A stereoselective synthesis of a 3,4,5-substituted piperidine of interest as a selective muscarinic (M_1) receptor agonist

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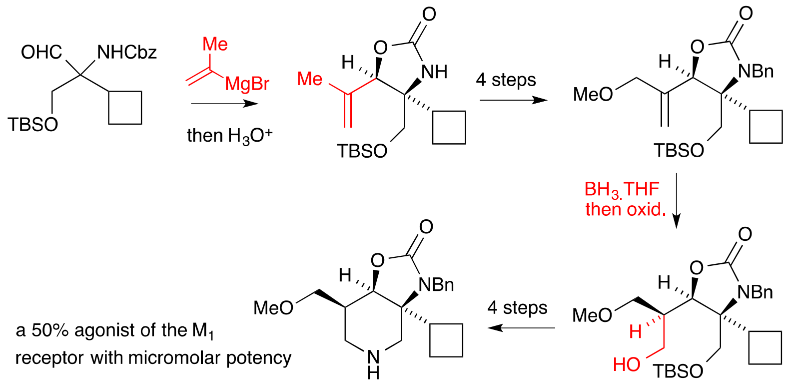

Dedicated to Steve Ley on the occasion of his 70th birthday.

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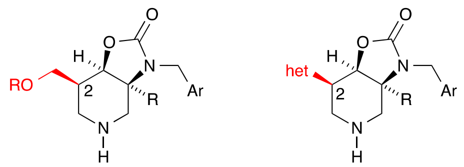
Abstract A stereoselective synthesis of (1*RS*,2*SR*,6*SR*)-7-benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxobicyclo[4.3.0]nonan-8-one, representative of a novel series of selective muscarinic (M_1) receptor agonists, is described.

Key words piperidines, oxazolidinones, hydroboration, muscarinic receptors, trifluoroacetimidates .

Agonists of muscarinic M_1 receptors have been identified as potential chemotherapeutic agents for the treatment of Alzheimer's disease.[1] In particular, they could provide alternatives to cholinesterase inhibitors that tend to lose efficacy over time. Indeed several M_1 receptor agonists have been found to alieviate the symptoms of Alzheimer's disease.[2] It is, however, crucial to find compounds selective for M_1 receptors to avoid side- effects arising from stimulation of other muscarinic receptor subtypes. Early modelling studies using the bovine rhodopsin as a substitute for the M_1 receptor, led to the identification of the oxazolidinonylpiperidines **1** and **2** as possibly selective M_1 agonists, see Figure 1.[3] We now describe a stereoselective synthesis of the first representative of these novel compounds.



1 **2**

Figure 1 Oxazolidinonylpiperidines of interest as M_1 receptor agonists

The first member of the series selected for synthesis was the 7-benzyl-6-cyclobutyl-2-methoxymethyl analogue **3**. The oxazolidinone **4** was identified as a likely precursor of the piperidine **3** and the alkenyloxazolidinone **5,** possibly accessible from the aldehyde **6**, was considered a plausible intermediate for the synthesis of the oxazolidinone **4**. The aldehyde **6** is the equivalent of an alkylated, reduced serine derivative but the presence of the cyclobutyl group limited the options available for its synthesis. In the end, it was decided to study a preparation of the aldehyde **6** from the ketone **7** that in turn would be prepared from the commercially available cyclobutane carboxylic acid **8**, see Figure 2. Although not unreasonable, it was recognised that the stereoselectivities of several of the steps in this proposed synthesis were difficult to predict.

