

Ar-*H*, rotamer 2), 7.53 (1H, dd, *J* 8.0, 1.1, Ar-*H*, rotamer 1), 7.59 (1H, dd, *J* 8.0, 1.1, Ar-*H*, rotamer 2), 7.83 (1H, dd, *J* 7.9, 1.5, Ar-*H*, rotamer 1);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.2, 42.7, 54.5, 54.8, 56.3, 60.1, 60.3, 67.3, 67.4, 67.5, 67.6, 67.8, 71.8, 72.3, 78.5, 78.7, 124.4, 124.5, 127.1, 127.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 129.1, 129.4, 130.3, 130.9, 133.4, 133.5, 135.9, 136.1, 136.2, 136.4, 137.6, 138.0, 155.0, 155.2;

Mp: 151-153 °C (ethyl acetate);

IR (neat) ν_{max}: 2941, 2810, 1698, 1422, 1319, 1071, 1016;

HRMS *m/z* Calculated for $C_{28}H_{30}BrN_2O_4$ (M^++H) 537.1383. Found 537.1379;

$[\alpha]_D^{20}$ +0.78 (*c* 0.46 in $CHCl_3$).

Crystallographic structural determination for compound 14

The reported data set was collected at 293K with graphite monochromatized MoK(α) radiation on a KappaCCD Single-Crystal X-Ray diffractometer equipped with an κ-axis goniometer and a CCD area detector (Nonius, 1998). The diffraction raw data were processed within the Denzo-SMN program package (Otwinowski & Minor, 1997) converting the information from the digital image frame to a file containing h, k, l indices, background and Lp corrected intensities of the diffraction spots, along with estimate of errors. A total of 257 image frames were collected, each by rotating the φ-axis 1°.

The Flack's *x* chirality parameter was used to determine the absolute configuration based on the anomalous scattering contribution to the measured diffraction intensities. The *x* parameter is defined as follows:

$$|F_{hkl}, x|^2 = (1-x)|F_{hk}l|^2 + x|F_{-h-k-l}|^2.$$

The *x* takes the value of 0 when the atomic coordinates and the crystal have the same chirality, when they are of opposed chirality the value *x* becomes 1. The Flack's *x* parameter was refined to a value of 0.018(9). In accordance to the calculated Flack's parameter, x and the Cahn-Ingold-Prelog sequence rules, the chiral carbon atoms C(1), C(2), C(5) and C(8) (labelled as,

respectively, C(17), C(18), C(13) and C(16) in Table 3 and Figures 1 and 2 below) were assigned as *R*, *R*, *S* and *R*, respectively.

Table 1. Experimental details for (1*R*,2*R* 5*S*,8*R*)-Benzyl 7-benzyl-8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 14

Crystal data

$C_{28}H_{29}BrN_2O_4$	D_x = 1.378 Mg m^{-3}
M_r = 537.43	Mo $K\alpha$ radiation
Orthorhombic, $P2_12_12_1$	Cell parameters from 3232 reflections
a = 7.68450 (10) Å	θ = 0.4–27.5°
b = 15.2060 (4) Å	μ = 1.62 mm^{-1}
c = 22.1725 (6) Å	T = 293 K
V = 2590.87 (10) Å^3	Prismatic block, Colourless
Z = 4	0.23 × 0.15 × 0.13 mm

Data collection

KappaCCD diffractometer	3706 reflections with $I > 2\sigma(I)$
CCD scan	R_{int} = 0.0576
Absorption correction: none	θ_{max} = 27.5°
5793 measured reflections	h = -9 → 9
5766 independent reflections	k = -19 → 19
	l = -28 → 28

Refinement

Refinement on F^2	Calculated weights $w = 1/[\sigma^2(F_o^2) + (0.0589P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.032	$(\Delta/\sigma)_{max}$ = 0.002
$wR(F^2)$ = 0.102	$\Delta\rho_{max}$ = 0.33 e Å^{-1}
S = 0.96	$\Delta\rho_{min}$ = -0.42 e Å^{-1}
5766 reflections	Extinction correction: none

316 parameters	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
H atoms constrained to parent site	Flack parameter: 0.018 (9)

Table 2. Geometric parameters (Å, °) for (1*R*,2*R*,5*S*,8*R*)-Benzyl 7-benzyl-8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 14

Br35—C34	1.906 (3)	O21—C17	1.435 (3)
O8—C7	1.470 (4)	N11—C9	1.357 (4)
O8—C9	1.344 (4)	N11—C12	1.458 (4)
O10—C9	1.209 (4)	N11—C18	1.443 (3)
O19—C18	1.433 (4)	N15—C14	1.476 (4)
O19—C20	1.406 (5)	N15—C16	1.476 (4)
O21—C13	1.445 (4)	N15—C22	1.476 (4)

C7—O8—C9	116.3 (3)	O21—C13—C12	109.9 (3)
C18—O19—C20	114.4 (3)	O21—C13—C14	109.9 (2)
C13—O21—C17	107.88 (19)	N15—C14—C13	113.6 (3)
C9—N11—C12	119.2 (2)	N15—C16—C17	110.6 (2)
C9—N11—C18	124.3 (2)	N15—C16—C29	112.8 (2)
C12—N11—C18	116.3 (2)	O21—C17—C16	110.3 (2)
C14—N15—C16	109.3 (2)	O21—C17—C18	110.0 (2)
C14—N15—C22	108.5 (2)	O19—C18—N11	111.5 (2)
C16—N15—C22	111.6 (2)	O19—C18—C17	104.7 (2)
O8—C7—C6	109.4 (3)	N11—C18—C17	110.9 (2)
O8—C9—O10	124.2 (3)	N15—C22—C23	112.2 (3)
O8—C9—N11	111.6 (3)	Br35—C34—C29	121.2 (2)
O10—C9—N11	124.2 (3)	Br35—C34—C33	116.3 (2)
N11—C12—C13	110.6 (2)		

Table 3. Hydrogen-bond parameters (Å, °) for (1*R*,2*R*,5*S*,8*R*)-Benzyl 7-benzyl-8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 14

	D—H	H...*A*	D...A	*D*—H...*A*
C7—H7A...O19	0.9700	2.5500	3.446 (4)	153.00
C7—H7B...O10	0.9700	2.3300	2.704 (5)	102.00
C12—H12B...O10	0.9700	2.3800	2.762 (4)	103.00
C13—H13...O10	0.9800	2.5100	3.141 (4)	122.00
C16—H16...Br35	0.9800	2.7600	3.205 (3)	108.00
C18—H18...O8	0.9800	2.2500	2.669 (4)	104.00
C30—H30...N15	0.9300	2.5500	2.879 (4)	101.00

Computer programs

Data collection: KappaCCD. Cell refinement: HKL Scalepack (Otwinowski & Minor 1997). Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997). Program(s) used to solve structure: SIR92. Program(s) used to refine structure: SHELXL-97 (Sheldrick, 1997). Molecular graphics: Platon and Mercury 1.4.

