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Modification of 1-Substituents in the 2-Azabicyclo[2.1.1]hexane Ring System; Approaches to Potential Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives

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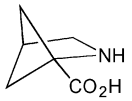
Successful nucleophilic substitution at a methylene attached to the bridgehead (1-) position of the 2-azabicyclo[2.1.1]hexane ring system opens the way to construction of novel derivatives having a wider range of functional groups attached to the 1-position via a methylene "spacer" (including the β-amino acid homologue of 2,4-methanoproline) and provides access to epibatidine analogues containing heterocyclic substituents and also to further homologation at the 1-position. Displacements with loss of a nucleofuge (e.g., loss of mesylate anion from the 1-mesyloxymethyl derivative) require thermal activation but proceed without the rearrangement initially anticipated in such a strained bicyclic ring system. A novel tricyclic carbamate intermediate **17** has been isolated; nucleophilic attack on **17** leads directly to the isolation of N-deprotected substitution products (with concomitant decarboxylation).

Introduction

There has been substantial recent interest in the 2-azabicyclo[2.1.1]hexane ring system, which forms the basis for the nonproteinogenic amino acid 2,4-methanoproline.[1] Early synthetic routes to the ring system were



2,4-methanoproline

based on photochemical intramolecular [2 + 2] cycloaddition strategies,[2] and there have been recent reports of alternative approaches, from 2-azabicyclo[2.2.0]hexane derivatives,[3] 3-halomethyl-1-aminocyclobutanes,[1,4] and *cis*-cyclobutene dicarboxylic anhydrides[5] so that the azabicyclic framework itself is now readily available.

Considerable recent effort has led to a significant widening of the range of methods for functionalization of the 2- and 5-/6-positions of the 2-azabicyclo[2.1.1]-hexane ring system.[3,5] In particular, Krow has recently introduced attractive approaches to 5(6)-*syn*,*anti*-difunctional derivatives[3a] and to control of lithiation at the 1- and 3-positions of *N*-Boc-2-azabicyclo[2.1.1]hexane leading to aldehydes and esters.[6] Other alternatives to the carboxylic acid group at the 1-position include nitriles[1] and pyridine derivatives,[2d] and hydride reduction of the cyano group[1] has been reported. However, we are not aware of any reports of displacement reactions at the 1-methylene position apart from replacement of a tosyl group by hydride in our own work (Scheme 1) in which we examined formal dyotropic rearrangements of *N*-chloro-derivatives of this strained ring system together with study of the elevated nitrogen inversion barrier.[7] The need to extend the range of functionalization at the 1-position is made more urgent by intense current activity in the construction of analogues of epibatidine[8] in the search for high affinity and high subtype selectivity

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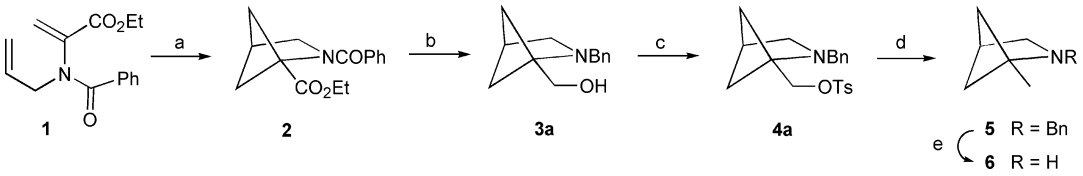
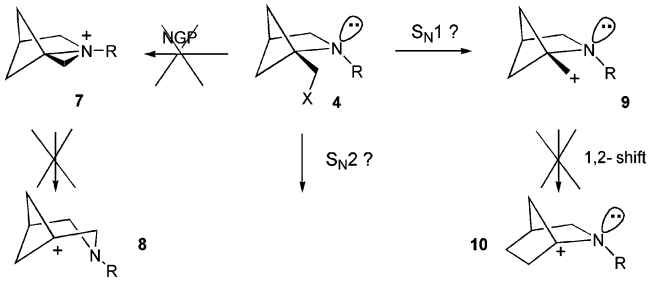
SCHEME 1[a]



[a] Reagents: (a) 254 nm (cf. ref 2a); (b) $LiAlH_4/Et_2O$, reflux (94%); (c) TsCl/pyridine, 4 °C (86%); (d) $LiAlH_4$/THF, reflux (92%); (e) H_2/Pd (100%).