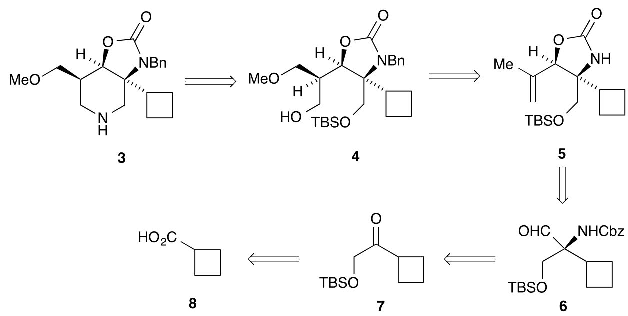
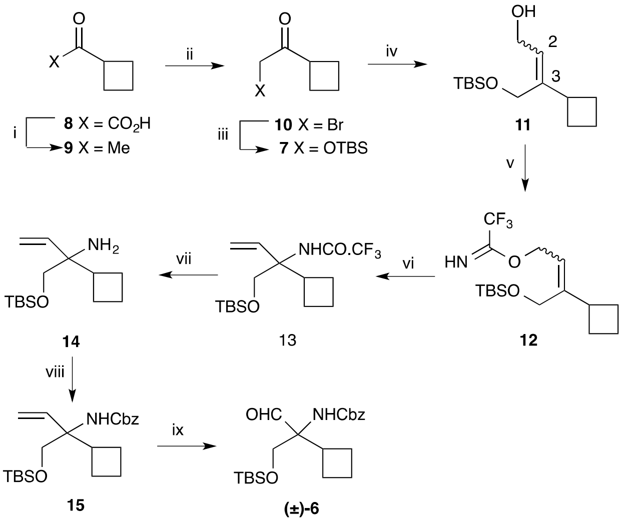


Figure 2 Proposed synthesis of the oxazolidinonylpiperidine **3**

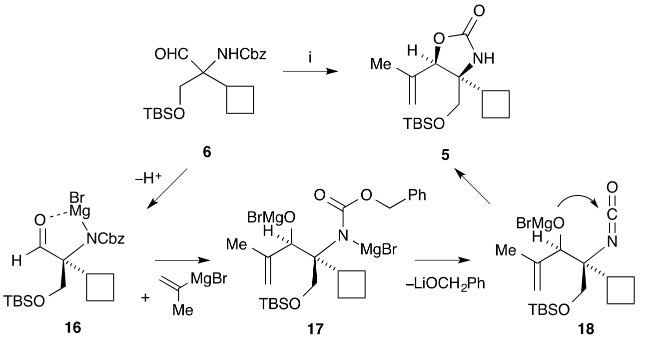
A synthesis of the racemic modification of the aldehyde **6** is outlined in Scheme 1. The *tert*-butyldimethylsilyloxymethyl ketone **7** was prepared in four steps from cyclobutanecarboxylic acid by conversion into the methyl ketone **9**, bromination of the ketone and hydrolysis of the known[4] bromide **10** to give the corresponding alcohol that was protected as its silyl ether **7**. A Wadsworth-Emmons-Horner reaction of the protected hydroxyketone **7** followed by reduction of the resulting αβunsaturated esters gave a 75 : 25 mixture of the geometrical isomers of the alcohols **11**, the major alcohol being identified as the (*Z*)-isomer on the basis of a significant nOe between 2-H and 3-CH. This mixture of alcohols was converted into the corresponding trifluoroacetimidates **12** by reaction with trifluoroacetonitrile, and heating the trifluoroacetimidates initiated a [3,3]-sigmatropic rearrangement to give the racemic tertiary trifluoroacetamide **13**.[5] Cleavage of the trifluoroacetamide was carried out under mild conditions using sodium borohydride in ethanol and the resulting amine **14** was converted into its Cbz-derivative **15** that was ozonolysed to give the required aldehyde (±)-**6**, see Scheme 1.



Scheme 1 *Synthesis of the aldehyde (±)-**6** Reagents and conditions* (i) MeLi, Et_2O, 0 °C to rt, 3 h (90%); (ii) Br_2, MeOH, 0 °C to 15 °C, 1.5 h (80%); (iii) (a) KOCHO, MeOH, heat under reflux, 12 h (71%) (b) TBSCl, imid., DMAP (cat.), TBAI (cat.), DCM, rt, 1 h (62%); (iv) (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt, 45 min, add **7**, rt, 2.5 h (b) DIBAL-H, hexanes, THF, –78 °C, 3h, rt, 30 min [89% from **7**, (*Z*) : (*E*) = 75 : 25]; (v) NaH, THF, rt, 1 h, add to CF_3CN, THF, –115 °C to –78 °C, 1 h (88%); (vi) xylene, heat under reflux 18 h (91%); (vii) $NaBH_4$, EtOH, 0 °C to rt, 18 h (80%); (viii) CBzCl, Et_3N, DCM, rt, 18 h (83%); (ix) O_3, DCM, –78 °C, then Ph_3P, rt (84%).