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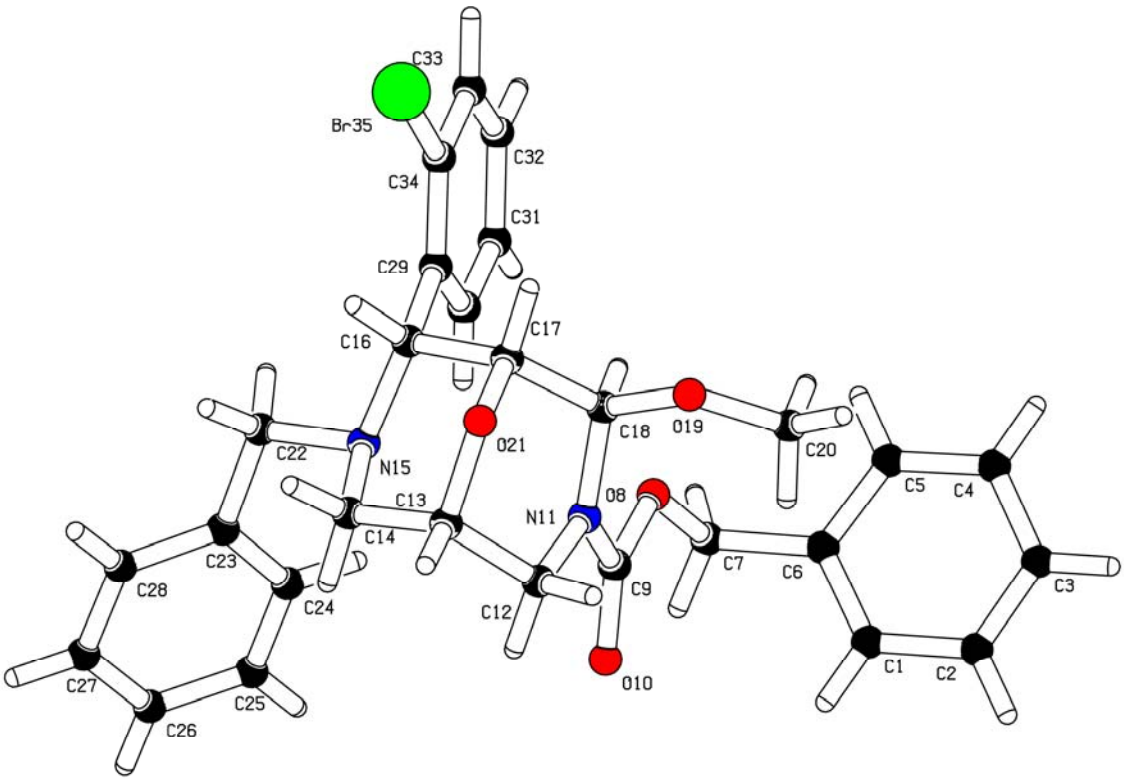


