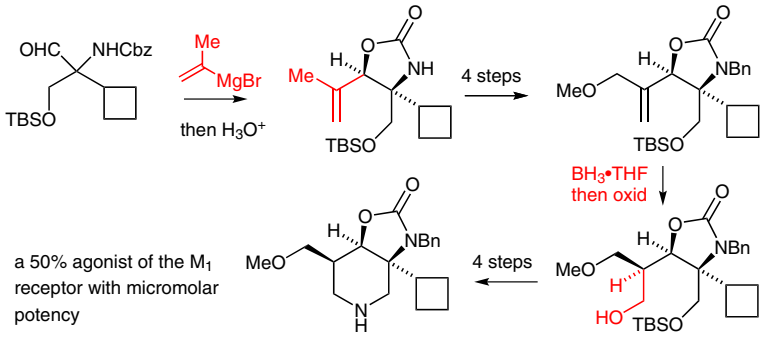
A Stereoselective Synthesis of a 3,4,5-Substituted Piperidine of Interest as a Selective Muscarinic (M_1) Receptor Agonist

Kenneth J. Broadley[a]
Maxime G. P. Buffat[b]
Robin H. Davies[† a]
Eric J. Thomas[*b]

[a] The Welsh School of Pharmacy, Redwood Building, King Edward VII Avenue, Cardiff, CF10 3NB, UK
[b] The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK
e.j.thomas@manchester.ac.uk
[†] Deceased October 2011

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, which is 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 would provide alternatives to cholinesterase inhibitors that tend to lose efficacy over time and, indeed, several M_1 receptor agonists have already been found to alleviate the symptoms of this illness.[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 computational studies using bacterial rhodopsin as a model for the M_1 receptor led to the identification of the 2-alkoxymethyl- and 2-hetaryl-oxazolidinonylpiperidines **1** and **2** as possible selective M_1 agonists (Figure 1).[3] We now describe a stereoselective synthesis of the first representative of this class of novel compounds.

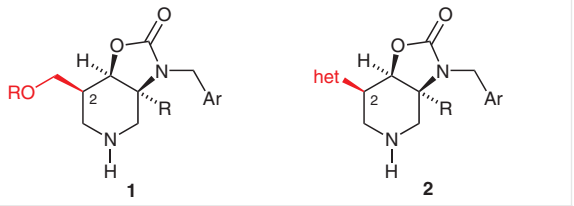
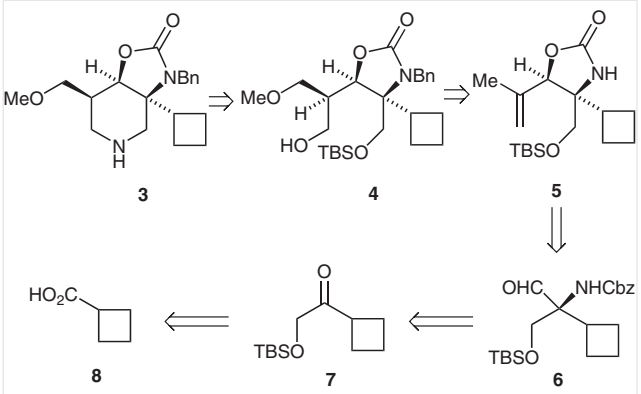


Figure 1 Oxazolidinonylpiperidines of interest as M_1 receptor agonists

The first member of the series selected for synthesis was 7-benzyl-6-cyclobutyl-2-methoxymethyl analogue **3** (Scheme 1). Oxazolidinone **4** was identified as a likely precursor of piperidine **3** and, in turn, alkenyloxazolidinone **5**, which was possibly accessible from aldehyde **6**, was considered to be a plausible intermediate for the synthesis of oxazolidinone **4**. Aldehyde **6** was recognised as 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 aldehyde **6** from ketone **7**, which would, in turn, be prepared from the commercially available cyclobutane carboxylic acid **8** (Scheme 1).

