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Stereocontrolled approaches to 2-(2-aminoalkyl)-1-hydroxycyclopropanes

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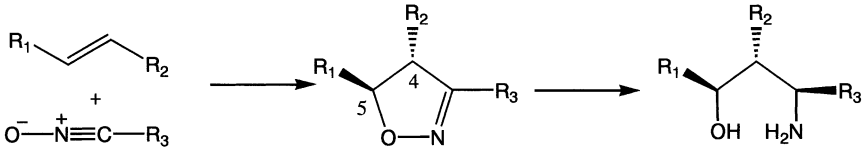
Abstract—(1*S*,2*S*)-2[(*S*)-Amino(4-methoxyphenyl)methyl]cyclopropan-1-ol together with a range of racemic 2-(2-aminoalkyl)-1-hydroxycyclopropanes were prepared by a stepwise procedure involving a 1,3-dipolar cycloaddition of a nitrile oxide to a cyclopropene followed by reduction of the derived bicycle.

Isoxazolines are readily obtained by cycloaddition of nitrile oxides to alkenes. The reduction of the ring is known to provide access to γ-aminoalcohols, in some cases with a high degree of stereo-control,[1–3] in a reaction effectively amounting to selective 1-hydroxy-2-aminoalkylation of an alkene (Scheme 1).

With alkyl or other non-coordinating groups at C-4 or C-5 of the isoxazoline, hydrogen addition takes place predominantly *anti* (*trans*) to the substituents to give the *syn*-1,3-disubstituted aminoalcohol. Hydroxyl or hydroxymethyl-substituents, however, direct the reducing agent to the *syn* face of the C=N bond, leading predominantly to the *anti*-aminoalcohol.[4,5] Although there has been considerable interest in the formation of isoxazolines by the cycloaddition of nitrile oxides to cyclopropenes, little is known about their subsequent ring-opening to 2-aminoalkyl-1-hydroxycyclopropanes. In view of the considerable range of biological activity shown by amino-substituted cyclopropanes,[6] we now report the results of such an examination.



Scheme 1.

Cycloadducts between a number of cyclopropenes and nitrile oxides were prepared by standard methods.[7] The adduct (**1**), formed from 2,4,6-trimethoxybenzonitrile oxide and 3-methyl-3-phenyl-cyclopropene did not react with lithium aluminium hydride (Scheme 2).

However, the corresponding adduct of 4-methoxybenzonitrile oxide, compound (**2**) was reduced to a single aminoalcohol (**8**) in reasonable yield (51%), as a pair of enantiomers. The structure of this product was confirmed by a single crystal X-ray determination, and is shown in Fig. 1. This can be explained in terms of a selective addition of hydride to the convex face of the azabicycle, fixing the stereochemistry at C-4, followed by N–O cleavage (Scheme 3).

Presumably in the case of (**1**), the two *o*-OMe groups cause the aryl group to be twisted out of the plane of the C=N

(1, Ar = 2,4,6-trimethoxy-C_6H_2)
(2, Ar = 4-methoxy-C_6H_4)

(8)

Scheme 2.

Keywords: isoxazolines; allyl alcohol; cyclopropenes; cyclopropanes.
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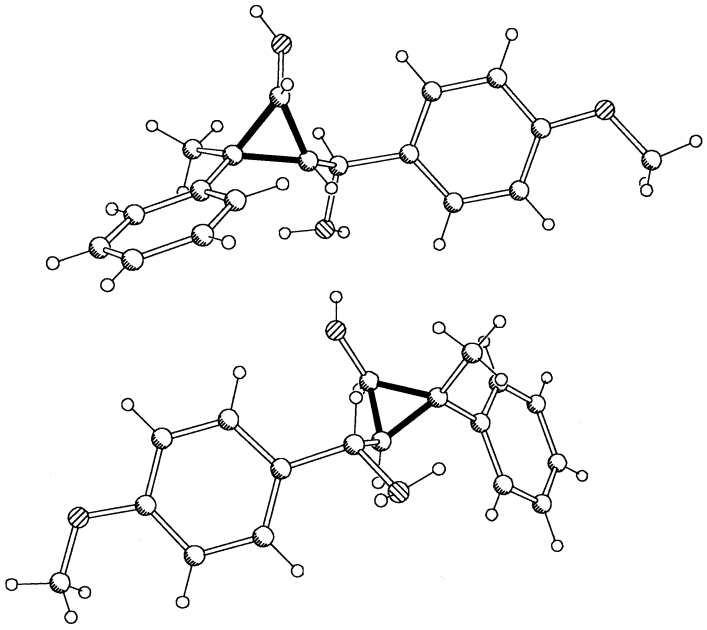
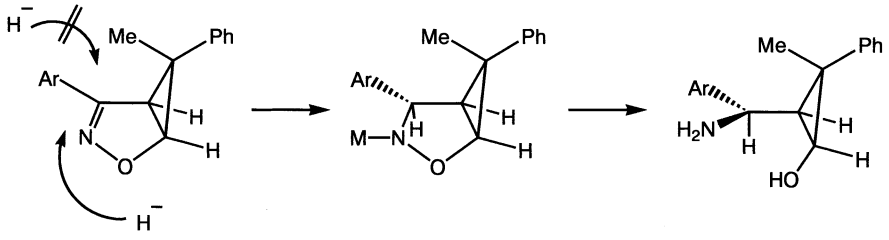


Figure 1. The single crystal X-ray structure of (**8**, Ar=4-methoxy-C_6H_4), showing both independent molecules in the asymmetric unit.

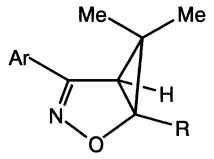


Scheme 3.

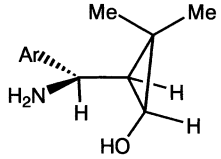
bond and to hinder the approach of the hydride to either face of the latter.

The corresponding adduct of 4-methoxybenzonitrile oxide with 3,3-dimethylcyclopropene, compound (**3**) was also reduced by lithium aluminium hydride to give (**9**) (68%); the stereochemistry was assigned by analogy to that for (**8**). However, the inclusion of an extra methyl group as in (**4**) led to a bicycle that did not react with lithium aluminium hydride. Again, this may reflect increased steric hindrance to the attack of hydride ion, in this case blocking the normally favoured convex face. In this case, reduction did occur with $NaBH_4$, $NiCl_2{\cdot}6H_2O$ in MeOH over 40 min but the product was a 68:32 mixture of diastereoisomeric aminoalcohols (**11**, R=Me) in which the cyclopropane ring had been removed. Reduction of (**3**) with this reagent combination was also successful, leading to (**10**, R=H), albeit only in low yield, while the bicycle (**2**) was reduced to a crystalline material provisionally characterised as (**13**).

Surprisingly, the butyl system (**5**) was, however, efficiently reduced to (**12**) on reaction with 2 mol equiv. of lithium aluminium hydride. Apparently the lack of reactivity of (**4**) reflects the presence of substituents at both C-1 and C-6. Reduction of the ester (**6**, R=Ph) with lithium aluminium hydride led only to the corresponding alcohol (**14**, R=Ph). However, the analogue (**7**, R=Me) also

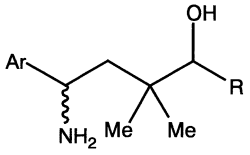


(3) R = H
(4) R = Me

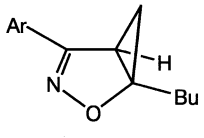


(9)

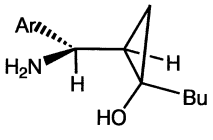
Ar = 4-methoxyphenyl



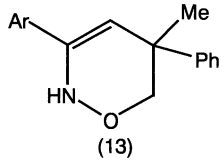
(10) R = H
(11) R = Me



(5)

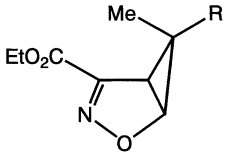


(12)

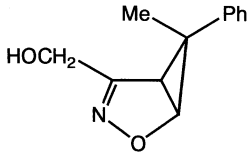


(13)

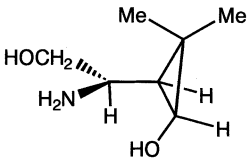
underwent cleavage of the isoxazoline to produce (**16**), albeit in low yield.