The next step was the conversion of the aldehyde **6** into the oxazolidinone **5**. This was achieved in one pot using an excess of isopropenylmagnesium bromide with a prolonged reaction time to facilitate cyclisation.[6] This reaction was highly stereoselective and gave the cyclised product **5** exclusively. The formation of this oxazolidinone is consistent with addition of the Grignard reagent onto the less hindered face of the chelated, deprotonated aldehyde **16** to give the adduct **17**. This cyclised *in situ*, possibly via the isocyanate **18** formed by loss of lithium benzyloxide, to give the oxazolidinone after work-up, see Scheme 2. The structure asigned to the oxazolidinone **5** was confirmed by X-ray difraction,[7] see Figure 3.

To convert the oxazolidinone **5** into the cyclisation precursor **4** it was necessary to oxidise the methyl group, benzylate the oxazolidinone and hydrate the alkene stereoselectively. These conversions are outlined in Scheme 3. Epoxidation of the alkene **5** gave a mixture of the epoxides **19** and **20**, ratio 77 : 23, that were reacted as a mixture with lithium 2,2,6,6-tetramethylpiperidide[8] to give the allylic alcohol **21**.



Scheme 2 *Preparation of the oxazolidinone **5** Reagents and conditions* (i) $CH_3C(MgBr)=CH_2$, THF, tol., –78 °C, 2h then rt, 48 h (66%).

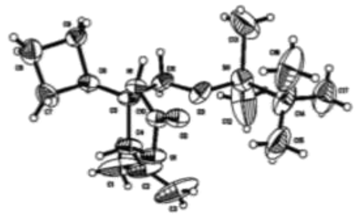
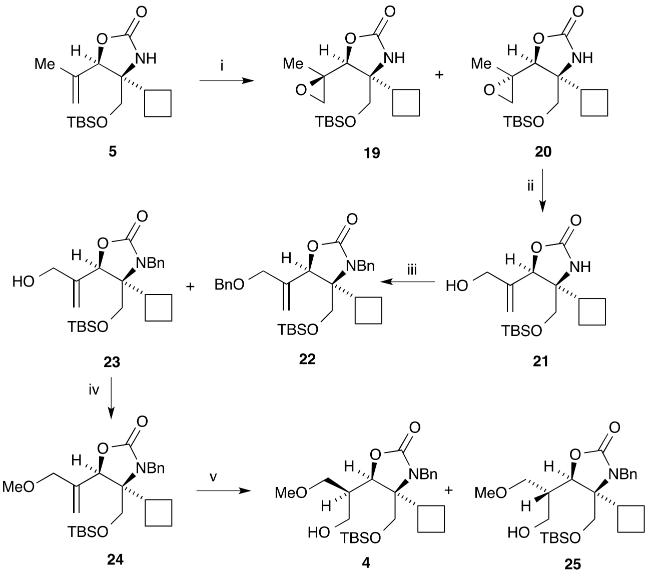


Figure 3 The structure of the oxazolidinone **5** as established by X-ray diffraction.

Alkylation using sodium hydride-benzyl bromide gave the *N*-benzyloxazolidinone **23** as the major product with the bis-benzylated material **22** as only a minor side-product. Methylation of the alcohol **23** led to the methyl ether **24** and hydroboration-oxidation of this alkene using borane in THF at 0 °C gave a mixture of the epimeric alcohols **4** and **25**, ratio **4** : **25** = 85 : 15,[9] see Scheme 3.



Scheme 3 *Synthesis of the (±)-oxazolidinone 4 Reagents and conditions* (i) (i) *m*CPBA, DCM, rt, 18 h (75%); (ii) 2,2,6,6-tetramethylpiperidine, THF, ^{n}BuLi, 0 °C to rt, 1 h, added to **19** and **20**, THF, 0 °C to rt, 3 h (67%); (iii) NaH, BnBr, THF, heat under reflux, 6 h (**23**, 79%; **22**, 6%); (iv) NaH, THF, MeI, rt, 18 h (90%); (v) BH_3, THF, 0 °C, 18 h, then EtOH, NaOAc, 30% aq. H_2O_2, heat under reflux 1 h (95%, **4** : **25** = 85 : 15).

The mixture of hydroboration products was not separated and the structure **4** of the major product, which turned out to be the required epimer, was only confirmed later in the synthesis. The stereoselectivity can be explained by participation of transition structure **26** in the hydroboration step, see Figure 4, but molecular modelling studies of the hydroboration were not carried out.