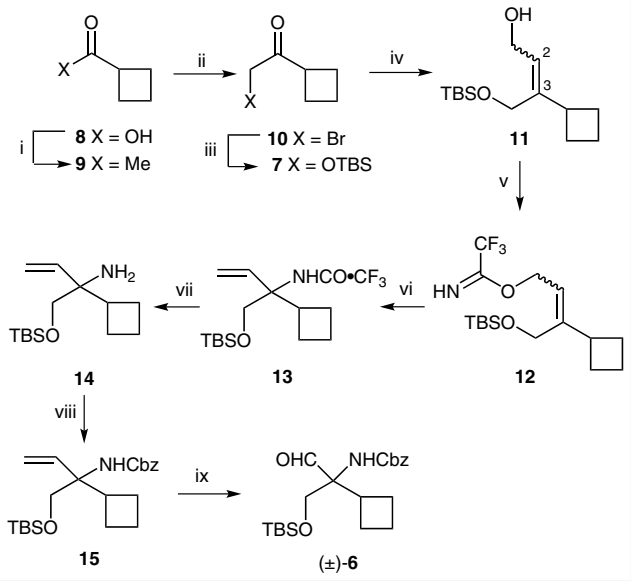
Although this synthesis looked reasonable, at the onset of the work it was difficult to be certain how to control the stereoselectivities of several of the steps.



Scheme 1 Proposed synthesis of oxazolidinonylpiperidine **3**

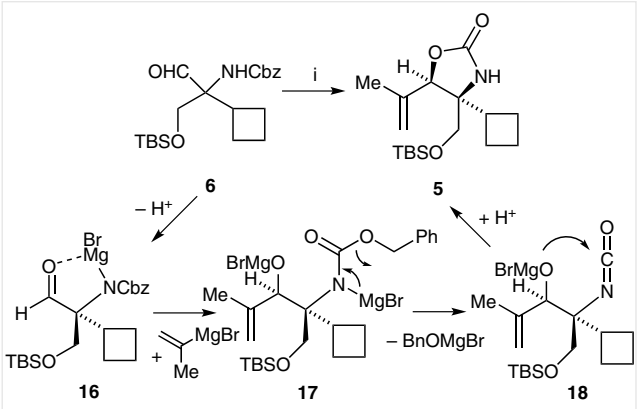
A synthesis of the racemic modification of aldehyde **6** is outlined in Scheme 2. *tert*-Butyldimethylsilyloxymethyl ketone **7** was prepared in four steps from cyclobutanecarboxylic acid **8** by conversion into methyl ketone **9**, bromination

of the ketone, and hydrolysis of the known[4] bromide **10** to give the corresponding alcohol, which was protected as its silyl ether **7**. A Wadsworth–Emmons–Horner reaction of protected hydroxyketone **7** followed by reduction of the resulting α,β-unsaturated esters gave a 75:25 mixture of the geometrical isomers of the alcohols **11**, with the major alcohol being identified as the *Z*-isomer on the basis of a significant NOE signal 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 racemic tertiary trifluoroacetamide **13**.[5] Cleavage of the trifluoroacetamide was carried out under mild conditions by using sodium borohydride in ethanol, and the resulting amine **14** was converted into its Cbz-derivative **15**, which was ozonolysed to give the required aldehyde (±)-**6** (Scheme 2).



Scheme 2 Synthesis of the aldehyde (±)-**6**. *Reagents and conditions*: (i) MeLi, Et_2O, 0 °C to r.t., 3 h (90%); (ii) Br_2, MeOH, 0 to 15 °C, 1.5 h (80%); (iii) a. KOCHO, MeOH, reflux, 12 h (71%); b. TBSCl, imid., DMAP (cat.), TBAI (cat.), CH_2Cl_2, r.t., 1 h (62%); (iv) a. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, r.t., 45 min, add **7**, r.t., 2.5 h; b. DIBAL-H, hexanes, THF, –78 °C, 3 h, r.t., 30 min [89% from **7**, *Z*/*E* = 75:25]; (v) NaH, THF, r.t., 1 h, add to CF_3CN, THF, –115 to –78 °C, 1 h (88%); (vi) xylene, reflux 18 h (91%); (vii) $NaBH_4$, EtOH, 0 °C to r.t., 18 h (80%); (viii) CbzCl, Et_3N, CH_2Cl_2, r.t., 18 h (83%); (ix) O_3, CH_2Cl_2, –78 °C, then Ph_3P, r.t. (84%).