Figure 1. Perspective view of the molecule of **14**

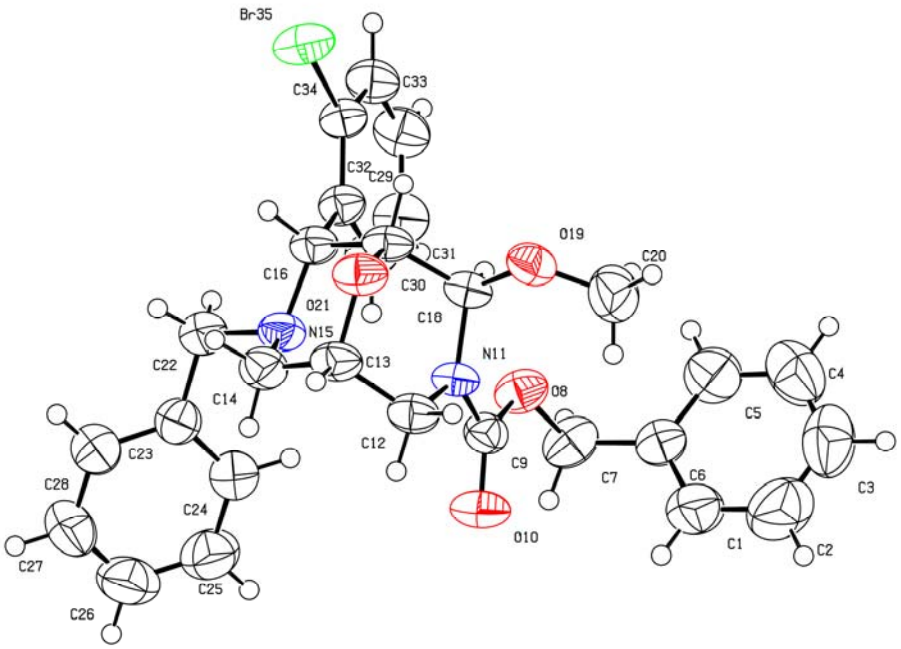
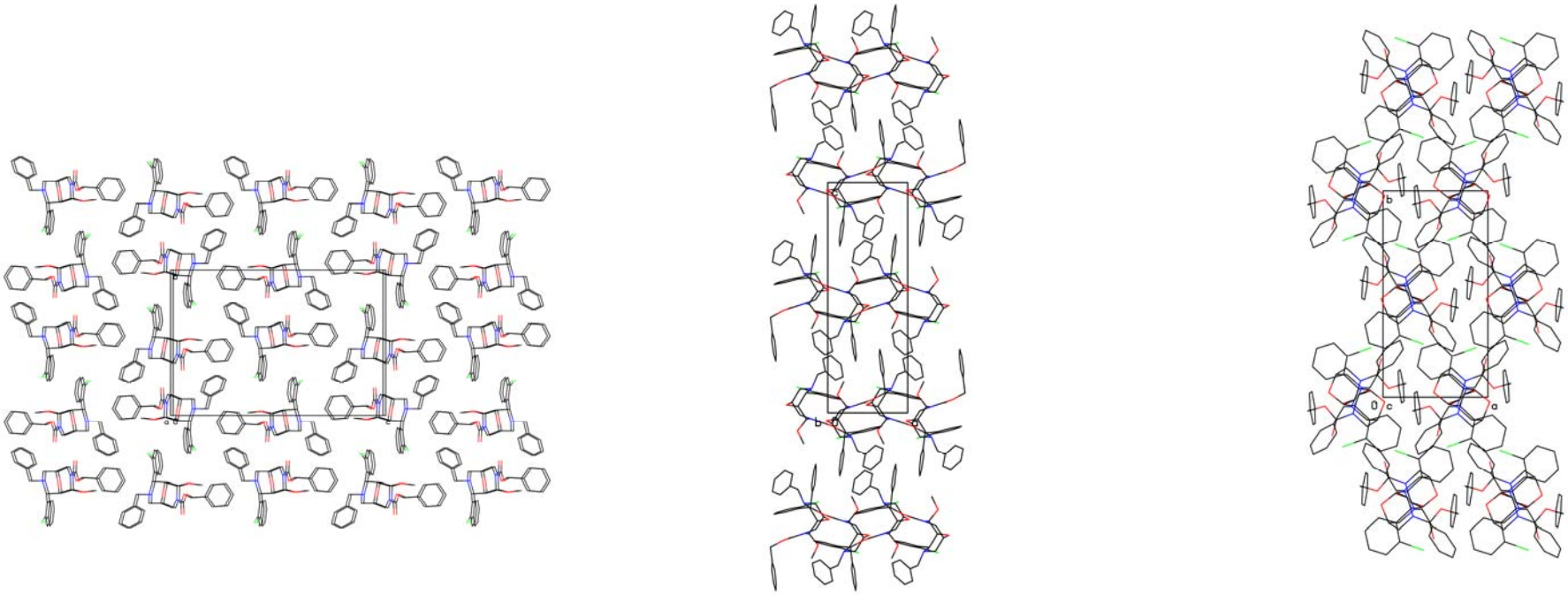


Figure 2. The molecular conformation of **14** is shown with the thermal displacement ellipsoids drawn at 50% probability and hydrogen atoms as spheres of arbitrary radius. The crystallographic numbering of the atoms is also shown.



a) b) c)

Figure 3. The packing of **14** in the a) a-direction b) b-direction c) c-direction (hydrogen atoms are omitted).

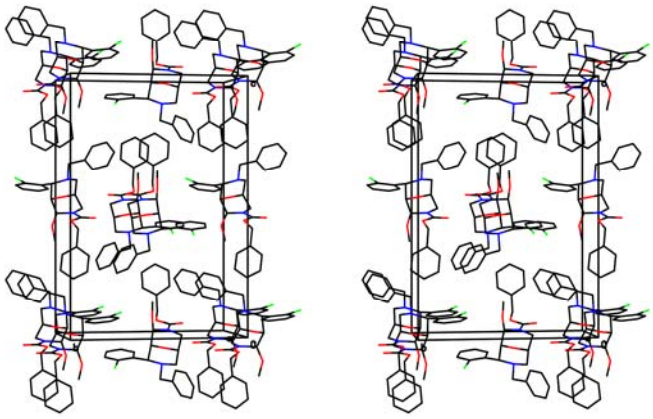
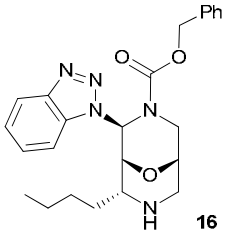


Figure 4. Stereographic view of the unit cell in **14**

(1*R*,2*R*,5*S*,8*R*)-Benzyl 2-(1H-benzo[*d*][1,2,3]triazol-1-yl)-8-butyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 16



16

A suspension of **11** (1.00 g, 4.03 mmol), benzotriazole (480 mg, 4.03 mmol), magnesium sulfate (40.3 mmol) and *n*-pentanal (347 mg, 4.03 mmol) in dichloromethane (20 mL) was stirred at room temperature for 10 min. The magnesium sulfate was removed by filtration. The solution was cooled to -20 °C, trifluoromethanesulfonic acid (604 mg, 4.03 mmol) was added and the solution allowed to slowly warm to room temperature and stirred overnight. The solution was then washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to yield **18** as a white amorphous solid (1.32 g, 75%) as a mixture of 4 rotamers in an approximate 33:22:27:18 ratio.

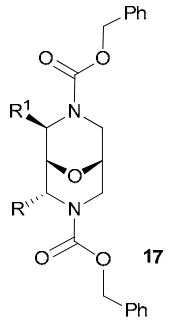
^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ: 0.91-0.97 (3H, m, C*H*$_3$CH$_2$), 1.36-1.37 (6H, m, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 3.07 (1H, d, *J* 12.4, 6-*H*$_{eq}$, rotamer 1), 3.08 (1H, d, *J* 13.1, 6-*H*$_{eq}$, rotamer 2), 3.11 (1H, d, *J* 13.2, 6-*H*$_{eq}$, rotamer 3), 3.16 (1H, d, *J* 12.3, 6-*H*$_{eq}$, rotamer 4), 3.25-3.33 (1H, m, 8-*H*), 3.39 (1H, d, *J* 13.1, 4-*H*$_{eq}$, rotamer 1 or 2), 3.43 (1H, d, *J* 12.4, 4-*H*$_{eq}$, rotamer 3 or 4), 3.89-3.98 (1H, m, 5-*H*), 3.99 (1H, d, *J* 13.0, 4-*H*$_{eq}$, rotamer 1 or 2), 4.04 (1H, d, *J* 13.0, 4-*H*$_{eq}$, rotamer