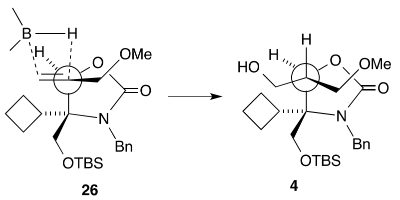
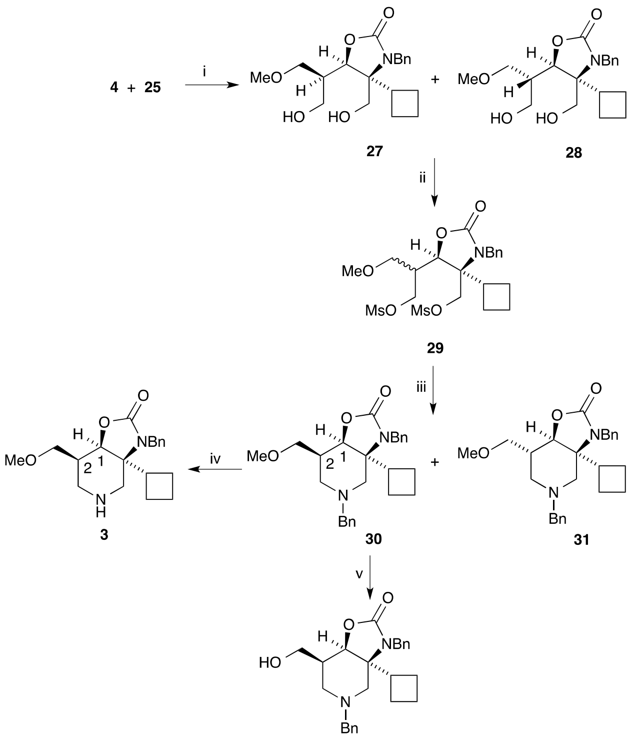


Figure 4 Facial selectivity of the hydroboration of alkene **24**

The completion of the synthesis of the oxazolidinonylpiperidine **3** is outlined in Scheme 4. Desilylation of the mixture of the hydroboration products **4** and **25** gave a mixture of the diols **27** and **28** that was converted into the *N*-benzylpiperidines **30** and **31**, ratio ca. 85 : 15, by reaction of the mesylates **29** with an excess of benzylamine.[10] Following separation of the major *N*-benzylpiperidine **30** by chromatography, a selective transfer hydrogenolysis of the piperidine *N*-benzyl group gave the required oxazolidinonylpiperidine **3**.[11]



Scheme 4 *Completion of a synthesis of the (±)-oxazolidinonylpiperidine* ***3*** *Reagents and conditions* (i) TBAF, THF, 0 °C to rt, 30 min (67%, **27** : **28** = 85 : 15); (ii) MsCl, Et_3N, DCM, 0 °C to rt, 1 h; (iii) $BnNH_2$, 80 °C, 18 h (**30**, 36%; mixture of **30** and **31**, 26%, **30** : **31** = 55 : 45); (iv) 10% Pd/C, HCO_2H, MeOH, rt, 20 min (71%); (v) BBr_3, DCM, THF, 0 °C, 4 h (61%).

The structures of the products shown in Scheme 4 were consistent with their spectroscopic data, although the configurations of the oxazolidinonylpiperidines at C2 were difficult to assign from their ^{1}H NMR spectra. The structures of these products were eventually confirmed by selective demethylation of the major *N*-benzylpiperidine **30** to give the alcohol **32** that was crystalline and whose structure was confirmed by X-ray diffraction,[7] see Figure 5. The vicinal coupling constant $J_{1,2}$ of the oxazolidinonylpiperidines was found to be diagnostic of their relative configuration at C2, being less than 5 Hz for the major products **3**, **30** and **32**, and greater than 8 Hz for the minor product **31**.

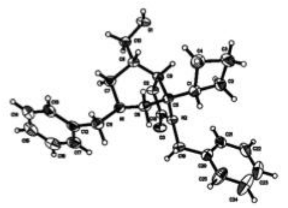


Figure 5 The structure of the (±)-oxazolidinonylpiperidine **32** as established by X-ray data.