The next step was the conversion of aldehyde **6** into oxazolidinone **5** (Scheme 3). This was achieved in one pot by 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** directly. 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 adduct **17**. The latter compound cyclised in situ on standing, possibly via isocyanate **18** formed by loss of bromomagnesium benzyloxide, to give the oxazolidinone **5** after work-up (Scheme 3). The structure assigned to this oxazolidinone was confirmed by X-ray diffraction analysis[7] (Figure 2).



Scheme 3 Preparation of the oxazolidinone **5**. *Reagents and conditions*: (i) MeC(MgBr)=CH_2, THF, toluene, –78 °C, 2 h then r.t., 48 h (66%).

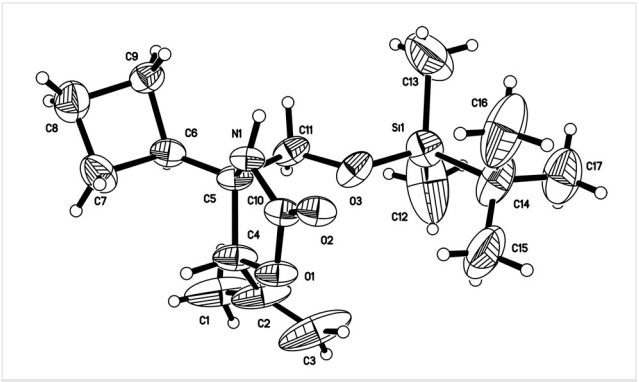
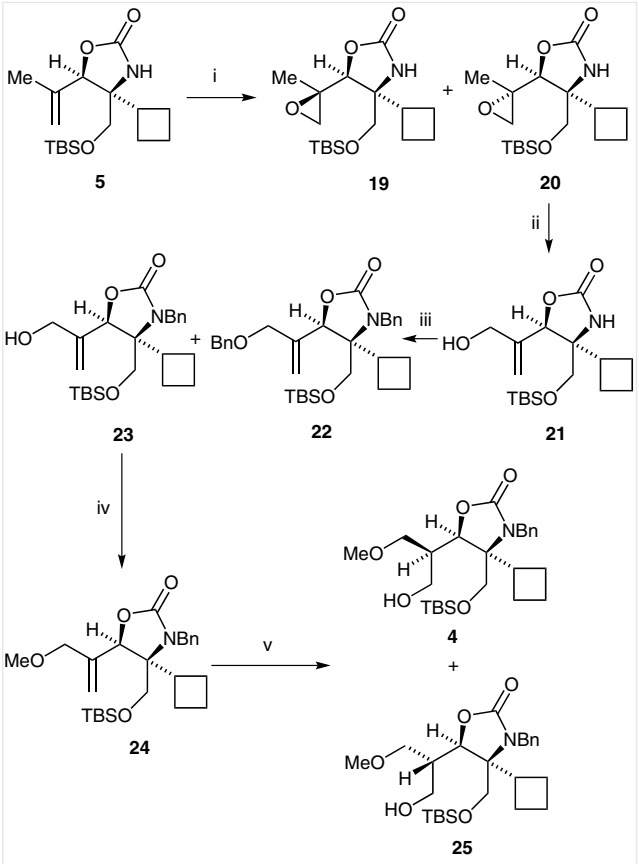


Figure 2 The structure of oxazolidinone **5** as established by X-ray diffraction analysis

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

Alkylation of **21** using sodium hydride–benzyl bromide gave *N*-benzyloxazolidinone **23** as the major product, with bis-benzylated material **22** formed only a minor side-product (ca. 5%). Methylation of alcohol **23** led to methyl ether **24** and hydroboration–oxidation of this alkene using borane in THF at 0 °C gave a mixture of epimeric alcohols **4** and **25** in a ratio of 85:15[9] (Scheme 4).



Scheme 4 Synthesis of (±)-oxazolidinone **4**. *Reagents and conditions*: (i) MCPBA, CH_2Cl_2, r.t., 18 h (75%); (ii) 2,2,6,6-tetramethylpiperidine, THF, *n*-BuLi, 0 °C to r.t., 1 h, added to **19** and **20**, THF, 0 °C to r.t., 3 h (67%); (iii) NaH, BnBr, THF, reflux, 6 h (**23**, 79%; **22**, 5%); (iv) NaH, THF, MeI, r.t., 18 h (90%); (v) BH_3, THF, 0 °C, 18 h, then EtOH, NaOAc, 30% aq. H_2O_2, reflux, 1 h (95%, **4**/**25** = 85:15).