(6) R = Ph
(7) R = Me

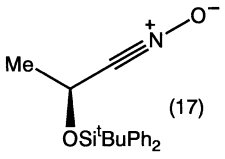


(14) R = Ph
(15) R = Me



(16)

Although this does represent a useful approach to racemic 2-aminoalkyl-1-hydroxycyclopropanes, it would have greater potential if there were a ready route to single enantiomers of 2-oxa-3-azabicyclo[3.1.0]hex-3-enes. Such compounds are in principle available by asymmetric induction in the cycloaddition of nitrile oxides to cyclopropenes; this might be achieved either by using a single enantiomer of cyclopropene or by using a chiral nitrile oxide. The first of these methods is made more practical by the availability of such cyclopropenes by catalytic asymmetric cyclopropenation of alkynes.[8] We have had limited success in the second, e.g. obtaining only very moderate diastereomer ratios in reactions of (**17**) with 3,3-dimethyl-cyclopropene or 1-butylcyclopropene.[9] However, a third approach is available based on Ukaji's catalytic asymmetric addition of nitrile oxides to allyl alcohol to give (**18**).[10]



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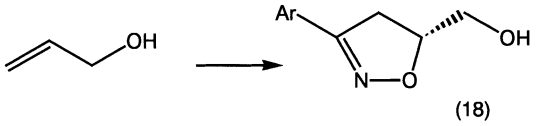
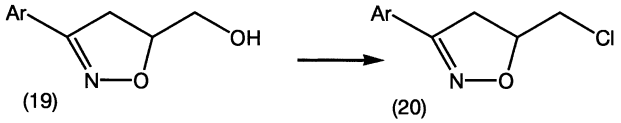
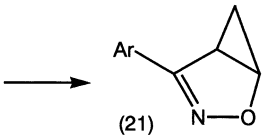


(18)

It is also known that, in the racemic series, such alcohols (as **19**) may be converted into the corresponding chlorides (**20**),[10] and that these may be dehydrochlorinated by base to give the bicycle (**21**).[12]



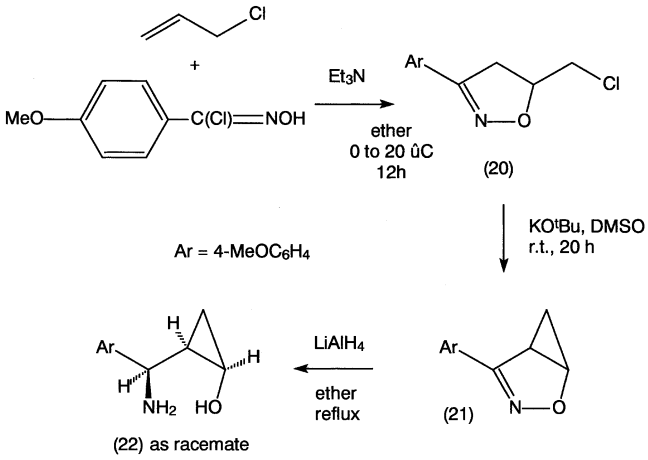
(19) (20)



(21)

Hydrogenation of the product was also reported, but led to complex mixtures.[12]

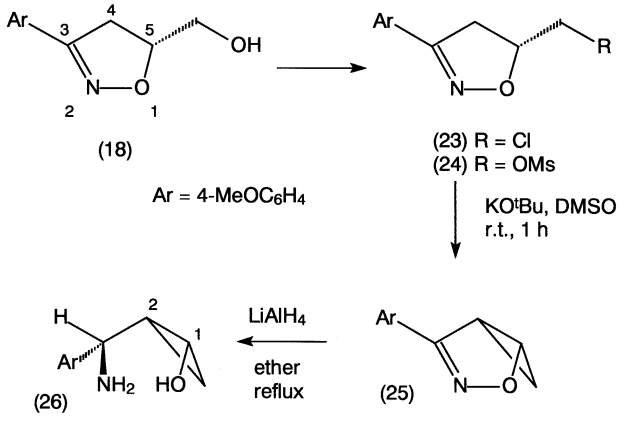
In order to test the efficiency of the method, it was first carried out on the chloride (**20**) prepared directly from allyl chloride.



(22) as racemate

The racemic aminoalcohol (**22**) was obtained as a single diastereoisomer in 88% yield. In the optically active series, allyl alcohol was converted into (**18**) (64, 99% ee) as described by Ukaji.[10] The alcohol (**18**) could be converted into the corresponding chloride (**23**) (ee 94%) by refluxing with thionyl chloride in pyridine;[11] however, the yield was poor (44%). Instead, the alcohol was converted into its mesylate (**24**) (85%) which could be transformed without purification into (**25**) on reaction with KOBu^t-DMSO for 1 h at room temperature (73% from (**17**), ee 99%). Reduction of this with lithium aluminium hydride led to a single enantiomer of the cyclopropane (**26**) in 98% yield.

Unfortunately, the original Ukaji papers only report the application of the asymmetric isoxazolination to allyl alcohol itself, leading to (**18**) with no additional substituents at either saturated ring carbon. Indeed, we have examined the reaction with a number of substituted allylic alcohols, and found only very poor enantiomeric excesses. This clearly limits the application of such methodology; however, a recent paper by Ukaji does report the successful application of the chiral reaction to *E*- and *Z*-2-buten-1-ol and to ethyl (*E*)-4-hydroxy-2-butenoate.[13] Moreover, stereoselective alkylation of C-4 of the isoxazoline (**18**) has been reported,[13] offering the potential for the introduction of a second substituent at C-2 of the 2-aminoalkylcyclopropane. To date, no routes appear to be available to introduce substituents at C-5 of (**18**) with control of absolute stereochemistry.



(18) (23) R = Cl
(24) R = OMs

(26) (25)

1. Experimental

1.1. General

Commercial reagents were used without further purification unless stated. Solvents were purified when necessary using standard methods;[14] dichloromethane was distilled over calcium hydride, diethyl ether, 1,4-dioxane and tetrahydrofuran over sodium wire. Chloroform was washed with water and dried with phosphorus pentoxide. Petroleum ether was of boiling point 40–60°C unless stated. Reactions requiring anhydrous conditions were performed using oven dried glassware (160°C) cooled under a stream of dry nitrogen or argon; the experiments were conducted under a positive atmosphere of one of these gases. Unless stated, organic solutions were dried over anhydrous magnesium sulfate, and evaporated at 14 mmHg; yields quoted are for purified compounds and any ratios given are calculated by comparing integrals in the ^{1}H NMR spectrum. New compounds were homogenous by TLC or GLC. GLC was conducted using a Carlo Erba HRGC 5300 (FID, on a capillary column). TLC was performed using Aldrich silica plates coated with silica gel 60 (F254). Compounds were visualised using an ultraviolet source, by exposure to iodine vapour or by contact with phosphomolybdic acid hydrate (2% in ethanol) followed by heating to 180°C. Column chromatography was conducted with Fisher Scientific Silica Gel 60 under medium pressure. HPLC was performed on a Milton Roy system (solvent delivering system: consta Metric 3000; variable wavelength detector: spectro Monitor 3100); the chiral column used was a Chiracel OD from Daicel Chemical Industries, 0.46×25 cm^2; solvent mixtures: 2-propanol/hexane 2, 5 and 10%, respectively; pressure: 30 psi; flowrate: 0.80 ml/min, UV-detection: 254 nm; concentration of sample 5–10 mg/1 l solvent.

Melting points are uncorrected. Infrared spectra were obtained as KBr discs or as liquid films on a Perkin–Elmer 1600 FTIR spectrometer. Low resolution mass spectra were obtained on a Finnigan 8430 spectrometer. Accurate mass measurements refer to ^{79}Br and ^{35}Cl isotopes unless stated and were obtained from the Swansea Mass Spectrometry Service. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyser. NMR spectra were recorded in $CDCl_3$, unless stated, on a Bruker AC250 at 250 MHz for protons, at 62.9 MHz for carbons and in the latter case were either broad-band or gated decoupled.

