A stereoselective synthesis of a 3,4,5-substituted piperidine of interest as a selective muscarinic (M₁) receptor agonist

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

Abstract A stereoselective synthesis of (1RS,2SR,6SR)-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 (M₁) receptor agonists, is described.

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

Agonists of muscarinic M₁ receptors have been identified as potential chemotherapeutic agents for the treatment of Alzheimer’s disease. In particular, they could provide alternatives to cholinesterase inhibitors that tend to lose efficacy over time. Indeed several M₁ receptor agonists have been found to alleviate the symptoms of Alzheimer’s disease. It is, however, crucial to find compounds selective for M₁ 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 M₁ receptor, led to the identification of the oxazolidinonylpiperidines 1 and 2 as possibly selective M₁ agonists, see Figure 1.3 We now describe a stereoselective synthesis of the first representative of these novel compounds.

Figure 1 Oxazolidinonylpiperidines of interest as M₁ 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 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 αβ-
unsaturated 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. 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.

To convert the oxazolidinone 16 into the cyclisation precursor 17, see Scheme 2. This reaction was highly stereoselective and gave the cyclised product 18 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 benzylxide, to give the oxazolidinone after work-up, see Scheme 2. The structure assigned to the oxazolidinone 5 was confirmed by X-ray diffraction, 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 to give the allylic alcohol 21.

Scheme 2 Preparation of the oxazolidinone 5 Reagents and conditions (i) CH₃C(MgBr)=CH₂, THF, toluene, −78 °C, 2 h then rt, 48 h (66%).

Scheme 3 Synthesis of the (±)-oxazolidinone 4 Reagents and conditions (i) (i) mCPBA, DCM, rt, 18 h (75%); (ii) 2,2,6,6-tetramethylpiperidide, THF, BuLi, 0 °C to rt, 1 h, added to 19 and 20, THF, 0 °C to rt, 3 h (67%); (iii) NaH, BuNBr, THF, heat under reflux, 6 h (23, 79%; 22, 66%); (iv) NaH, THF, Me₂I, rt, 18 h (90%); (v) Bu₃SnH, THF, 0 °C, 18 h, then EtOH, NaOAc, 30% aq. H₂O₂, heat under reflux 1 h (95%), 4 : 25 = 85 : 15.

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

Alkylation using sodium hydride-benzyl bromide gave the N-benzylxazolidinone 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, see Scheme 3.

Scheme 1 Synthesis of the aldehyde (±)-6 Reagents and conditions (i) MeLi, Et₂O, 0 °C to rt, 3 h (90%); (ii) Br₂, MeOH, 0 °C to 15 °C, 1.5 h (80%); (iii) (a) KOCHO, MeOH, heat under reflux, 12 h (71%) (b) TBSCI, imid., DMAP (cat.), TBAI (cat.), DCM, rt, 1 h (62%); (iv) (a) (EtO)₂P(O)CH₂CH₂OH, NaH, THF, rt, 45 min, add 7, rt, 2.5 h (b) DIBAL-H, hexanes, THF, −78 °C, 3 h, rt, 30 min (89% from 7). (ii) CH₂=CH₂, THF, 0 °C to rt, 3 h (80%); (v) NaH, THF, rt, 1 h, add to CF₃CN, THF, −115 °C to −78 °C, 1 h (88%); (vi) xylene, heat under reflux 18 h (91%); (vii) NaBH₄, EtOH, 0 °C to rt, 18 h (80%); (viii) CBr₃Cl, Et₃N, DCM, rt, 18 h (83%); (ix) O₃, DCM, −78 °C, then Ph₂P, 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 propargylmagnesium bromide with a prolonged reaction time to facilitate cyclisation. 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 benzylxide, to give the oxazolidinone after work-up, see Scheme 2. The structure assigned to the oxazolidinone 5 was confirmed by X-ray diffraction, 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 to give the allylic alcohol 21.
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

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 hydrolysis 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, Et3N, DCM, 0 °C to rt, 1 h; (iii) BnNH2, 80 °C, 18 h (30, 36%); mixture of 30 and 31, 26%, 30 : 31 = 55 : 45; (iv) 10% Pd/C, HCO2H, MeOH, rt, 20 min (71%); (v) BBr3, 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 1H 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 J1,2 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 M1 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 substituents at C2. This work will be described in full elsewhere.

**Acknowledgment**

We thank Dr. J. Raftery for help with X-ray data.

**References and Notes**


3. Davies, R. H. unpublished observations.


(6) [4RS,5SR]-4-(tert-Butyldimethylsilyloxy)methyl)-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 (MgSO₄) 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 diastereomer, Rf = 0.30 (ethyl acetate : light petroleum = 1 : 4) as a white solid, m.p. 110-112 °C (Found: C, 53.36; H, 7.01; N, 4.20; C₂₃H₂₈NO₃Si requires C, 53.31; H, 6.98; N, 4.20; %).

(6a) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H.

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(7) Rf = 0.28 (ethyl acetate : light petroleum = 1 : 2) (Found: M⁺, 420.2410. C₂₈H₃₆NO₃Si requires M⁺, 420.2413; m/z 420.2 (23%); m/z 420.2 (23%).


(9) [4RS,5SR]-4-(tert-Butyldimethylsilyloxy)methyl)-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 (MgSO₄) 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 diastereomer, Rf = 0.30 (ethyl acetate : light petroleum = 1 : 4) as a white solid, m.p. 110-112 °C (Found: C, 53.36; H, 7.01; N, 4.20; C₂₃H₂₈NO₃Si requires C, 53.31; H, 6.98; N, 4.20; %).

(10) [1R5S,4R]-7-Benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diazaoxazolidin-2-one (4) A solution of formic acid (93 µL, 0.025 mmol, 0.4 eq.) in MeOH (1 mL) was added to the N-benzylpiperidene 30 (26 mg, 0.062 mmol) and 10% Pd/C (41 mg) under N₂ 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%). Rf = 0.38 (MeOH : ether = 1 : 10 saturated in ammonia) (Found: M⁺, 330.3941. C₂₇H₃₈NO₃ requires M⁺, 330.3940; m/z 330.3 (22%); m/z 330.3 (22%).

(11) [1R5S,4R]-7-Benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diazaoxazolidin-2-one (4) A solution of formic acid (93 µL, 0.025 mmol, 0.4 eq.) in MeOH (1 mL) was added to the N-benzylpiperidene 30 (26 mg, 0.062 mmol) and 10% Pd/C (41 mg) under N₂ 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%). Rf = 0.38 (MeOH : ether = 1 : 10 saturated in ammonia) (Found: M⁺, 330.3941. C₂₇H₃₈NO₃ requires M⁺, 330.3940; m/z 330.3 (22%); m/z 330.3 (22%).

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