The mixture of hydroboration products was not separated, and the structure of the major product, which turned out to be the required epimer **4**, was only confirmed later in the synthesis. The stereoselectivity can be explained by the preferred participation of transition structure **26** in the hydroboration step (Figure 3), but this rationalisation is only speculative because molecular modelling studies of the hydroboration were not carried out.

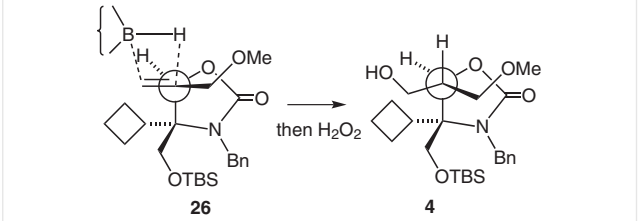


Figure 3 Facial selectivity of the hydroboration of alkene **24**

The completion of the synthesis of oxazolidinonylpiperidine **3** is outlined in Scheme 5. Desilylation of the mixture of hydroboration products **4** and **25** gave a mixture of diols **27** and **28**, which was converted into *N*-benzylpiperidines **30** and **31** (ratio ca. 85:15), by reaction of the mixture of mesylates **29** with an excess of benzylamine.[10] Following separation of the major component *N*-benzylpiperidine **30** by chromatography, a selective transfer hydrogenolysis of the piperidine *N*-benzyl group gave the required oxazolidinonylpiperidine **3**.[11]

The structures of the products shown in Scheme 5 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 alcohol **32**, which was crystalline and whose structure was confirmed by X-ray diffraction[7] (Figure 4). The vicinal coupling constants $J_{1,2}$ of the oxazolidinonylpiperidines were 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**, consistent with the boat-like conformation of the piperidine ring in alcohol **32**.

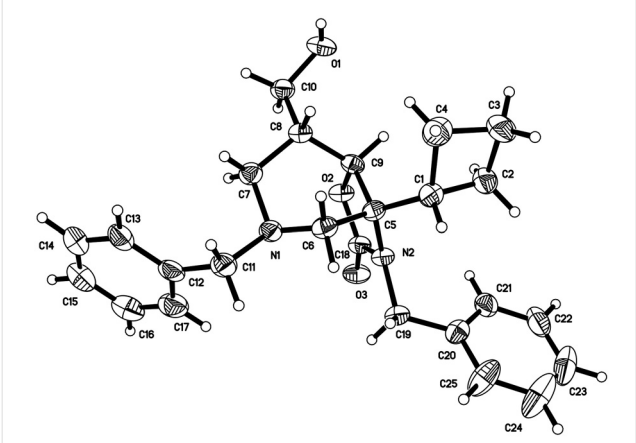
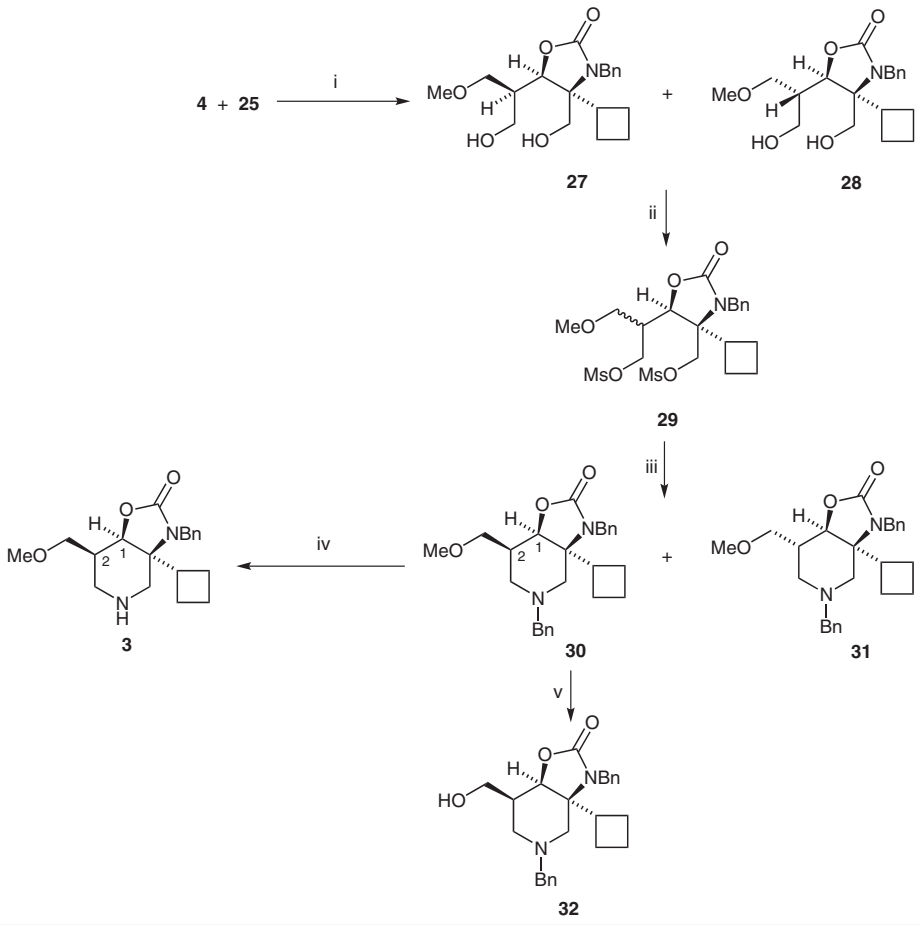