1.1.1. 6-Methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1). 2,4,6-Trimethoxybenzonitrile oxide[15] (438 mg, 2.1 mmol) in dichloromethane (10 ml) was added to 3-methyl-3-phenylcyclopropene (300 mg, 2.3 mmol) in dichloromethane (5 ml) and stirred for 12 h. Evaporation gave a colourless oil. Storage in a freezer for 18 h gave *6-methyl-6-phenyl-4-(2,4,6-trimethoxy-phenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**1**) (670 mg, 94%) as a white solid, mp 106°C (Found: C 70.8, H 6.2, N 4.2. $C_{20}H_{21}NO_4$ requires: C 70.78, H 6.24, N 4.13) which showed δ_H 1.33 (3H, s, CH_3), 3.18 (1H, d, J=5.6 Hz, H-5), 3.88 (6H, s, 2OCH_3), 3.89 (3H, s, OCH_3), 5.01 (1H, d, J=5.6 Hz, H-1), 6.22 (2H, s, CH, aromatic), 7.22–7.41 (5H, m, aromatic); δ_C 13.3 (CH_3), 20.8 (C-6), 45.0 (C-5), 55.4 (OCH_3), 55.9 (OCH_3), 73.4 (C-1), 90.8 (CH, aromatic), 100.6, 126.3, 127.9, 128.6, 144.0, 153.6, 160.0, 162.6 (C-4); ν_{max} 3008 s, 2929 s, 2839 s, 1604 s, 1500 s, 1459 s, 1413 s, 1344 s, 1226 s, 1205 s, 1156 s, 1134 s, 1068 s, 1034 s, 1015 s, 1002 s, 992 s, 846 s, 755 s, 700 s, 627 s, cm^{-1}; *m/z*, % 340, 3; 339, 3 (M$^+$); 311, 23; 310, 24; 309, 11; 308, 10; 281, 9; 280, 9; 265, 5; 192, 88; 193, 100; 165, 11; 146, 27; 117, 12.

1.1.2. 4-(4-Methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (2). Triethylamine (1.46 ml, 10.5 mmol) was added dropwise to a stirred solution of *N*-hydroxy-4-methoxy-benzimidoyl chloride (1.94 g, 10.5 mmol) and 3-methyl-3-phenylcyclopropene (1.50 g, 11.5 mmol) in ether (20 ml) at 0°C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 6 h and then treated with hydrochloric acid (2%, 15 ml) to dissolve the precipitate. The aqueous layer was extracted with ether (3×15 ml) and the combined organic layers were dried and evaporated to give crude *4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene* as a 85:15 mixture of *endo* and *exo* isomers. Chromatography (petrol/ether, 3:1 to 1:5) gave the major isomer, *endo*-Me (**2**) (2.13 g, 73%), a white solid, mp 95°C (Found: C 77.3, H 6.0, N 5.3. $C_{18}H_{17}NO_2$ requires: C 77.40, H 6.13, N 5.01) showed δ_H 1.24 (3H, s, CH_3), 3.25 (1H, d, J=5.8 Hz, H-5), 3.87 (3H, s, OCH_3), 5.07 (1H, d, J=5.8 Hz, H-1), 6.95–7.00 (2H, m, aromatic), 7.27–7.42 (5H, m, aromatic), 7.73–7.77 (2H, m, aromatic); δ_C 12.6 (CH_3), 21.1 (C-6), 40.9 (C-5), 55.4 (OCH_3), 74.5 (C-1), 114.2, 122.1, 126.7, 126.8, 128.8, 128.9, 143.0, 158.3, 161.4 (C-4); ν_{max} 1608 s, 1515 s, 1498 s, 1420 s, 1370 s, 1251 s, 1177 s, 1023 s, 1004 s, 994 s, 868 s, 847 s, 808 s, 759 s, 748 s, 696 s cm^{-1}; *m/z*, % 279, 3 (M$^+$); 264, 2; 250, 11; 146, 42; 145, 100; 133, 27; 131, 25; 117, 11; 103, 10; 91; 10; 77, 10; and the minor isomer, *exo*-Me (480 mg, 16%), a white solid, mp 122°C (Found: C 77.3, H 6.1, N 5.1. $C_{18}H_{17}NO_2$ requires: C 77.40, H 6.13, N 5.01) which showed δ_H 1.44 (3H, s, CH_3), 3.14 (1H, d, J=5.5 Hz, H-5), 3.85 (3H, s, OCH_3), 5.02 (1H, d, J=5.5 Hz, H-1), 6.89–6.95 (2H, m, aromatic), 7.16–7.27 (5H, m, aromatic), 7.64–7.70 (2H, m, aromatic); δ_C 24.4 (C-6), 24.7 (CH_3), 40.7 (C-5), 55.3 (OCH_3), 73.7 (C-1), 114.1, 122.3, 127.1, 128.4, 128.7, 129.5, 137.0, 158.1, 161.0 (C-4); ν_{max} 1608 s, 1514 s, 1458 s, 1444 s, 1377 s, 1303 s, 1252 s, 1176 s, 1021 s, 858 s, 839 s, 704 s cm^{-1}; *m/z*, % 279, 22 (M$^+$); 264, 4; 250, 43; 146, 54; 145, 100; 133, 23; 131, 24; 117, 13; 115, 12; 103, 7.

1.1.3. 4-(4-Methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (3). Methyllithium (29.6 ml, 1.5 M) was added dropwise to a stirred solution of 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane (5.3 g, 20 mmol) in dry ether (15 ml) at −78°C.[16] The mixture was allowed to reach room temperature, cooled again to −40°C, then quenched with water (5 ml), extracted with ether (3×10 ml) and the combined organic layers were dried. *N*-Hydroxy-4-methoxybenzimidoyl chloride (3 g, 0.016 mol) was dissolved in the above solution (containing 3,3-dimethylcyclopropene) and the mixture was cooled to −15°C. Triethylamine (2.25 ml, 0.016 mol) was added dropwise; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2%, 30 ml) to dissolve the

precipitate. The aqueous layer was extracted with ether (3×20 ml) and the combined organic layers were dried and evaporated. The residue was purified by chromatography (petrol/ether, 2.5:1) to give *4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**3**) (2.42 g, 69%) as a white solid, mp 64°C (Found: C 71.5, H 6.9, N 6.6. $C_{13}H_{15}NO_2$ requires: C 71.87, H 6.96, N 6.45) which showed δ_H 0.91 (3H, s, CH_3), 1.18 (3H, s, CH_3), 2.27 (1H, d, J=5.6 Hz, H-5), 3.84 (3H, s, OCH_3), 4.64 (1H, d, J=5.6 Hz, H-1), 6.91–6.96 (2H, m, aromatic), 7.64–7.68 (2H, m, aromatic); δ_C 12.7 (CH_3), 13.4 (C-6), 22.5 (CH_3), 39.5 (C-5), 55.3 (OCH_3), 74.4 (C-1), 114.1, 122.4, 128.8, 158.0, 161.1 (C-4); ν_{max} 1607 s, 1515 s, 1462 s, 1421 s, 1303 s, 1253 s, 1175 s, 1030 s, 999 s, 869 s, 851 s, 834 s cm^{-1}; *m/z*, % 217, 16 (M^+); 188, 46; 134, 35; 133, 100; 103, 13; 81, 13. *Bis(4-methoxyphenyl)furoxan*[7,18] (260 mg, 10%) was isolated as a by-product.

1.1.4. 4-(4-Methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (4). Methyllithium (7.54 ml, 1.5 M) was added dropwise to a stirred solution of 1,2,2-tribromo-1,3,3-trimethylcyclopropane (1.73 g, 5.4 mmol) in ether (15 ml) at −78°C.[16] The mixture was allowed to reach room temperature, cooled again to −40°C, then quenched with water (5 ml) and extracted with ether (3×10 ml). The combined organic layers were dried; *N*-Hydroxy-4-methoxybenzimidoyl chloride (1 g, 5.4 mmol) was added to the stirred solution (containing 1,3,3-trimethylcyclopropene) and cooled to −15°C. A solution of triethylamine (0.75 ml, 5.4 mmol) in dry ether (10 ml) was added dropwise; triethylammonium chloride precipitated. After 24 h at room temperature, it was washed with hydrochloric acid (2%, 20 ml) and water (2H 30 ml), dried and evaporated; chromatography (petrol/ether, 3:1) gave *4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**4**) (820 mg, 66%) as a white solid, mp 79°C (Found: C 73.0, H 7.5, N 6.3. $C_{14}H_{17}NO_2$ requires: C 72.70, H 7.41, N 6.06) which showed δ_H 0.85 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.27 (1H, s, H-5), 3.81 (3H, s, OCH_3), 6.86–6.92 (2H, m, aromatic), 7.58–7.63 (2H, m, aromatic); δ_C 13.6 (CH_3), 14.0 (CH_3), 17.0 (C-6), 21.7 (CH_3), 41.8 (C-5), 55.3 (OCH_3), 79.9 (C-1), 114.0, 122.9, 128.5, 158.4, 161.0 (C-4); ν_{max} 1609 s, 1584 m, 1515 s, 1459 s, 1427 s, 1420 s, 1255 s, 1176 s, 1030 s, 903 s, 876 s, 842 s, 821 s cm^{-1}; *m/z*, % 231, 10 (M^+); 216, 40; 188, 100; 173, 23; 133, 64; 83, 73; 43, 37. A by-product *3-(4-methoxyphenyl)-5-methyl-5-prop-1-ynyl-4,5-dihydroisoxazole* [δ_H 1.67 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.23 (1H, d, J=16.3 Hz, first of H-4), 3.52 (1H, d, J=16.3 Hz, second of H-4), 3.87 (3H, s, OCH_3), 6.85–6.9 (2H, m, aromatic), 7.53–7.58 (2H, m, aromatic); δ_C 3.8 (C/C–CH_3), 27.8 (CH_3), 48.7 (C-4), 55.3 (OCH_3), 79.9 (C-5), 80.3 (C/C), 81.4 (C/C), 114.1, 122.2, 128.1, 156.9, 161.1 (C-3); *m/z*, % 229, 100 (M^+)] together with a small amount of *bis(4-methoxyphenyl)furoxan*,[7,18] a beige solid (total 136 mg, compounds not separated) was also isolated.