3 or 4); 4.12-4.24 (2H, m, 4-H_{ax} + 1-*H*, rotamer 1), 4.32 (1H, d, *J* 3.0, 1-*H*, rotamer 2), 4.41 (1H, d, *J* 3.4, 1-*H*, rotamer 3), 4.52 (1H, d, *J* 3.3, 1-*H*, rotamer 4), 5.0-5.3 (2H, m, CH_2Ph), 6.68 (1H, s, 2-*H*, rotamer 1), 6.73 (1H, s, 2-*H*, rotamer 2), 6.81 (s, 1H, 2-*H*, rotamer 3), 6.86 (s, 1H, 2-*H*, rotamer 4), 7.0-7.5 (7H, m, Ar-*H*); 7.84-7.87 (1H, m, Ar-*H*); 8.08 (1H, d, *J* 8.5, Ar-*H*);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 14.0, 22.7, 28.3, 28.3, 32.6, 32.6, 43.9, 44.0, 44.4, 44.5, 50.1, 50.2, 50.3, 56.9, 57.0, 57.7, 57.7, 62.7, 63.5, 65.5, 65.9, 65.9, 67.8, 68.1, 68.3, 69.7, 70.0, 72.1, 72.6, 72.9, 109.9, 110.2, 118.4, 120.0, 120.1, 124.0, 124.1, 126.3, 126.4, 127.6, 127.7, 127.9, 128.1, 128.1, 128.3, 128.4, 128.6, 132.3, 132.6, 135.6, 135.7, 135.9, 136.0, 144.2, 144.3, 145.7, 145.8, 154.4. 155.1, 155.3, 155.9;

IR (neat) ν_{max}: 2955, 2931, 1711, 1416, 1301, 1266, 1233, 1121, 1097.

General procedure for the preparation of oxabispidine *bis*-carbamates, 17

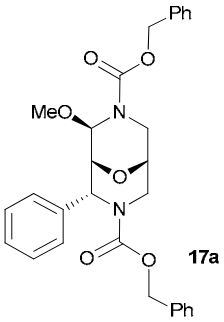


17

Oxabispidine hemiaminal ether **13** or aminal **16**, prepared as described above, was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C. Sodium hydride (60% suspension in mineral oil, 1.1 molar equivalents) was added in a portionwise fashion (CAUTION, hydrogen evolution!) with stirring. Following a further 10 min stirring, benzyl chloroformate (1.1 molar equivalents) was added in a dropwise fashion, maintaining the temperature below 5 °C. The mixture was stirred for a further 10 min at this temperature, then allowed to warm to room temperature and stirred overnight. The mixture was poured into water and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting *i*-hexane – ethyl acetate to give **17**.

Following the general procedure, the data are reported as follows: (a) Substrate (quantity); (b) Sodium hydride; (c) Benzyl chloroformate; (d) yield; and (e) rotamer ratio.

(1*R*,2*R*,5*S*,8*R*)-Dibenzyl 2-methoxy-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylate 17a (R^1 = OMe; R = Ph)



17a

13a (1.37 g, 3.72 mmol); (b) 164 mg, 4.09 mmol; (c) 698 mg, 4.09 mmol; (d) colourless gum, 2.40 g, 83%; and (e) 65:35.

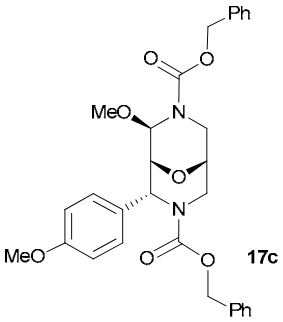
^{1}H NMR (400 MHz, 25 °C, d_6-DMSO) δ: 2.91 (3H, s, OC*H*$_3$, major rotamer), 2.9 (3H, s, OC*H*$_3$, minor rotamer), 3.23 (1H, dd, *J* 13.1, 2.9, 6-*H*$_{ax}$, major rotamer), 3.36 (2H, dd, *J* 13.3, 2.8, 6-*H*$_{ax}$, minor rotamer + 4-*H*$_{ax}$, major rotamer), 3.45 (1H, dd, *J* 13.2, 2.6, 4-*H*$_{ax}$, minor rotamer), 3.62 (1H, d, *J* 13.1, 6-*H*$_{eq}$, major rotamer), 3.70 (1H, d, J 13.1, 6-*H*$_{eq}$, minor rotamer), 4.01 (1H, dd, *J* 13.2, 8.1, 4-*H*$_{eq}$, minor rotamer), 4.13 (1H, dd, *J* 13.2, 8.5, 4-*H*$_{eq}$, major rotamer), 4.16-4.22 (1H, m, 5-*H*, minor rotamer), 4.23-4.30 (1H, m, 5-*H*, major rotamer), 4.27 (1H, d, *J* 8.9, 1-*H*$_{eq}$, minor rotamer), 4.34 (1H, d, *J* 8.8, 1-*H*$_{eq}$, major rotamer), 4.40 (1H, s, 2-*H*, major rotamer), 4.45 (1H, s, 2-*H*, minor rotamer), 4.79 (1H, d, *J* 12.4, PhC*H*$_2$), 4.96-5.15 (4H, m, 8-*H*, minor rotamer + PhC*H*$_2$), 5.23 (1H, d, *J* 8.6, 8-*H*, major rotamer), 7.08-7.37 (15H, m, Ar-*H*);

^{13}C NMR (125 MHz, 25 °C, $CDCl_3$) δ: 42.6, 43.4, 44.3, 45.4, 54.9, 55.2, 57.7, 58.6, 65.0, 65.1, 66.9, 67.5, 72.2, 73.0, 79.0, 79.6, 125.7, 126.0, 127.3, 127.5, 127.7, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 135.6, 136.0, 136.1, 136.4, 138.5, 138.8, 155.1, 155.5, 156.8, 157.2;

IR (neat) ν_{max}: 2933, 1698, 1646, 1419;

$[\alpha]_D^{20}$ -5.39 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Dibenzyl 2-methoxy-8-(4-methoxyphenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylate 17c (R^1 = OMe; R = 4-$MeOC_6H_4$)

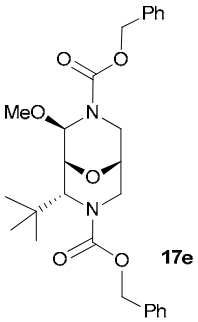


17c

(a) **13c** (1.49 g, 3.75 mmol); (b) 165 mg, 4.13 mmol; (c) 704 mg, 4.13 mmol; (d) colourless gum, 1.74 g, 81%; and (e) 65:35.