Figure 4 The structure of (±)-oxazolidinonylpiperidine **32** as established by X-ray crystallography data

This work has resulted in the synthesis of the first member of a novel series of compounds, oxazolidinonylpiperidines, which are of interest as potential selective ligands for muscarinic receptors. Indeed, methyl ether **3** was found to be a 50% partial agonist of the 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, together with the overall strategy. This chemistry has been applied to the synthesis of oxazolidinonylpiperidines **1** and **2**, with both alkoxymethyl and hetaryl substituents at



Scheme 5 Completion of a synthesis of (±)-oxazolidinonylpiperidine **3**. *Reagents and conditions*: (i) TBAF, THF, 0 °C to r.t., 30 min (67%, **27**/**28** = 85:15); (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 1 h; (iii) $BnNH_2$, 80 °C, 18 h (**30**, 36%; mixture of **30** and **31**, 26%, **30**/**31** ratio 55:45); (iv) 10% Pd/C, HCO_2H, MeOH, r.t., 20 min (71%); (v) BBr_3, CH_2Cl_2, THF, 0 °C, 4 h (61%).

C2. This work will be described in full elsewhere together with the preliminary results of an alternative synthetic strategy.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560753.

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 equiv) was added over 1 h to aldehyde **6** (15.5 g, 39.6 mmol) in THF (800 mL) at –78 °C, and the reaction mixture was stirred at –78 °C for 2 h, then allowed to warm to r.t. overnight. The reaction mixture was stirred for another 36 h at r.t. before sat. aq NH_4Cl (500 mL) was added. The aqueous phase was extracted with Et_2O (3 × 500 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (EtOAc–light petroleum, 1:10) of the residue gave the title compound **5** (8.5 g, 66%) as a single diastereoisomer as a white solid; mp 110–112 °C; R_f = 0.30 (EtOAc–light petroleum, 1:4). IR: 3240, 3137, 2952, 2935, 2892, 2859, 1756, 1465, 1384, 1344, 1254, 1106, 903, 840, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, 2 × $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.69–2.18 (m, 6 H, 3 × CH_2), 1.80 (s, 3 H, 3′-H_3), 2.70 (pent, *J* = 8.2 Hz, 1 H, 4-CH), 3.43 (s, 2 H, 4-CH_2), 4.50 (s, 1 H, 5-H), 5.04 (s, 1 H, 1′-H), 5.13 (s, 1 H, 1′-H), 5.86 (s, 1 H, NH). ^{13}C (100 MHz, $CDCl_3$): δ = –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, 158.9. MS (CI+): *m*/*z* (%) = 343 (75) [M^+ + 18], 326 (100) [M^+ + 1]. HRMS: *m*/*z* [M^+ + H] calcd for $C_{17}H_{32}NO_3Si$: 326.2152; found: 326.2150. Anal. Calcd for $C_{17}H_{31}NO_3Si$: C, 62.73; H, 9.60; N, 4.30; found: C, 62.76; H, 9.62; N, 4.20.