1.1.5. 1-Butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene (5). Methyllithium (8.8 ml, 1.5 M) was added dropwise to a stirred solution of 1,1,2-tribromo-2-butylcyclo-propane (2.0 g, 6.0 mmol) in dry ether (15 ml) at −78°C.[16] The mixture was allowed to reach room temperature, cooled again to −40°C, quenched with water (5 ml), extracted with ether (3×10 ml) and the combined organic layers were dried. *N*-Hydroxy-4-methoxybenzimidoyl chloride (970 mg, 6.0 mmol) was dissolved in the ethereal solution (containing 1-butylcyclopropene) and the mixture was cooled to −15°C. Triethylamine (0.83 ml, 6.0 mmol) was added dropwise; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h. Work up and chromatography (petrol/ether, 2.5:1) as given earlier gave *1-butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**5**) (585 mg, 46%) as a white solid, mp 53–54°C (Found: C 73.0, H, 7.8, N 5.8. $C_{15}H_{19}NO_2$ requires: C 73.44, H 7.81, N 5.71) which showed δ_H 0.51 (1H, dd, J=3.9, 5.2 Hz, H_{endo}-6), 0.93 (3H, t, J=7.2 Hz, CH_3), 1.10 (1H, dd, J=5.2, 9.3 Hz, H_{exo}-6), 1.33–1.60 (4H, m, $CH_2CH_2CH_2CH_3$), 1.85–2.12 (2H, m, $CH_2CH_2CH_2CH_3$), 2.59 (1H, dd, J=3.9, 9.3 Hz, H-5), 3.85 (3H, s, OCH_3), 6.91–6.96 (2H, m, aromatic), 7.68–7.73 (2H, m, aromatic); δ_C 12.2 (C-6), 14.0 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 29.1 (C-5), 31.3 (CH_2), 55.3 (OCH_3), 75.3 (C-1), 114.0, 122.7, 128.5; 161.4 and 162.1 (C-4 and aromatic C); ν_{max} 2957 s, 2935 s, 1608 s, 1517 s, 1426 s, 1254s, 1029 s, 883 s, 828 s cm^{-1}; *m/z*, % 245, 5 (M^+); 161, 11; 160, 100; 133, 6; 106, 4; 77, 10; 57, 18. *Bis(4-methoxyphenyl)furoxan* (95 mg, 12%) was isolated as a by-product.

1.1.6. Ethyl 6-methyl-6-phenyl-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene-4-carboxylate (6, R=Ph). Triethylamine (0.29 ml, 2.1 mmol) in ether (5 ml) was added dropwise to a stirred solution of ethyl 2-chloro-2-(hydroximino)acetate (317 mg, 2.1 mmol) and 3-methyl-3-phenylcyclopropene (300 mg, 2.3 mmol) in ether (15 ml) at 0°C; triethylammonium chloride precipitated. After stirring at room temperature for 24 h, work up as given earlier gave crude *ethyl 6-methyl-6-phenyl-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene-4-carboxylate* as a mixture of *endo* and *exo* isomers (75:25) which was separated by chromatography (petrol/ether, 3:1). The major isomer, *endo*-Me (**6**, R=Ph) (150 mg, 29%), a colourless oil (Found $[M+NH_4]^+$: 263.1402. $C_{14}H_{15}NO_3+NH_4$ requires: 263.1396) showed δ_H 1.18 (3H, s, CH_3), 1.41 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.31 (1H, d, J=5.6 Hz, H-5), 4.40 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 5.17 (1H, d, J=5.6 Hz, H-1), 7.23–7.41 (5H, m, aromatic); δ_C 13.2 (CH_3), 14.1 ($CO_2CH_2CH_3$), 19.8 (C-6), 39.4 (C-5), 62.3 ($CO_2CH_2CH_3$), 77.0 (C-1), 127.1, 128.9, 141.6, 153.4 (C=O), 160.2 (C-4); ν_{max} 1741 s, 1721 s, 1601 w, 1258 s, 1221 s, 1127 s, 993 s, 779 s, 756 s, 700 s cm^{-1}; *m/z* (CI, NH_4^+), % 263, 25 $[M+NH_4]^+$; 246, 10 $[MH]^+$; 218, 100; 201, 18; 146, 51; 145, 70. The minor isomer, *exo*-Me (**11**, R=Ph) (50 mg, 10%), a colourless oil showed δ_H 1.31 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 1.38 (3H, s, CH_3), 3.20 (1H, d, J=5.4 Hz, H-5), 4.30 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 5.11 (1H, d, J=5.4 Hz, H-1), 7.18–7.36 (5H, m); δ_C 14.0 ($CO_2CH_2CH_3$), 22.8 (C-6), 24.2 (CH_3), 39.6 (C-5), 62.0 ($CO_2CH_2CH_3$), 75.8 (C-1), 127.4, 128.7, 129.6, 136.4, 153.6 (C=O), 160.5 (C-4); ν_{max} 1742 s, 1721 s, 1261 s, 1181 s, 1118 s, 702 s cm^{-1}; *m/z*, % 216, 16 ($M^+-CH_3CH_2$); 146, 33; 145, 100; 131, 25; 117, 15; 115, 19; 103, 12; 91, 8; 77, 12.

1.1.7. Ethyl 6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylate (7, R=Me). Triethylamine (2.76 ml, 0.020 mol) was added dropwise to a stirred solution of ethyl

2-chloro-2-(hydroximino)acetate (3 g, 0.020 mol) and 3,3-dimethylcyclopropene (prepared from 1,1-dibromo-3-chloro-2,2-dimethylcyclopropane (6.5 g, 0.025 mol) and methyllithium (36.3 ml, 1.5 M) as given earlier) in ether at −15°C; triethylammonium chloride precipitated. After stirring at room temperature for 12 h, work up as given earlier and chromatography (petrol/ether, 2.5:1) gave a colourless oil, ethyl 6,6-dimethyl-2-oxa-3-azabicyclo-[3.1.0]-hex-3-ene-4-carboxylate (**7**, R=Me)[17] (1.62 g, 45%) which showed δ_H 0.84 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.36 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 2.73 (1H, d, J=5.5 Hz, H-5), 4.33 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.74 (1H, d, J=5.5 Hz, H-1); δ_C 11.8 (C-6), 12.7 (CH_3), 14.0 ($CO_2CH_2CH_3$), 21.9 (CH_3), 38.5 (C-5), 62.0 ($CO_2CH_2CH_3$), 77.1 (C-1), 153.0 (C=O), 160.4 (C-4); ν_{max} 1723 s, 1262 s, 1204 s, 1121 s, 1000 s, 896 s, 779 s cm^{-1}; *m/z*, % 183, 1 (M^+); 168, 2; 156, 4; 154, 3; 138, 6; 126, 15; 110, 15; 96, 7; 84, 39; 83, 79; 82, 100; 55, 48; 41, 37.

1.1.8. Attempted reduction of 6-methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (1) with $LiAlH_4$. A solution of 6-*endo*-methyl-6-phenyl-4-(2,4,6-trimethoxyphenyl)-2-oxa-3-azabicyclo-[3.1.0]-hex-3-ene (**1**) (270 mg, 0.8 mmol) in dry THF (10 ml) was added to a suspension of $LiAlH_4$ (49 mg, 1.3 mmol) in dry ether (8 ml). The mixture was refluxed for 24 h. Drops of sat. aq. Na_2SO_4 were then added until no further reaction with the excess of $LiAlH_4$ was observed. To the white-grey suspension dichloromethane (15 ml) (or alternatively ethyl acetate) and a small amount of anhydrous $MgSO_4$ were added. The suspension was filtered through a layer of anhydrous $MgSO_4$. The solvent was removed from the filtrate under vacuum to give the crude product. Only starting material (243 mg, 90%) was recovered.