^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ: 3.06 (3H, s, 2-OCH_3, major rotamer), 3.15 (3H, s, 2-OCH_3, minor rotamer), 3.49 (1H, dd, *J* 13.2, 3.2, 6-H_{ax}, minor rotamer), 3.61 (1H, dd, *J* 13.2, 2.7, 6-H_{ax}, major rotamer), 3.64 (3H, s, ArOCH_3), 3.65-3.82 (1H, m, 4-H_{ax}), 3.62 (1H, d, *J* 13.1, 6-H_{eq}, major rotamer), 3.70 (1H, d, *J* 13.1, 6-H_{eq}, minor rotamer), 4.07 (1H, d, *J* 7.7, 4-H_{eq}, minor rotamer), 4.13 (1H, d, *J* 8.9, 4-H_{eq}, major rotamer), 4.15 (1H, d, *J* 8.0, 1-H_{eq}, minor rotamer), 4.26 (1H, d, *J* 8.0, 1-H_{eq}, major rotamer), 4.69 (1H, s, 2-*H*, major rotamer), 4.83 (1H, s, 2-*H*, minor rotamer), 4.91-5.21 (5H, m, 8-*H*, PhCH_2), 6.65 (2H, d, *J* 8.5, Ar-*H*, major rotamer), 6.77 (2H, d, *J* 8.5, Ar-*H*, minor rotamer), 6.80-7.40 (7H, Ar-*H*).

(1*R*,2*R*,5*S*,8*R*)-Dibenzyl 2-*tert*-butyl-8-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylate 17e (R^1 = OMe; R = ^{t}Bu)



17e

(a) **15e** (1.26 g, 3.63 mmol); (b) 160 mg, 3.99 mmol; (c) 681 mg, 3.99 mmol; (d) colourless gum, 1.49 g, 85%; and (e) The ^{1}H NMR spectrum gives the appearance of a mixture of 2 rotamers in

an approx. 60:40 ratio and has been assigned accordingly. However, the ^{13}C NMR spectrum reveals the appearance of 4 distinct rotameric species.

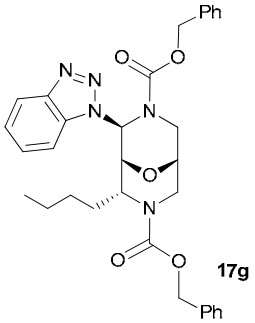
^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ: 1.00 (9H, s, ^{t}Bu, minor rotamer), 1.02 (9H, s, ^{t}Bu, major rotamer), 2.98-3.11 (1H, m, 8-*H*), 3.28 (3H, s, OCH_3, minor rotamer), 3.39 (3H, s, OCH_3, major rotamer), 3.45-3.60 (2H, m, 4-H_{ax}, + 6-H_{ax}), 4.08-4.31 (3H, m, 4-H_{eq} + 6-H_{eq} + 5-*H*), 4.35 (1H, d, *J* 9.2, 1-H_{eq}, major rotamer), 4.43 (1H, d, *J* 9.2, 1-H_{eq}, minor rotamer), 5.09-5.28 (4H, m, PhCH_2), 5.48 (1H, s, 2-*H*, minor rotamer), 5.60 (1H, s, 2-*H*, major rotamer), 7.32-7.40 (10H, m, Ar-*H*);

^{13}C NMR (125 MHz, 25 °C, $CDCl_3$) δ: 27.4, 27.5, 27.7, 35.3, 35.4, 35.5, 35.6, 41.6, 41.7, 42.1, 42.2, 55.5, 56.0, 64.0, 64.1, 64.5, 64.6, 68.1, 68.3, 69.7, 70.3, 70.4, 70.6, 71.0, 71.3, 80.2, 80.6, 83.5, 84.1, 127.0, 127.6, 127.8, 128.1, 128.4, 128.5, 128.6, 128.8, 135.5, 135.6, 136.1, 136.5, 137.7, 138.0, 155.8, 156.0, 156.4, 156.5;

IR (neat) ν_{max}: 2959, 1697, 1412, 1233, 1216, 1102, 1069;

$[\alpha]_D^{20}$ -2.06 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Dibenzyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-8-butyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylate 17g (R^1 = Bt; R = ^{n}Bu)



17g

(a) **16** (1.32 g, 3.02 mmol); (b) 133 mg, 3.32 mmol; (c) 566 mg, 3.32 mmol; (d) colourless gum, 1.23 g, 2.55 mmol, 84%; and (e) The ^{1}H NMR spectrum gives the appearance of a mixture of 2 rotamers in an approx. 60:40 ratio and has been assigned accordingly. However, the ^{13}C NMR spectrum reveals the appearance of 4 distinct rotameric species.

^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ: 0.84 (3H, t, *J* 7.0, 4'-CH_3, minor rotamer), 0.92 (3H, t, *J* 7.0, 4'-CH_3, major rotamer), 1.36-1.60 (4H, m, 2'-, 3'-CH_2), 1.75-1.92 (1H, m, 1'-CH_2), 2.26-2.35 (1H, m, 1'-CH_2, minor rotamer), 2.45-2.54 (1H, m, 1'-CH_2, major rotamer), 3.63 (1H, d, *J*

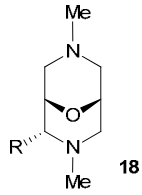
13.9, 6-H_{eq}, minor rotamer), 3.64 (1H, d, *J* 14.0, 6-H_{eq}, major rotamer), 3.96-4.14 (5H, m, 4-H_2, 5-*H*, 6-H_{ax}, 8-*H*), 4.57 (1H, d, *J*, 4.1, 1-*H*, rotamer 1), 4.63 (1H, d, *J*, 4.2, 1-*H*, rotamer 2), 4.84-5.25 (4H, m, CH_2Ph), 6.81 (1H, s, 2-*H*, major rotamer), 6.85 (1H, s, 2-*H*, minor rotamer), 7.01 (2H, m, Ar-*H*), 7.30-7.44 (10H, m, Ar-*H*), 7.82-7.87 (2H, m, Ar-*H*);