This work has resulted in the synthesis of the first member of a novel series of compounds, oxazolidinonylpiperidines, of interest as potentially selective ligands for muscarinic receptors. Indeed the methyl ether **3** was found to be a 50% partial agonist of muscarinic M_1 receptors with micromolar potency, as measured by the relaxation responses of rat duodenum compared with the full agonist McN-A-343. Of interest in the synthetic work was the stereoselectivities of the Grignard addition and hydroboration steps and the overall strategy. This chemistry has been applied to the synthesis of oxazolidinonylpiperidines with both alkoxymethyl and hetaryl sybstituents at C2. This work will be decribed in full elsewhere.

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References and Notes

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(6) **(4*SR*,5*RS*)-4-(*tert*-Butyldimethylsilyloxymethyl)-4-cyclobutyl-5-propen-2-yl-1,3-oxazolidin-2-one (5)** Propen-2-ylmagnesium bromide (0.5 M in toluene, 297 mL, 148.5 mmol, 3.75 eq.) was added over 1 h to the aldehyde **6** (15.5 g, 39.6 mmol) in THF (800 mL) at –78 °C, and the reaction mixture stirred at –78 °C for 2 h then allowed to warm to rt overnight. The reaction mixture was stirred for another 36 h at rt before saturated aqueous ammonium chloride (500 mL) was added. The aqueous phase was extracted with ether (3 × 500 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10) of the residue gave the *title compound* **5** (8.5 g, 66%) as a single diastereoisomer, R_f = 0.30 (ethyl acetate : light petroleum = 1 : 4) as a white solid, m.p. 110-112 °C (Found: C, 62.76; H, 9.62; N, 4.20%. $C_{17}H_{31}NO_3Si$ requires C, 62.73; H, 9.60; N, 4.30; Found: M⁺ + H, 326.2150, $C_{17}H_{32}NO_3Si$ requires *M*, 326.2152); ν_{max}/cm^{-1} 3240, 3137, 2952, 2935, 2892, 2859, 1756, 1465, 1384, 1344, 1254, 1106, 903, 840 and 777; δ_H (400 MHz, $CDCl_3$) 0.02 (6 H, s, 2 × $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.69-2.18 (6 H, m, 3 × CH_2), 1.80 (3 H, s, 3′-H_3), 2.70 (1 H, pent, *J* 8.2 Hz, 4-CH), 3.43 (2 H, s, 4-CH_2), 4.50 (1 H, s, 5-H), 5.04 and 5.13 (each 1 H, s, 1′-H) and 5.86 (1 H, s, NH); δ_C (100 MHz, $CDCl_3$) –5.9, –5.8, 17.4, 18.1, 19.9, 22.4, 24.3, 25.7, 39.4, 63.9, 65.0, 82.2, 113.9, 138.0 and 158.9; *m/z* (CI+) 343 (M⁺ + 18, 75%) and 326 (M⁺ + 1, 100).

(7) **X-Ray data** Oxazolidinone **5**: $C_{17}H_{31}NO_3Si$; unit cell parameters: *a* 12.250(3) *b* 13.606(3) *c* 12.818(3); P21/c, CCDC number 1413285. Alcohol **32**: $C_{25}H_{30}N_2O_3$; unit cell parameters: *a* 22.546(14) *b* 9.314(10) *c* 10.283(9); P21/c, CCDC number 1413286.