1.1.9. Attempted reduction of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (4) with $LiAlH_4$. A solution of 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (300 mg, 1.3 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (59 mg, 1.6 mmol) in dry ether (8 ml). The mixture was refluxed for 72 h. TLC did not show any conversion; more $LiAlH_4$ (133 mg) was added and the mixture was refluxed for further 24 h. Work-up as given earlier gave only starting material (**4**).

1.1.10. 3-[Amino(4-methoxyphenyl)methyl]-2-methyl-2-phenylcyclopropanol (8). A solution of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**2**) (390 mg, 1.4 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (90 mg, 2.8 mmol) in dry ether (10 ml). The mixture was refluxed for 20 h. Drops of sat. aq. Na_2SO_4 were then added until no further reaction with the excess of $LiAlH_4$ was observed. To the white-grey suspension dichloromethane (15 ml) (or alternatively ethyl acetate) and a small amount of anhydrous $MgSO_4$ were added. The suspension was filtered through a layer of anhydrous $MgSO_4$. The solvent was removed under vacuum to give the crude product. The residue was recrystallised from ethyl acetate to give *3-[amino(4-methoxyphenyl)-methyl]-2-methyl-2-phenyl-cyclopropanol* (**8**) (200 mg, 51%) as a white solid, mp 116–120°C (Found: C 76.3, H 7.7, N 5.1. $C_{18}H_{21}NO_2$ requires: C 76.30, H 7.47, N 4.94) which showed δ_H 1.45 (1H, dd, J=7.1, 10.1 Hz, H-3), 1.63 (3H, s, CH_3), 1.98 (3H, br s, NH_2 and OH), 3.64 (1H, d, J=7.1 Hz, H-1), 3.82 (3H, s, OCH_3), 4.16 (1H, d, J=10.1 Hz, C*H*–NH_2), 6.87–6.92 (2H, m, aromatic), 7.16–7.35 (5H, m, aromatic), 7.41–7.45 (2H, m, aromatic); δ_C 13.8 (CH_3), 28.3 (C-2), 36.6 (C-3), 50.4 (CH–NH_2), 55.3 (OCH_3), 58.0 (C-1), 114.0, 125.9, 127.2, 127.7, 128.4, 137.6, 147.0, 158.7; ν_{max} 3418 br s, 3145 br s, 1512 s, 1247 s, 1034 s, 701 s cm^{-1}; *m/z*, % 266, 1 (M^+−OH); 237, 28; 149, 41; 136, 100; 134, 22; 57, 20; 43, 18.

1.2. Crystal structure determination for 8

Crystal data: $C_{18}H_{21}NO_2$, M=283.36, triclinic, space group $P\bar{1}$, a=10.3811(7), b=11.7378(7), c=13.2022(8) Å, α=77.928(2), β=89.118(2), γ=80.323(2)°, V=1550.42(17) $Å^3$, Z=4, D_c=1.214 g cm^{-3}, μ=0.08 mm^{-1} (Mo Kα, λ=0.71073 Å), T=160 K. Of 12,506 reflections measured on a Bruker AXS SMART CCD diffractometer, 7049 were unique (θ<29.0°, R_{int}=0.0169). The structure was solved by standard direct methods and refined on F^2 values; H atoms bonded to O and N were freely refined, others were constrained with a riding model. R=0.0518 (F values, $F^2>2\sigma$), R_2=0.1364 (F^2 values, all data), goodness-of-fit=1.016, final difference map extremes +0.82 and −0.46 e $Å^{-3}$. Software: Bruker SMART, SAINT, and SHELXTL.[†]

1.2.1. 3-[Amino(4-methoxyphenyl)methyl]-2,2-dimethylcyclopropanol (9). 4-(4-Methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**3**) (550 mg, 2.5 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (192 mg, 5.1 mmol) in ether (10 ml). The mixture was refluxed for 20 h. Work-up as given earlier and recrystallisation from ether/petrol gave *3-[amino(4-methoxyphenyl)-methyl]-2,2-dimethylcyclopropanol* (**9**) (380 mg, 68%) as a white solid, mp 102–103°C (Found: C 70.5, H 8.8, N 6.5. $C_{13}H_{19}NO_2$ requires: C 70.56, H 8.65, N 6.33), δ_H 0.77 (1H, dd, J=6.8, 10.1 Hz, H-3), 1.03 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.78 (3H, br s, NH_2 and OH), 3.08 (1H, d, J=6.8 Hz, H-1), 3.77 (3H, s, OCH_3), 3.89 (1H, d, J=10.1 Hz, C*H*–NH_2), 6.82–6.86 (2H, m, aromatic), 7.31–7.34 (2H, m, aromatic); δ_C 13.3 (CH_3), 19.1 (C-2), 26.4 (CH_3), 35.7 (C-3), 50.6 (CH–NH_2), 55.3 (OCH_3), 57.9 (C-1), 113.9, 127.5, 138.2, 158.5; ν_{max} 3126 br s, 2950 s, 1610 s, 1581 s, 1512 s, 1303 s, 1272 s, 1248 s, 1178 s, 1148 s, 1038 s, 951 s, 831 s cm^{-1}; *m/z*, % 204, 12 (M^+−OH); 175, 58; 149, 46; 136, 100; 134, 34; 121, 10; 109, 12; 58, 5.

1.2.2. 4-Amino-4-(4-methoxyphenyl)-2,2-dimethylbutan-1-ol (10). Sodium borohydride (348 mg, 9.2 mmol) was added in portions to a stirred solution of 4-(4-methoxyphenyl)-6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**3**) (400 mg, 1.8 mmol) and $NiCl_2{\cdot}6H_20$ (875 mg, 3.7 mmol) in methanol (50 ml) at −15°C. After 5 min the mixture was allowed to reach room temperature and stirred for 20 min. Methanol was removed under reduced pressure,

[†] Crystallographic data have been deposited at the CCDC, 12, Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition reference number 169658.

aq. ammonia (*d* 0.88, 40 ml) and dichloromethane (40 ml) were added carefully, and the black mixture was stirred under air until the organic layer became almost clear (about 20 min). The aqueous layer was extracted with dichloro-methane (3×40 ml), the combined organic layers were dried and evaporated to give a yellow oil (337 mg). Chromatography (petrol/ether, 2.5:1, then ether) gave a pale yellow oil, *4-amino-4-(4-methoxy-phenyl)-2,2-dimethyl-butan-1-ol* (**10**, R=H) (90 mg, 22%) (M^+ (223) not observed) which showed δ_H 1.16 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.54 (1H, dd, *J*=9.8, 12.5 Hz, first of H-3), 1.96 (1H, dd, *J*=7.1, 12.5 Hz, second of H-3), 2.10 (1H, br s, OH), 2.80 (1H, d, *J*=10.2 Hz, first of H-1), 2.93 (1H, d, *J*=10.2 Hz, second of H-1), 3.82 (3H, s, OCH_3), 4.26 (1H, dd, *J*=7.1, 9.8 Hz, H-4), 6.86–6.90 (2H, m, aromatic), 7.29–7.33 (2H, m, aromatic); δ_C 27.9 (CH_3), 28.7 (CH_3), 39.5 (C-2), 50.0 (C-3), 55.2 (OCH_3), 61.1 (C-1), 62.0 (C-4), 113.7, 127.5, 137.0, 158.4; ν_{max} 3342 br m, 2952 s, 1513 s, 1245 s cm^{-1}; *m/z*, % 203, 3; 202, 28; 201, 42; 200, 33; 186, 5; 171, 8; 158, 14; 146, 45; 145, 100; 133, 19; 131, 9; 118, 10; 116, 10; 96, 7; 89, 8; 75, 6.