^{13}C NMR (125 MHz, 25 °C, $CDCl_3$) δ: 14.0, 14.1, 22.5, 22.7, 29.7, 29.7, 30.0, 30.0, 43.6, 44.3, 49.2, 49.7, 60.6, 60.9, 65.5, 65.9, 67.5, 67.7, 68.1, 68.4, 69.7, 70.1, 72.8, 73.0, 118.5, 118.5, 126.5, 126.6 127.8, 128.1, 128.3, 128.4, 128.5, 128.6, 128.6, 135.7, 136.1, 136.3, 136.3, 144.3, 144.4, 155.6. 155.7, 156.3, 156.1;

IR (neat) ν_{max}: 2958, 1712, 1264, 1222, 1101;

$[\alpha]_D^{20}$ -7.79 (*c* 1.0 in $CHCl_3$).

General procedure for the preparation of *N,N'*-dimethyloxabispidines, 18

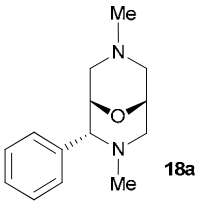


18

Oxabispidine acetal *bis*-carbamate **17**, prepared as described above, was dissolved in diethyl ether (50 mL/g substrate). Lithium aluminum hydride (3.3 molar equivalents of a 1M solution in THF) was added in a dropwise fashion with stirring. (CAUTION: hydrogen evolution!). The mixture was stirred for 24 h, then quenched by addition of water (0.25 mL/g substrate). Following a further 10 min stirring, 15% w/v aqueous sodium hydroxide (0.25 mL/g substrate) was added, and stirring continued for a further 10 min. A further charge of water (0.75 mL/g) was added, and stirring continued for a further 15 min. The mixture was filtered through celite and the filter cake washed three times with diethyl ether (20 mL). The combined filtrate and washings were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified on a Biotage SCX column, eluting with methanol (to remove residual benzyl alcohol) followed by 2M ammonia in methanol.

Following the general procedure, the data are reported as follows: (a) substrate (quantity); (b) diethyl ether; (c) lithium aluminum hydride; (d) water quench volume; (e) sodium hydroxide; (f) second water volume; and (g) yield.

(1*S*,2*R*,5*R*)-3,7-Dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 18a (R = Ph)



18a

(a) **17a** (1.55 g, 3.09 mmol); (b) 78 mL; (c) 10.2 mL; (d) 0.39 mL; (e) 0.39 mL; (f) 1.16 mL; and (g) colourless gum, 0.57 g, 80%.

^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) δ: 2.04 (1H, dd, *J* 11.9, 3.4, 8-H_{ax}), 2.10 (3H, s, N(3)-CH_3), 2.22 (3H, s, N(7)-CH_3), 2.48 (1H, dd, *J* 10.8, 2.9, 6-H_{ax}), 2.72 (1H, ddd, *J* 11.7, 4.2, 1.4, 4-H_{ax}), 2.74 (1H, d, *J* 11.3, 8-H_{eq}), 3.06 (1H, d, *J* 11.4, 6-H_{eq}), 3.16 (1H, d, *J* 11.9, 4-H_{eq}), 3.48 (1H, d, *J* 3.7, 2-*H*), 3.68 (1H, t, *J* 3.5, 1-*H*), 3.96 (1H, t, *J* 3.6, 5-*H*), 7.25-7.37 (5H, m, Ar-*H*);

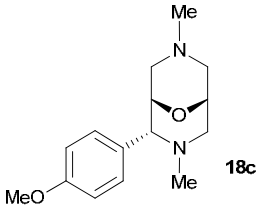
^{13}C NMR (125 MHz, 25 °C, $CDCl_3$) δ: 45.8, 47.3, 53.8, 58.4, 58.9, 68.8, 72.3, 73.1, 127.4, 128.5, 139.8;

IR (neat) ν_{max}: 2936, 2785, 1450, 1265, 1088, 1055;

HRMS *m/z* Calculated for $C_{14}H_{21}N_2O$ (M^++H) 233.1648. Found 233.1649;

[α]$_D^{20}$ -8.74 (*c* 1.0 in $CHCl_3$).

(1*S*,2*R*,5*R*)-2-(4-Methoxyphenyl)-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 18c (R = 4-$MeOC_6H_4$)



18c

(a) **17c** (1.74 g, 3.25 mmol); (b) 87 mL; (c) 11.5 mL; (d) 0.44 mL; (e) 0.44 mL; (f) 1.30 mL; and (g) colourless gum, 0.74 g, 87%.

^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ: 2.01 (1H, dd, *J* 12.0, 3.9, 8-H_{ax}), 2.07 (3H, s, N(3)-CH_3), 2.20 (3H, s, N(7)-CH_3), 2.45 (1H, ddd, *J* 11.4, 4.0, 1.7, 6-H_{ax}), 2.69 (1H, ddd, *J* 11.7, 4.4, 1.7, 4-H_{ax}), 2.75 (1H, d, *J* 11.9, 8-H_{eq}), 3.02 (1H, d, *J* 11.4, 6-H_{eq}), 3.12 (1H, d, *J* 11.8, 4-H_{eq}), 3.40 (1H, d, *J* 4.1, 2-*H*), 3.63 (1H, t, *J* 3.6, 1-*H*), 3.81 (3H, s, CH_3OAr), 3.94 (1H, t, *J* 4.1, 5-*H*), 6.88 (2H, d, *J* 8.6, Ar 3-*H* + 5-*H*), 7.32-7.36 (2H, m, Ar 2-*H* + 6-*H*);

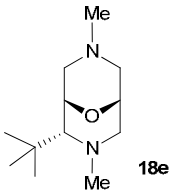
^{13}C NMR (100 MHz, 25 °C, $CDCl_3$) δ: 45.8, 47.3, 53.9, 55.2, 58.5, 59.0, 68.9, 71.6, 73.3, 113.7, 129.4, 132.0, 158.8;

IR (neat) ν_{max}: 2936, 2785, 1448, 1262;

HRMS *m/z* Calculated for $C_{15}H_{23}N_2O_2$ (M^++H) 263.1754. Found 263.1755;

[α]$_D^{20}$ -6.84 (*c* 0.8 in $CHCl_3$).