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(9) **(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*SR*)- and -(*RS*)-1-hydroxy-3-methoxyprop-2-yl]-1,3-oxazolidin-2-ones (4) and (25)** Borane (1 M in THF, 8.2 mL, 8.22 mmol, 5 eq.) was added dropwise to the alkene **24** (660 mg, 1.48 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 18 h before ethanol (7.1 mL), saturated aqueous sodium acetate (23 mL) and hydrogen peroxide (30% in H_2O, 8 mL) were added. The reaction mixture was heated under reflux for 1 h then cooled. The aqueous phase was extracted with ether (3 × 35 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 4) of the residue gave the *title compounds* **4** and **25** (648 mg, 95%), as a mixture of diastereoisomers, **4** : **25** = 85 : 15, R_f = 0.21 (ethyl acetate : light petroleum = 1 : 2) (Found: M⁺ + H, 464.2835. $C_{25}H_{42}NO_5Si$ requires *M*, 464.2833); ν_{max}/cm^{-1} 3443, 2930, 2892, 2859, 1732, 1468, 1409, 1357, 1297, 1255, 1169, 1104, 1036, 840 and 777; δ_H (400 MHz, $CDCl_3$) major epimer **4** 0.04 and 0.05 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.50-2.05 (6 H, m, 3 × CH_2), 2.22 (1 H, br. s, OH), 2.37 (1 H, m, 2′-H), 2.57 (1 H, m, 4-CH), 3.36 (3 H, s, OCH_3), 3.57 and 3.63 (each 1 H, dd, *J* 6.0, 9.5 Hz, 3′-H), 3.66 (2 H, s, 4-CH_2), 3.85-3.94 (2 H, m, 1′-H_2), 4.17 (1 H, d, *J* 15.8 Hz, PhHC*H*), 4.48 (1 H, d, *J* 6.0 Hz, 5-H), 4.66 (1 H, d, *J* 15.8 Hz, PhHC*H*) and 7.24-7.40 (5 H, m, ArH); minor epimer **25** 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 2.83 (1 H, br. t, *J* 5.5 Hz, OH), 3.36 (3 H, s, OCH_3), 3.72 (1 H, dd, *J* 9.5, 3.5 Hz, 3′-H), 3.79 (1 H, dd, *J* 9.5, 5.5 Hz, 3′-H′), 4.55 (1 H, d, *J* 7.8 Hz, 5-H) and 4.70 (1 H, d, *J* 15.7 Hz, PhHC*H*); δ_C (100 MHz, $CDCl_3$) major epimer **4** –5.9, –5.8, 17.2, 17.9, 23.1, 23.3, 25.7, 38.7, 40.8, 45.8, 59.1, 61.2, 62.3, 68.5, 73.3, 77.4, 127.3, 127.6, 128.5, 138.4 and 159.1; minor epimer **25** –5.8, 17.1, 17.9, 23.1, 23.4, 25.6, 38.7, 40.3, 45.8, 59.3, 60.8, 64.4, 68.8, 73.6, 75.4, 127.2, 127.6, 128.4, 138.5 and 159.5; *m/z* (CI+) 464 (M⁺ + 1, 1%) and 90 (100).