1.2.3. 5-Amino-5-(4-methoxyphenyl)-3,3-dimethylpentan-2-ol (11). Sodium borohydride (131 mg, 3.4 mmol) was added in portions with stirring to 4-(4-methoxyphenyl)-1,6,6-trimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**4**) (160 mg, 0.7 mmol) and $NiCl_2{\cdot}6H_20$ (329 mg, 1.4 mmol) in methanol (30 ml) at −20°C under nitrogen. After 5 min, the mixture was allowed to reach room temperature and stirred for 40 min. After work-up as given earlier, the residue was passed over a short column of silica, eluting with ether, to give a pale yellow oil, *5-amino-5-(4-methoxy-phenyl)-3,3-dimethylpentan-2-ol* (**11**, R=Me) (115 mg, 70%) as a 62:38 mixture of diastereomers (no M^+ was observed). The major isomer showed: δ_H 0.98 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.09 (3H, d, 6.4 Hz, CH_3), 1.69 (1H, dd, *J*=10.0, 12.5 Hz, first of H-4), 1.98 (1H, br s, OH), 2.07 (1H, dd, *J*=7.2, 12.5 Hz, second of H-4), 3.14 (1H, q, *J*=6.4 Hz, H-2), 3.84 (3H, s, OCH_3), 4.34 (1H, dd, *J*=7.2, 10.0 Hz, H-5), 6.88–6.92 (2H, m, aromatic), 7.30–7.34 (2H, m, aromatic); δ_C 14.9 (CH_3), 20.5 (C-1), 25.7 (CH_3), 42.0 (C-3), 51.7 (C-4), 55.3 (OCH_3), 58.5 (C-5), 63.2 (C-2), 113.8, 127.2, 139.4, 158.2 (all aromatic C). The minor isomer showed: δ_H 1.00 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.13 (3H, d, 6.4 Hz, CH_3), 1.62 (1H, dd, *J*=8.4, 12.9 Hz, first of H-4), 1.98 (1H, br s, OH), 2.06 (1H, dd, *J*=8.4, 12.9 Hz, second of H-4), 2.96 (1H, q, *J*=6.4 Hz, H-2), 3.84 (3H, s, OCH_3), 4.18 (1H, t, *J*=8.4 Hz, H-5), 6.88–6.92 (2H, m, aromatic), 7.30–7.34 (2H, m, aromatic); δ_C 15.6 (CH_3), 24.5 (C-1), 27.8 (CH_3), 40.3 (C-3), 50.0 (C-4), 55.3 (OCH_3), 59.6 (C-5), 63.8 (C-2), 113.7, 127.7, 136.9, 156.1; ν_{max} (mixture) 2955 s, 1511 s, 1244 s cm^{-1}; *m/z*, % 220, 12 (M^+−OH); 219, 28; 218, 17; 176, 19; 163, 100; 162, 75; 161, 73; 148, 16; 134, 16; 121, 15; 91, 8; 77, 8.

1.2.4. 2-[Amino(4-methoxyphenyl)methyl]-1-butylcyclopropanol (12). 1-Butyl-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (400 mg, 1.6 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (124 mg, 3.3 mmol) in dry ether (10 ml). The mixture was refluxed for 27 h. Work-up as for (**8**) gave a yellow oil, *2-[amino(4-methoxyphenyl)methyl]-1-butylcyclopropanol* (**12**) (330 mg, 81%); further purification was not required (M^+ not observed) which showed δ_H 0.68 (1H, dd, *J*=5.7, 9.5 Hz, H_{cis}-3), 0.78 (1H, dd, *J*=5.7, 6.2 Hz, H_{trans}-3), 0.84 (3H, t, *J*=7.1 Hz, CH_3), 0.93 (1H, ddd, *J*=5.8, 6.2, 9.5 Hz, H-2), 1.24–1.53 (6H, m, $CH_2CH_2CH_2CH_3$), 2.68 (3H, br s, NH_2 and OH), 3.77 (3H, s, OCH_3), 4.06 (1H, d, *J*=5.8 Hz, C*H*–NH_2), 6.83–6.87 (2H, m, aromatic), 7.29–7.32 (2H, m, aromatic); δ_C 14.1 (CH_3), 15.4 (C-3), 22.6 (CH_2), 27.8 (CH_2), 28.9 (C-2), 38.5 (CH_2), 53.2 (CH–NH_2), 55.3 (OCH_3), 58.7 (C-1), 114.0, 127.2, 138.6, 158.6; ν_{max} 3340 br s, 2956 s, 2931 s, 1513 s, 1246 s cm^{-1}; *m/z*, % 233, 10; 232, 33 (M^+−OH); 189, 35; 176, 19; 162, 8; 147, 100; 136, 83; 121, 20; 102, 37; 91, 21; 85, 15; 77, 18; 57, 33.

1.2.5. Reduction of 4-(4-methoxyphenyl)-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene with sodium borohydride. Sodium borohydride (271 mg, 7.2 mmol) was added in portions to a stirred solution of 4-(4-methoxyphenyl)-6-*endo*-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene (**2**) (400 mg, 1.4 mmol) and $NiCl_2{\cdot}6H_20$ (681 mg, 2.9 mmol) in methanol (50 ml) at −35°C. After 5 min the mixture was allowed to reach room temperature and stirred for 10 min. Work-up as for (**10**) gave a yellow oil (295 mg). A white precipitate (65 mg) formed when this was treated with ether, mp 162°C (Found: C 78.1, H 6.8, N 4.9. $C_{18}H_{19}NO_2$ requires: C 76.84, H 6.81, N 4.98) which was provisionally characterised as (**13**) and showed δ_H 1.32 (3H, s, CH_3), 3.21 (1H, d, *J*=17 Hz), 3.30 (1H, d, *J*=17 Hz), 3.84 (3H, s, OCH_3), 5.8 (1H, s), 6.92–6.96 (2H, m, aromatic), 7.18–7.36 (5H, m, aromatic), 7.84–7.88 (2H, m, aromatic); δ_C 20.3 (CH_3), 48.1 (CH_2), 51.2, 55.3 (OCH_3), 99.9 (CH), 114.0, 126.2, 126.3, 127.3, 128.4, 129.5, 147.4, 162.1 (q), 170.8 (q); ν_{max} 3078 br s, 1516 s, 1333 s, 1256 s, 1177 s, 1122 s, 1058 s, 1034 s, 832 s, 697 s cm^{-1}; *m/z*, % 281, 42; 266, 27; 263, 25; 248, 18; 236, 23; 221, 15; 204, 9; 176, 28; 164, 68; 162, 68; 134, 100; 121, 39; 115, 25; 103, 23; 91, 28; 77, 40.

1.2.6. [6-(4-Methoxyphenyl)-6-methyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]methanol (14). A solution of methyl *endo*-6-methyl-6-phenyl-2-oxa-3-azabicyclo[3.1.0]-hex-3-ene-4-carboxylate (**6,** R=Ph) (60 mg, 0.24 mmol) in dry ether (5 ml) was added to a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (5 ml). The mixture was refluxed for 2 h. Work-up as for (**8**) gave pure *[6-(4-methoxyphenyl)-6-methyl-2-oxa-3-aza-bicyclo[3.1.0]hex-3-en-4-yl]methanol* (**14**, R=Ph) (40 mg, 80%). The compound was not fully characterised but showed δ_H 1.21 (3H, s, CH_3), 2.99 (1H, br s, OH), 3.02 (1H, d, *J*=5.5 Hz, H-5), 4.51 (2H, s, CH_2OH), 4.98 (1H, d, *J*=5.5 Hz, H-1), 7.20–7.40 (5H, m, aromatic); δ_C 12.8 (CH_3), 20.5 (C-6), 40.8 (C-5), 58.1 (CH_2OH), 74.7 (C-1), 126.3, 128.7, 142.4, 160.4 (C-4).