(1*S*,2*R*,5*R*)-2-*tert*-Butyl-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 18e (R = ^{t}Bu)



18e

(a) **17e** (1.49 g, 3.09 mmol); (b) 75 mL; (c) 10.2 mL; (d) 0.37 mL; (e) 0.37 mL; (f) 1.12 mL; and (g) colourless gum, 0.49 g, 75%.

^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) δ: 1.07 (9H, s, $(CH_3)_3C$), 2.12 (3H, s, N(7)-CH_3), 2.21 (1H, d, *J* 3.3, 2-*H*), 2.28 (1H, dd, *J* 12.5, 4.3, 6-H_{ax}), 2.30-2.32 (4H, m, 8-H_{ax} + N(3)-CH_3), 2.62 (1H, ddd, *J* 11.7, 4.7, 1.6, 4-H_{ax}), 2.89 (1H, d, *J* 11.8, 4-H_{eq}), 2.93 (1H, d, *J* 11.8, 6-H_{eq}), 3.02 (1H, d, *J* 11.9, 8-H_{eq}), 3.75 (1H, t, *J* 3.5, 1-*H*), 3.78 (1H, t, *J* 3.9, 5-*H*);

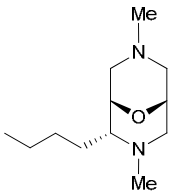
^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.2, 32.9, 47.5, 48.9, 56.6, 58.5, 60.9, 68.1, 70.2, 73.7;

IR (neat) ν_{max}: 2959, 2793, 1461, 1265, 1083, 1055;

HRMS *m/z* Calculated for $C_{12}H_{25}N_2O$ (M^++H) 213.1961. Found 213.1952;

[α]$_D^{20}$ -3.85 (*c* 1.0 in $CHCl_3$).

(1*S*,2*R*,5*R*)-2-Butyl-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 18g (R = ^{n}Bu)



18g

(a) **17g** (1.23 g, 2.55 mmol); (b) 62 mL; (c) 8.4 mL; (d) 0.31 mL; (e) 0.31 mL; (f) 0.92 mL; and (g) colourless oil, 0.38 g, 70%.

^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) δ: 0.87 (3H, t, *J* 7.2, CH_3CH_2), 1.19-1.32 (5H, m, $CH_3CH_2CH_2CH_2$), 1.73-1.76 (1H, m, $CH_3CH_2CH_2CH_2$), 2.16-2.25 (8H, m, N(3)-CH_3 + N(7)-CH_3

+ 2-*H* + 8-H_{ax}), 2.36 (1H, ddd, *J* 11.4, 4.1, 1.6, 6-H_{ax}), 2.53 (1H, ddd, *J* 11.6, 4.4, 1.7, 4-H_{ax}), 2.86 (1H, d, *J* 11.2, 6-H_{eq}), 2.87 (1H, d, *J* 11.6, 4-H_{eq}), 2.91 (1H, d, *J* 11.8, 8-H_{eq}), 3.66 (1H, t, *J* 3.9, 1-*H*), 3.79 (1H, t, *J* 4.2, 5-*H*);

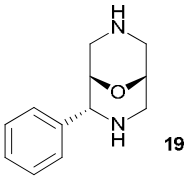
^{13}C NMR (100 MHz, 25 °C, $CDCl_3$) δ: 14.1, 23.2, 28.2, 29.6, 45.2, 47.8, 54.1, 58.7, 59.5, 65.6, 68.6, 70.4;

IR (neat) ν_{max}: 2933, 2786, 1457, 1272, 1090, 1048;

HRMS *m/z* Calculated for $C_{12}H_{25}N_2O$ (M^++H) 213.1961. Found 213.1953;

$[\alpha]_D^{20}$ -3.83 (*c* 1.0 in $CHCl_3$).

(1*S*,2*R*,5*R*)-2-Phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 19



19

A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium on charcoal (0.15 g, 0.15 mmol) followed by a solution of **13a** (0.5 g, 0.4 mmol) in methanol (30 mL). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3 way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluting 0–10% methanol in dichloromethane, to afford **19** (0.23 g, 82%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (2H, br. s, N*H*), 2.80 (1H, d, *J* 13.8, 8-H_{eq}), 2.99-3.02 (1H, m, 8-H_{ax}), 3.12 (1H, d, *J* 13.3, 6-H_{eq}), 3.32 (1H, d, *J* 11.8, 4-H_{eq}), 3.36-3.39 (1H, m, 6-H_{ax}), 3.57-3.66 (3H, m, 5-*H* + 4-H_{ax} + 1-*H*), 4.57 (1H, s, 2-*H*), 7.26-7.39 (5H, m, Ar-*H*);

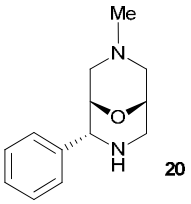
^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 50.5, 51.1, 63.9, 67.0, 72.3, 126.5, 127.4, 128.7, 141.0;

IR (CH_2Cl_2) ν_{max}: 3301, 3087, 3027, 2882, 2689;

HRMS *m/z* Calculated for $C_{12}H_{17}N_2O$ (M^++H) 205.1335. Found 205.1330;

$[\alpha]_D^{20}$ -50.7 (*c* 1.0 in $CHCl_3$).