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

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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 equiv) was added dropwise to 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 EtOH (7.1 mL), sat. aq NaOAc (23 mL) and H_2O_2 (30% in H_2O, 8 mL) were added. The reaction mixture was heated to reflux for 1 h then cooled. The aqueous phase was extracted with Et_2O (3 × 35 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (EtOAc–light petroleum, 1:4) of the residue gave the title compounds **4** and **25** (648 mg, 95%), as a mixture of diastereoisomers (**4**/**25** ratio 85:15); R_f = 0.21 (EtOAc–light petroleum, 1:2). HRMS: *m*/*z* [M^+ + H] calcd for $C_{25}H_{42}NO_5Si$: 464.2833; found: 464.2835. IR: 3443, 2930, 2892, 2859, 1732, 1468, 1409, 1357, 1297, 1255, 1169, 1104, 1036, 840, 777 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ (major epimer **4**) = 0.04 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.50–2.05 (m, 6 H, 3 × CH_2), 2.22 (br. s, 1 H, OH), 2.37 (m, 1 H, 2′-H), 2.57 (m, 1 H, 4-CH), 3.36 (s, 3 H, OCH_3), 3.57 (dd, *J* = 6.0, 9.5 Hz, 1 H, 3′-H), 3.63 (dd, *J* = 6.0, 9.5 Hz, 1 H, 3′-H), 3.66 (s, 2 H, 4-CH_2), 3.85–3.94 (m, 2 H, 1′-H_2), 4.17 (d, *J* = 15.8 Hz, 1 H, PhHC*H*), 4.48 (d, *J* = 6.0 Hz, 1 H, 5-H), 4.66 (d, *J* = 15.8 Hz, 1 H, PhHC*H*), 7.24–7.40 (m, 5 H, ArH); δ (minor epimer **25**) = 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 2.83 (br. t, *J* = 5.5 Hz, 1 H, OH), 3.36 (s, 3 H, OCH_3), 3.72 (dd, *J* = 9.5, 3.5 Hz, 1 H, 3′-H), 3.79 (dd, *J* = 9.5, 5.5 Hz, 1 H, 3′-H′), 4.55 (d, *J* = 7.8 Hz, 1 H, 5-H), 4.70 (d, *J* = 15.7 Hz, 1 H, PhHC*H*). ^{13}C (100 MHz, $CDCl_3$): δ (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, 159.1; δ (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, 159.5. MS (CI+): *m*/*z* (%) = 464 (1) [M^+ + 1], 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 equiv) and Et_3N (0.20 mL, 1.42 mmol, 3 equiv) were added successively to a mixture of diols **27** and **28** (166 mg, 0.475 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 1 h before the addition of Et_2O (5 mL) and sat. aq NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of bis-mesylates **29** (228 mg), which was used without purification. Bis-mesylates **29** (228 mg) were dissolved in benzylamine (15 mL) and the solution was heated at 80 °C for 18 h. After cooling to r.t., the benzylamine was removed by distillation under reduced pressure. Chromatography (EtOAc–light petroleum, 1:20 to 1:10) of the residue achieved partial separation of piperidines **30** and **31** to give the title compound **30** (72 mg, 36%); R_f = 0.28 (EtOAc–light petroleum, 1:2). HRMS: *m*/*z* [M]$^+$ calcd for $C_{26}H_{32}N_2O_3$: 420.2413; found: 420.2410. IR: 3083, 3060, 3029, 2924, 2872, 2811, 1744, 1494, 1453, 1405, 1349, 1294, 1201, 1168, 1117, 1090, 1060, 1028, 978, 818, 746 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ = 1.40–1.78 (m, 5 H, cyclobutyl H), 2.00 (m, 1 H, cyclobutyl H), 2.10 (d, *J* = 12.5 Hz, 1 H, 5-H), 2.22 (m, 1 H, 2-H), 2.36 (t, *J* = 10.5 Hz, 1 H, 3-H), 2.41 (d, *J* = 12.5 Hz, 1 H, 5-H′), 2.49 (pent, *J* = 8.7 Hz, 1 H, 6-CH), 2.58 (dd, *J* = 7.25, 10.5 Hz, 1 H, 3-H′), 3.32–3.37 (m, 6 H, 2-CH, OCH_3, $PhCH_2$), 3.57 (t, *J* = 8.5 Hz, 1 H, 2-CH′), 3.91 (d, *J* = 16.0 Hz, 1 H, PhHC*H*), 4.28 (d, *J* = 16.0 Hz, 1 H, PhHC*H*), 4.51 (d, *J* = 2.5 Hz, 1 H, 1-H), 7.21–7.34 (m, 10 H, ArH). ^{13}C (100 MHz, $CDCl_3$): δ = 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, 159.1; MS (EI): *m*/*z* (%) = 420 (1) [M^+], 91 (100). The second fraction was a mixture of the title compounds **30** and **31** (53 mg, 26%); **30**/**31** ratio 55:45; R_f = 0.28–0.22 (EtOAc–light petroleum, 1:2). HRMS: *m*/*z* [M]$^+$ calcd for $C_{26}H_{32}N_2O_3$: 420.2413; found: 420.2412. IR: 3083, 3061, 3029, 2927, 2869, 2823, 1746, 1495, 1453, 1436, 1403, 1355, 1334, 1193, 1170, 1106, 1053, 1027, 996, 923, 809, 743 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ (minor epimer **31**) = 2.75–2.85 (m, 2 H, 3-H, 5-H), 3.24 (d, *J* = 12.8 Hz, 1 H, PhHC*H*), 3.47 (dd, *J* = 3.0, 9.5 Hz, 1 H, 2-CH), 3.53 (dd, *J* = 5.25, 9.5 Hz, 1 H, 2-CH′), 4.02 (d, *J* = 15.5 Hz, 1 H, PhHC*H*), 4.40 (d, *J* = 8.7 Hz, 1 H, 1-H), 4.45 (d, *J* = 15.5 Hz, 1 H, PhHC*H*). ^{13}C (100 MHz, $CDCl_3$): δ (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, 158.4. MS (CI+): *m*/*z* (%) = 421 (100) [M^+ + 1].