1.2.7. 3-(1-Amino-2-hydroxyethyl)-2,2-dimethylcyclopropanol (16). Lithium aluminium hydride (414 mg, 10.9 mmol) was added in small portions to a solution of methyl 6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene-4-carboxylate (**7**, R=Me) (1 g, 5.4 mmol) in dry ether (50 ml). The mixture was stirred for 2 h at room temperature. Drops of sat. aq. Na_2SO_4 were added as given earlier. The resulting suspension was filtered through a layer of anhydrous $MgSO_4$ and a clear solution (I) was obtained. Washing the filter residue with ethyl acetate (2×15 ml)

gave solution (II). Solution (I) was concentrated to give a crude mixture of *3-(1-amino-2-hydroxyethyl)-2,2-dimethylcyclopropanol* (**16**, R=Me) and *[6,6-dimethyl-2-oxa-3-azabicyclo[3.1.0]hex-3-en-4-yl]methanol* (**15**, R=Me) (ratio, 71:29; total 400 mg). Solution (II) was left to stand overnight and colourless crystals formed, identified as (**16**, R=Me) (110 mg, 14%), mp 109–111°C (Found: C 58.1, H 10.4, N 9.8. $C_7H_{15}NO_2$ requires: C 57.90, H 10.41, N 9.65) which showed δ_H (CD_3OD) 0.40 (1H, dd, J=7.0, 10.2 Hz, H-3), 1.04 (3H, s, CH_3), 1.21 (3H, s, CH_3), 2.88 (1H, ddd, J=4.5, 7.2, 10.2 Hz, C*H*–NH_2), 3.10 (1H, d, J=7.0 Hz, H-1), 3.43 (1H, dd, J=7.2, 10.3 Hz, first H of C*H*$_2$OH), 3.67 (1H, dd, J=4.5, 10.3 Hz, second H of C*H*$_2$OH), 4.90 (4H, br s, 2H, OH and NH_2); δ_C (CDOD) 14.3 (CH_3), 19.9 (C-2), 27.3 (CH_3), 32.4 (C-3), 50.5 (CH–NH_2), 58.8 (C-1), 68.3 (CH_2OH); ν_{max} 3376 br s, 3319 s, 3263 s, 3086 br s, 2973 br s, 2688 br s, 1601 s, 1459 s, 1418 s, 1332 s, 1196 s, 1146 s, 1043 s, 978 s, 893 s, 863 s, 709 s, 667 s, 520 s cm^{-1}; *m/z*, % 146, 3 (M^++1); 116, 9; 114, 18; 99, 10; 97, 10; 81, 26; 60, 100; 58, 30; 43, 58.5. Compound (**15**, R=Me) showed: δ_H 0.85 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.41 (1H, d, J=5.5 Hz, H-5), 4.32 (2H, s, CH_2OH), 4.52 (1H, d, J=5.5 Hz, H-1).

1.2.8. [(5*R*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (18) (Ar=4-MeOC$_6$H$_4$). Diethylzinc (1.2 mol equiv., 1.1 M in toluene or 1.0 M in hexane) was added at 0°C to a $CHCl_3$ (6 ml) solution of allyl alcohol (2.7 mmol) under argon and the mixture was stirred for 10 min. A $CHCl_3$ (6 ml) solution of (*R*,*R*)-DIPT (0.2 mol equiv.) was added and the mixture was stirred for 1 h. A $CHCl_3$ (6 ml) solution of with *N*-hydroxy-4-methoxybenzimidoyl chloride (500 mg, 2.7 mmol, 1.0 mol equiv.) and 1,4-dioxane (1.5 mol equiv.) was added; the resulting solution was stirred for 24 h at 0°C. Sat. aq. NH_4Cl was added, followed by hydrochloric acid (2%). The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were dried and evaporated. Chromatography (petrol/ethyl acetate, 1:1) gave *[(5R)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol* (**18**) (379 mg, 68%) with 97% ee, $[\alpha]_D^{30}$=+140° (*c* 0.4, MeOH) (lit.[13,19]: $[\alpha]_D^{25}$=+120° (*c* 0.4, MeOH)), a white crystalline solid, mp 157°C (Found: C 64.3, H 6.6, N 6.81. $C_{11}H_{13}NO_3$ requires: C 63.76, H 6.32, N 6.76) which showed δ_H 1.89 (1H, br s, OH), 3.23 (1H, dd, J=7.9, 16.5 Hz, first of H-4), 3.36 (1H, dd, J=10.5, 16.5 Hz, second of H-4), 3.64 (1H, dd, J=4.7, 12.1 Hz, first H of C*H*$_2$OH), 3.81 (3H, s, OCH_3), 3.83 (1H, dd, J=3.2, 12.1 Hz, second H of C*H*$_2$OH), 4.82 (1H, dddd, J=3.2, 4.7, 7.9, 10.6 Hz, H-5), 6.86–6.90 (2H, m, aromatic), 7.55–7.59 (2H, m, aromatic); δ_C (CD_3OD) 37.9 (C-4), 56.1 (OCH_3), 64.4 (CH_2OH), 83.0 (C-5), 115.5, 123.7, 129.6, 158.4, 163.0 (C-3); ν_{max} 3361 br s, 1611 s, 1520 s, 1364 s, 1263 s, 1183 s, 1106 m, 1053 s, 929 s, 904 s, 833 s, 813 s cm^{-1}; *m/z*, % 207, 100 (M^+); 176, 68; 148, 27; 121, 56; 92, 13; 77, 23.

When the reaction was repeated on a larger scale (27 mmol) the work-up procedure was altered, due to the poor solubility of (**18**): after stirring for 24 h, the mixture was quenched with a few drops of a sat. aq. NH_4Cl and filtered through anhydrous $MgSO_4$ when a clear solution (I) was obtained. Washing the filter residue with hot ethyl acetate gave solution (II). The solutions were concentrated (separately) and the residue recrystallised from ethyl acetate. Solution (I) yielded 14% (80% ee), solution (II) yielded 64% (99% ee) (total yield 78%). The reaction was also repeated using modified conditions: stirring for 24 h at room temperature gave a yield of 76% (93% ee); stirring for 24 h at −70°C gave 95% (79% ee).

1.2.9. [(5*RS*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (Ar=4-MeOC$_6$H$_4$) (19). Triethylamine (2.7–2.8 mmol) was added dropwise to a stirred solution of *N*-hydroxy-4-methoxybenz-imidoyl chloride (500 mg, 13.5 mmol) (2.7 mmol) and allyl alcohol (1.1 ml, 16.2 mmol) in ether (20 ml) at 0°C; triethylammonium chloride precipitated. The mixture was stirred at room temperature for 12 h and then treated with hydrochloric acid (2%, 10 ml), extracted with ethyl acetate (3×10 ml) and the combined organic layers dried. The solvent was removed and the residue was recrystallised from ethyl acetate/petrol to give *[(5RS)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol* (**19**) (1.6 g, 57%) as a white crystalline solid; mp 135°C. NMR, IR and MS data were identical to those given for (5*R*)-(**18**)) (described earlier).

1.2.10. (5*RS*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (20). The procedure given in Section 1.2.9 was used to react allyl chloride (0.33 ml, 4.05 mmol) with *N*-hydroxy-4-methoxybenzimidoyl chloride (250 mg, 1.35 mmol), yielding *(5RS)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole* (**20**) (185 mg, 61%) as a white solid; mp 70°C. NMR, IR and MS data were identical to those given for the enantiomerically pure compound (see Section 1.2.11).

1.2.11. (5*R*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (23). A solution of [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**18**) (200 mg, 0.96 mmol) and thionyl chloride (0.7 ml, 9.6 mmol) in pyridine (10 ml) was stirred for 6 h at 100°C. Excess thionyl chloride was removed by flash distillation, dichloromethane (20 ml) and hydrochloric acid (2%, 20 ml) were added. The aqueous layer was extracted with dichloromethane (2×20 ml). The combined organic layers were washed with hydrochloric acid (2%, 2×40 ml) and water (40 ml), dried and evaporated. Chromatography of the residue (petrol then petrol/ether, 1:1) gave *(5R)-5-chloromethyl-3-(4-methoxyphenyl)-4,5-dihydro-isoxazole* (**23**) (96 mg, 44%), $[\alpha]_D^{26}$=−50.4° (*c* 0.4, $CHCl_3$), a white solid mp 85°C (Found: C 58.6, H 5.2, N 6.4. $C_{11}H_{12}ClNO_2$ requires: C 58.54, H 5.36, N 6.21) which showed δ_H 3.29 (1H, dd, J=6.4, 16.9 Hz, first of H-4), 3.37 (1H, dd, J=10.3, 16.9 Hz, second of H-4), 3.54 (1H, dd, J=7.6, 11.2 Hz, first H of CH_2Cl), 3.69 (1H, dd, J=4.4, 11.2 Hz, second H of CH_2Cl), 3.82 (3H, s, OCH_3), 4.94 (1H, dddd, J=4.4, 6.4, 7.6, 10.3 Hz, H-5), 6.89–6.93 (2H, m, aromatic), 7.58–7.62 (2H, m, aromatic); δ_C 38.8 (C-4), 44.8 (CH_2Cl), 55.3 (OCH_3), 79.5 (C-5), 114.1, 121.5, 128.3, 155.7, 161.2 (C-3); ν_{max} 1609 s, 1598 s, 1517 s, 1460 s, 1420 s, 1360 s, 1311 s, 1255 s, 1180 s, 1040 s, 1021 s, 911 s, 887 s, 836 s, 816 s, 677 s, 608 s, 538 s cm^{-1}; *m/z*, % 227, 26; 225, 70 (M^+); 176, 62; 148, 33; 133, 13; 132, 121, 100; 107, 13; 92, 28; 77, 50; 63, 18.