(1*S*,2*R*,5*S*)-7-Methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 20



20

To a 3-necked flask, fitted with a low temperature thermometer, that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of N_2 was added lithium aluminium hydride (0.06 g, 1.6 mmol) followed by diethyl ether (5 mL). The resulting suspension was cooled to 0 °C and then a solution of **13a** (0.2 g, 0.54 mmol) in diethyl ether (4 mL) was added slowly. The resulting mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 3 h. To the reaction mixture was added water (0.06 mL) and the mixture was allowed to stir for 10 min. After this time 15% NaOH (0.06 mL) followed by water (0.18 mL) was added and the resulting white granular suspension was allowed to stir for 15 min. An excess of solid sodium bicarbonate was added and the mixture was stirred for a further 20 min. The suspension was filtered through a plug of celite, which was then washed with ether, and the filtrate concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluting 0–10% methanol in dichloromethane, to afford **20** (0.08 g, 72%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 2.11 (3H, s, NC*H*$_3$), 2.25 (1H, ddd, *J* 11.7, 3.7, 1.5, 8-*H*$_{ax}$), 2.58 (1H, dt, *J* 11.3, 2.9, 6-*H*$_{ax}$), 2.66 (1H, d, *J* 11.7, 8-*H*$_{eq}$), 2.95 (1H, d, *J* 11.4, 6-*H*$_{eq}$), 3.25 (1H, d, *J* 13.8, 4-*H*$_{eq}$), 3.48 (1H, dt, *J* 13.8, 2.9, 4-*H*$_{ax}$), 3.73 (1H, t, *J* 3.7, 5-*H*), 3.86 (1H, t, *J* 3.4, 1-*H*), 4.44 (1H, d, *J* 2.8, 2-*H*), 7.26-7.37 (5H, m, Ar-*H*);

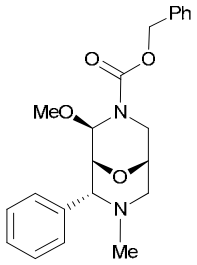
^{13}C NMR (100 MHz, $CDCl_3$): δ: 46.7, 50.8, 54.5, 59.5, 62.4, 67.0, 72.1, 126.1, 126.9, 128.5, 140.4;

IR ($CHCl_2$) ν_{max}: 3294, 3060, 3057, 2934, 2789;

HRMS *m/z* Calculated for $C_{13}H_{19}N_2O$ (M^++H) 219.1492. Found 219.1492;

$[\alpha]_D^{20}$ -62.6 (*c* 1.0 in $CHCl_3$).

(1*R*,2*R*,5*S*,8*R*)-Benzyl 2-methoxy-7-methyl-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate



To a solution of **13a** (2.6 g, 7.1 mmol) in dichloromethane (78 mL) was added methyl iodide (0.66 mL, 10.6 mmol) and potassium carbonate (1.5 g, 10.6 mmol). The reaction was stirred at room temperature for 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of dichloromethane and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluting diethyl ether in petroleum ether, to afford (1*R*,2*R*,5*S*,8*R*)-benzyl 2-methoxy-7-methyl-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (2.0 g, 73%) as a 60:40 mixture of rotamers as a pale yellow oil.

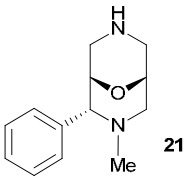
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (3H, s, NC*H*$_3$, minor rotamer), 2.01 (3H, s, NC*H*$_3$, major rotamer), 2.71-2.74 (1H, m, 6-*H*, both rotamers), 2.99 (1H, d, *J* 11.8, 6-*H*, minor rotamer), 3.07 (1H, d, *J* 11.8, 6-*H*, major rotamer), 3.12 (3H, s, OC*H*$_3$, major rotamer), 3.20 (3H, s, OC*H*$_3$, minor rotamer), 3.44-3.47 (1H, m, 4-*H*, both rotamers), 3.57-3.62 (1 H, m, 4-*H*, major rotamer), 3.64-3.69 (1H, m, 4-*H*, minor rotamer), 3.78 (1H, d, *J* 3.7, 5-*H*, major rotamer), 3.83 (1H, d, *J* 3.6, 5-*H*, minor rotamer), 3.90-3.91 (1H, m, 1-*H*, minor rotamer), 4.00-4.03 (1H, m, 1-*H*, major rotamer), 4.04 (1H, d, *J* 13.6, 8-*H*, minor rotamer), 4.09 (1H, d, *J* 13.3, 8-*H*, major rotamer), 4.94 (1H, s, 2-*H*, major rotamer), 5.13 (1H, s, 2-*H*, minor rotamer), 5.16-5.47 (2H, m, C*H*$_2$Ph), 7.08-7.36 ppm (10H, m, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$): δ 42.3, 42.8, 44.7, 54.5, 54.7, 59.3, 59.5, 67.0, 67.3, 67.5, 67.6, 70.8, 71.3, 75.1, 75.5, 78.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 136.1, 137.0, 137.5, 137.8, 155.0, 157.1;

IR ($CDCl_3$) ν_{max}: 3030, 2930, 2889, 1706;

HRMS *m/z* Calculated for $C_{22}H_{27}N_2O_4$ (M^++H) 383.1965. Found 383.1969.

(1*S*,2*R*,5*R*)-3-Methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 21



21

A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium on charcoal followed by a solution of (1*R*,2*R*,5*S*,8*R*)-benzyl 2-methoxy-7-methyl-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (1.3 g, 3.4 mmol) in methanol (70 mL). The vessel was then evacuated and back filled (x 3) with H_2 via a 3 way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting: 0–10% methanol in dichloromethane, to yield (1*S*,2*R*,5*R*)-3-methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **21** (0.68 g, 92%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (3H, s, NCH_3), 2.80 (1H, ddd, *J* 11.8, 3.9, 2.4 Hz, 8-H_{ax}), 2..96 (2H, s, 6-*H*), 3.15 (1H, d, *J* 11.8 Hz, 8-H_{eq}), 3.18 (1H, d, *J* 13.7 Hz, 4-H_{eq}), 3.39 (1H, ddd, *J* 13.7, 3.6, 2.5 Hz, 4-H_{ax}), 3.57-3.58 (1H, m, 5-*H*), 3.68 (1H, d, *J* 3.6 Hz, 2-*H*), 3.86 (1H, t, *J* 3.8 Hz, 1-*H*), 7.30-7.40 ppm (5H, m, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 45.0, 49.4, 59.8, 67.6, 72.0, 72.5, 127.6, 128.0, 128.8, 138.7;

IR ($CDCl_3$) ν_{max}: 3312, 3060, 2924, 2792;

HRMS *m/z* Calculated for $C_{13}H_{19}N_2O$ (M^++H) 219.1492. Found 219.1492;

$[\alpha]_D^{20}$ -152.5 (*c* 1.0 in $CHCl_3$).

References

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ii. S. E. Sen and S. L. Roach, *Synthesis*, 1995, 756.