(10) **(1*RS*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-ones (30) and (31)** Freshly distilled methane sulfonyl chloride (0.112 mL, 1.42 mmol, 3 eq.) and Et_3N (0.20 mL, 1.42 mmol, 3 eq.) were added successively to a mixture of the diols **27** and **28** (166 mg, 0.475 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 1 h before the addition of ether (5 mL) and saturated aqueous ammonium chloride (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave a mixture of the bis-mesylates **29** (228 mg) that was used without purification. The bis-mesylates **29** (228 mg) were dissolved in benzylamine (15 mL) and the solution heated at 80 °C for 18 h. After cooling to rt, the benzylamine was removed by distillation under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 20 to 1 : 10) of the residue achieved partial separation of the piperidines **30** and **31** to give the *title compound* **30** (72 mg, 36%), R_f = 0.28 (ethyl acetate : light petroleum = 1 : 2) (Found: M⁺, 420.2410. $C_{26}H_{32}N_2O_3$ requires *M*, 420.2413); ν_{max}/cm^{-1} 3083, 3060, 3029, 2924, 2872, 2811, 1744, 1494, 1453, 1405, 1349, 1294, 1201, 1168, 1117, 1090, 1060, 1028, 978, 818 and 746; δ_H (400 MHz, $CDCl_3$) 1.40-1.78 (5 H, m, cyclobutyl H), 2.00 (1 H, m, cyclobutyl H), 2.10 (1 H, d, *J* 12.5 Hz, 5-H), 2.22 (1 H, m, 2-H), 2.36 (1 H, t, *J* 10.5 Hz, 3-H), 2.41 (1 H, d, *J* 12.5 Hz, 5-H′), 2.49 (1 H, pent, *J* 8.7 Hz, 6-CH), 2.58 (1 H, dd, *J* 7.25, 10.5 Hz, 3-H′), 3.32-3.37 (6 H, m, 2-CH, OCH_3, $PhCH_2$), 3.57 (1 H, t, *J* 8.5 Hz, 2-CH′), 3.91 and 4.28 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.51 (1 H, d, *J* 2.5 Hz, 1-H) and 7.21-7.34 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.6, 22.9, 23.3, 36.7, 39.2, 44.7, 50.6, 53.0, 59.1, 61.9, 64.4, 72.0, 74.3, 127.2, 127.3, 127.9, 128.3(2), 128.9, 138.0, 138.3 and 159.1; *m/z* (EI) 420 (M⁺, 1%) and 91 (100). The second fraction was a mixture of the title compounds **30** and **31** (53 mg, 26%), **30** : **31** = 56 : 44, R_f = 0.28 - 0.22 (ethyl acetate : light petroleum = 1 : 2) (Found: M⁺, 420.2412. $C_{26}H_{31}N_2O_3$ requires *M*, 420.2413); ν_{max}/cm^{-1} 3083, 3061, 3029, 2927, 2869, 2823, 1746, 1495, 1453, 1436, 1403, 1355, 1334, 1193, 1170, 1106, 1053, 1027, 996, 923, 809 and 743; δ_H (400 MHz, $CDCl_3$) minor epimer **31** 2.75-2.85 (2 H, m, 3-H, 5-H), 3.24 (1 H, d, *J* 12.8 Hz, PhHC*H*), 3.47 (1 H, dd, *J* 3.0, 9.5 Hz, 2-CH), 3.53 (1 H, dd, *J* 5.25, 9.5 Hz, 2-CH′), 4.02 (1 H, d, *J* 15.5 Hz, PhHC*H*), 4.40 (1 H, d, *J* 8.7 Hz, 1-H) and 4.45 (1 H, d, *J* 15.5 Hz, PhHC*H*); δ_C (100 MHz, $CDCl_3$) minor epimer **31** 16.9, 23.3, 23.7, 41.2, 41.6, 44.4, 53.3(2), 59.1, 62.4, 63.6, 71.8, 73.8, 127.4(2), 128.0, 128.3, 128.4, 129.3, 137.9, 138.1 and 158.4; *m/z* (CI+) 421 (M⁺ + 1, 100%).

(11) **(1*RS*,2*SR*,6*SR*)-7-Benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (3)** A solution of formic acid (93 μL, 0.025 mmol, 0.4 eq.) in MeOH (1 mL) was added to the *N*-benzylpiperidine **30** (26 mg, 0.062 mmol) and 10% Pd/C (41 mg) under N_2 and the reaction mixture was stirred at rt for 20 min. Potassium carbonate (50 mg) was added, the reaction mixture was filtered through celite and the residue was washed with ether. After concentration under reduced pressure, chromatography (MeOH : ether = 1 : 50, saturated in ammonia) of the residue gave the *title compound* **3** (14 mg, 71%), R_f = 0.38 (MeOH : ether = 1 : 10 saturated in ammonia) (Found: M⁺, 330.1941. $C_{19}H_{26}N_2O_3$ requires *M*, 330.1943); ν_{max}/cm^{-1} 3343, 3086, 3062, 3029, 2935, 2871, 2832, 2815, 1742, 1672, 1496, 1454, 1432, 1409, 1345, 1199, 1167, 1146, 1112, 1090, 1071, 984, 759 and 707; δ_H (400 MHz, $CDCl_3$) 1.54-2.00 (7 H, m, 3 × CH_2, 6-CH), 2.12 (1 H, m, 2-H), 2.37 (1 H, d, *J* 14.2 Hz, 5-H), 2.57 (1 H, t, *J* 12.0 Hz, 3-H), 2.61 (1 H, d, *J* 14.2 Hz, 5-H′), 2.91 (1 H, dd, *J* 6.5, 12.0 Hz, 3-H′), 3.31 (1 H, dd, *J* 6.0, 9.0 Hz, 2-CH), 3.36 (3 H, s, CH_3), 3.52 (1 H, t, *J* 9.0 Hz, 2-CH′), 4.22 and 4.43 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.71 (1 H, d, *J* 2.7 Hz 1-H) and 7.24-7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.5, 22.2, 22.8, 35.8, 38.5, 40.7, 44.6, 45.0, 59.0,

63.4, 71.4, 73.6, 127.8, 127.8, 128.7, 138.1 and 158.7; *m/z* (CI+) 331 (M^+ + 1, 60%) and 91 (100).