1.2.12. [(5*R*)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl mesylate (24). Methanesulfonyl chloride

(0.03 ml, 0.43 mmol, 0.6 mol equiv.) was added to [(5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (**18**) (150 mg, 0.72 mmol) and triethylamine (0.06 ml, 0.43 mmol, 0.6 mol equiv.) in dichloromethane (5 ml) and stirred for 20 min at room temperature. More triethylamine (0.06 ml, 0.43 mmol, 0.6 mol equiv.) and methanesulfonyl chloride (0.03 ml, 0.43 mmol, 0.6 mol equiv.) were added (a total of 1.2 mol equiv. of MsCl and base were used). After an additional 20 min, water (10 ml) was added and the aqueous layer was extracted with dichloromethane (3×15 ml). The combined organic layers were washed with water (30 ml), dried and evaporated. The residue was recrystallised from ethyl acetate/petrol to give *[(5R)-3-(4-methoxyphenyl)-4,5-dihydro-isoxazol-5-yl]methyl mesylate* (**24**) (175 mg, 85%), $[\alpha]_D^{26}=-137.6°$ (*c* 1.0, $CHCl_3$) as colourless crystals, mp 161°C (Found: C 50.4, H 5.1, N 5.0. $C_{12}H_{15}NO_5S$ requires: C 50.52, H 5.30, N 4.91) which showed δ_H 3.07 (3H, s, SO_2CH_3), 3.25 (1H, dd, *J*=7.0, 16.8 Hz, first of H-4), 3.46 (1H, dd, *J*=10.8, 16.8 Hz, second of H-4), 3.83 (3H, s, OCH_3), 4.32 (1H, dd, *J*=4.9, 11.4 Hz, first H of CH_2O), 4.37 (1H, dd, *J*=4.1, 11.4 Hz, second H of CH_2O), 4.97 (1H, dddd, *J*=4.1, 4.9, 7.0, 10.8 Hz, CH–O), 6.89–6.93 (2H, m, aromatic), 7.56–7.69 (2H, m, aromatic); δ_C 37.2 (C-4), 37.8 (SO_2CH_3), 55.4 (OCH_3), 69.5 (CH_2O), 77.5 (C-5), 114.2, 121.2, 128.3, 156.0, 161.4 (C-3); ν_{max} 1607 s, 1594 s, 1517 s, 1458 s, 1422 s, 1320 s, 1254 s, 1004 s, 972 s, 907 s, 875 s, 834 s, 817 s cm^{-1}; *m/z*, % 285, 42 (M^+); 176, 100; 160, 9; 148, 18; 147, 20; 134, 10; 132, 11; 107, 7; 92, 11; 77, 17.

1.2.13. (1*S*,5*S*)-4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo-[3.1.0]hex-3-ene (25). Potassium *t*-butoxide (1.62 g, 14.5 mmol) was added in small portions to (5*R*)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-ylmethyl mesylate (1.38 g, 4.8 mmol) (crude **24**, prepared from chiral alcohol **18** (1.0 g, 4.8 mmol) as described earlier) in anhydrous dimethyl sulfoxide (15 ml) at room temperature. After stirring for 1 h, water (30 ml) was added and the aqueous layer was extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with water (2×80 ml), dried and evaporated; chromatography of the residue (petrol/ethyl acetate, 3:1) gave *(1S,5S)-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**25**) (670 mg, 73% over two steps), $[\alpha]_D^{26}=-154.6°$ (*c* 1.0, $CHCl_3$) as a white solid, mp 109°C (Found: C 69.6, H 5.9, N 7.6. $C_{11}H_{11}NO_2$ requires: C 69.83, H 5.86, N 7.40) which showed δ_H 0.43 (1H, ddd, *J*=2.2, 3.8, 5.5 Hz, H_{endo}-6), 1.04 (1H, dt, *J*=5.5, 9.2 Hz, H_{exo}-6), 2.84 (1H, ddd, *J*=3.8, 5.5, 9.2 Hz, H-5), 3.83 (3H, s, OCH_3), 4.99 (1H, dt, *J*=2.2, 5.5 Hz, H-1), 6.91–6.95 (2H, m, aromatic), 7.70–7.74 (2H, m, aromatic); δ_C 8.0 (C-6), 25.9 (C-5), 55.3 (OCH_3), 63.9 (C-1), 114.1, 121.6, 128.7, 161.2 and 161.3 (aromatic C and C-4); ν_{max} 1608 s, 1584 s, 1517 s, 1425 s, 1377 s, 1308 s, 1249 s, 1189 s, 1178 s, 1113 s, 1081 s, 1028 s, 975 s, 936 s, 871 s, 848 s, 823 s, 790 s, 665 m, 603 s, 532 s cm^{-1}; *m/z*, % 189, 25 (M^+); 160, 100; 134, 10; 115, 5; 107, 7; 103, 6; 92, 13; 77, 17; 64, 10.

1.2.14. (1*RS*,5*RS*)-4-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene (21). (5*RS*)-5-Chloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**19**) (2.5 g, 0.011 mol) was treated with potassium *t*-butoxide (3.73 g, 0.033 mol) as given earlier. The crude product was recrystallised from ether/petrol to give *(1RS,5RS)-4-(4-methoxyphenyl)-2-oxa-3-azabicyclo[3.1.0]hex-3-ene* (**21**) (1.09 g, 52%), as a white solid, mp 83°C. Analytical data were identical to those of the enantiomerically pure compound (see Section 1.2.13).

1.2.15. (1*S*,2*S*)-2-[(*S*)-Amino(4-methoxyphenyl)methyl]-cyclopropan-1-ol (26). A solution of azabicycle (**25**) (200 mg, 1.06 mmol) in dry ether (15 ml) was added to a suspension of $LiAlH_4$ (80 mg, 2.12 mmol) in ether (10 ml) and the mixture was refluxed for 16 h. Work-up as for (**8**) gave *(1S,2S)-2-[(S)-amino(4-methoxyphenyl)-methyl]-cyclopropan-1-ol* (**26**) (118 mg, 58%) as a white solid, mp 80–83°C, $[\alpha]_D^{26}=+65.5°$ (*c* 0.4, MeOH) (Found: C 68.2, H 8.1, N 7.2. $C_{11}H_{15}NO_2$ requires: C 68.37, H 7.82, N 7.25) which showed δ_H 0.56 (1H, dt, *J*=3.3, 6.7 Hz, H_{cis}-3 (relative to H-1)), 0.76 (1H, td, *J*=6.7, 9.2 Hz H_{trans}-3 (relative to H-1)), 0.94 (1H, tdd, *J*=6.7, 7.0, 9.2 Hz, H-2), 2.60 (3H, br s, NH_2 and OH), 3.45 (1H, dt, *J*=3.3, 6.7 Hz, H-1), 3.74 (3H, s, OCH_3), 3.91 (1H, d, *J*=7.0 Hz, C*H*–NH_2), 6.81–6.85 (2H, m, aromatic), 7.28–7.32 (2H, m, aromatic); δ_C 10.6 (C-3), 24.0 (C-2), 49.8 (CH–NH_2), 52.9 (C-1), 55.2 (OCH_3), 113.8, 127.3, 138.4, 158.5; ν_{max} 3340 br s, 2999 s, 2934 s, 2836 s, 1614 s, 1514 s, 1462 s, 1252 s, 1177 s, 1035 s, 834 s cm^{-1}; *m/z*, % 177, 10; 176, 67 (M^+-OH); 173, 25; 158, 13; 149, 37; 147, 100; 136, 53; 134, 99; 121, 23; 109, 18; 91, 21; 77, 18.

1.2.16. (1*RS*,2*RS*)-2-[(*RS*)-Amino(4-methoxyphenyl)-methyl]cyclopropan-1-ol (22). A solution of azabicycle (**21**) (100 mg, 0.53 mmol) in dry ether (10 ml) was added to a suspension of $LiAlH_4$ (40 mg, 1.06 mmol) in ether (10 ml) and the mixture refluxed for 24 h. Work-up as for (**8**) gave *(1RS,2RS)-2-[(RS)-amino(4-methoxyphenyl)-methyl]-cyclopropan-1-ol* (**22**) (90 mg, 88%) as a yellow oil. Spectroscopic data were identical to those of the enantiomerically pure compound (see Section 1.2.15).

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