(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 equiv) in MeOH (1 mL) was added to *N*-benzylpiperidine **30** (26 mg, 0.062 mmol) and 10% Pd/C (41 mg) under N_2, and the reaction mixture was stirred at r.t. for 20 min. K_2CO_3 (50 mg) was added, the reaction mixture was filtered through Celite, and the residue was washed with Et_2O. After concentration under reduced pressure, chromatography (MeOH–Et_2O, 1:50, saturated in ammonia) of the residue gave

the title compound **3** (14 mg, 71%); R_f = 0.38 (MeOH–Et_2O, 1:10 saturated in ammonia). HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{26}N_2O_3$: 330.1943; found: 330.1941. IR: 3343, 3086, 3062, 3029, 2935, 2871, 2832, 2815, 1742, 1672, 1496, 1454, 1432, 1409, 1345, 1199, 1167, 1146, 1112, 1090, 1071, 984, 759, 707 cm^{-1}. ^1H (400 MHz, $CDCl_3$): δ = 1.54–2.00 (m, 7 H, 3 × CH_2, 6-CH), 2.12 (m, 1 H, 2-H), 2.37 (d, *J* = 14.2 Hz, 1 H, 5-H), 2.57 (t, *J* = 12.0 Hz, 1 H, 3-H), 2.61 (d, *J* = 14.2 Hz, 1 H, 5-H′), 2.91 (dd, *J* = 6.5, 12.0 Hz, 1 H, 3-H′), 3.31 (dd, *J* = 6.0, 9.0 Hz, 1 H, 2-CH), 3.36 (s, 3 H, CH_3), 3.52 (t, *J* = 9.0 Hz, 1 H, 2-CH′), 4.22 (d, *J* = 15.7 Hz, 1 H, PhHC*H*), 4.43 (d, *J* = 15.7 Hz, 1 H, PhHC*H*), 4.71 (d, 1 H, *J* = 2.7 Hz, 1-H), 7.24–7.39 (m, 5 H, ArH). ^{13}C (100 MHz, $CDCl_3$): δ = 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(2), 128.7, 138.1, 158.7. MS (CI+): *m*/*z* (%) = 331 (60) $[M^+ + 1]$, 91 (100).