at the nicotinic acetylcholine receptor (nAChR).[9] We have described epibatidine isomers[10] and homologues based on azabicyclic alternatives to the 7-azabicyclo[2.2.1]heptane skeleton[11] that have high affinity at the nicotinic acetylcholine receptor (nAChR), and modeling studies suggest that attachment of a heterocyclic substituent separated by one or more methylene spacers at the 1-position of 2-azabicyclo[2.1.1]hexane should also provide appropriate N−N distances and orientation for effective interaction at the receptor. Although Piotrowski has utilized the photochemical route to produce 2-azabicyclo[2.1.1]hexane derivatives having pyridine substituents directly attached to the 1-position,[2d] we were anxious to widen the range of potential nAChR agonists by extending the chain length and the range of available attached heterocycles[12] at the 1-position. We here describe successful substitution reactions at the 1-methylene position, opening the way to the isolation of useful intermediates for further elaboration. Manipulation of *N*-protecting groups is also described together with a convenient refinement of the substitution process that involves participation by *N*-alkoxycarbonyl protecting groups.

SCHEME 2



Discussion

Scheme 1 summarizes the preparation of **2** from *N*-benzoyl *N*-allyldehydroalanine ethyl ester **1** using the reliable photolytic approach originally established by Pirrung[2a] and Clardy and Hughes[2b,c] and includes our earlier conversion of the 1-ethoxycarbonyl group into methyl via the tosylate **4a** (by displacement using the sterically undemanding hydride ion).[7] This proceeded efficiently to give **5** and hence the secondary amine **6** (via hydrogenolysis), which provided the *N*-chloroamine with sodium hypochlorite solution.[7] We did not expect to be able to achieve ready S_N2 displacement of a leaving group at the hindered ("pseudo-neopentyl") 1-methylene group in **4** using other, more sterically demanding nucleophiles.

Some possible substitution pathways from **4** are shown in Scheme 2. Any thought of a "double displacement" leading to substitution via neighboring group participation of the amino-nitrogen lone pair is unlikely on the basis of the orientation of the lone pair and the strain in intermediate **7** (although this strain could, in principle, be released by C−N bond cleavage to **8** to yield 3-azabicyclo[3.1.1]heptane isomers). We did not expect to achieve useful S_N1 substitution in view of the propensity of the strained azabicyclo[2.1.1]hexane system for skeletal rearrangement or fragmentation.[7] However, further consideration is justified when the limited options for rearrangement of the primary carbocation **9** are considered. The strained rearranged bridgehead cation **10** should be intrinsically inaccessible; resonance stabilization by the (almost orthogonal) nitrogen lone pair is clearly impossible, and the electronegative nitrogen would further destabilize the hypothetical cation **10**.

Initial scoping studies were carried out starting with the readily available *N*-benzyl-protected alcohol **3a** in order to establish whether displacement reactions were feasible. Conversion of **3a** into the mesylate **11a** (88%) was followed by successful but slow displacement with KCN in the presence of 18-crown-6 at 80 °C, giving the

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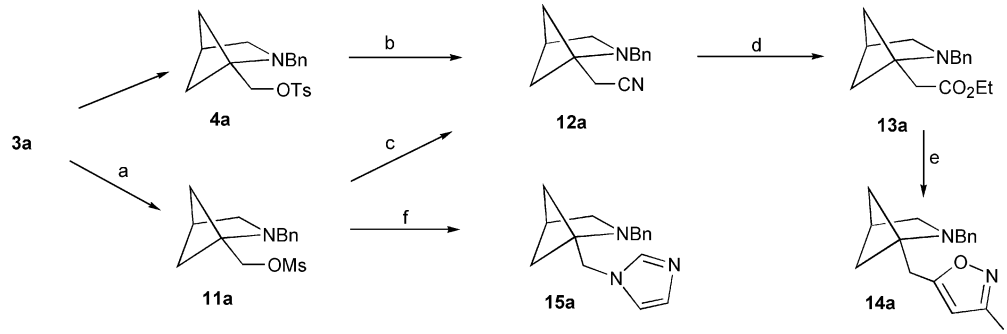
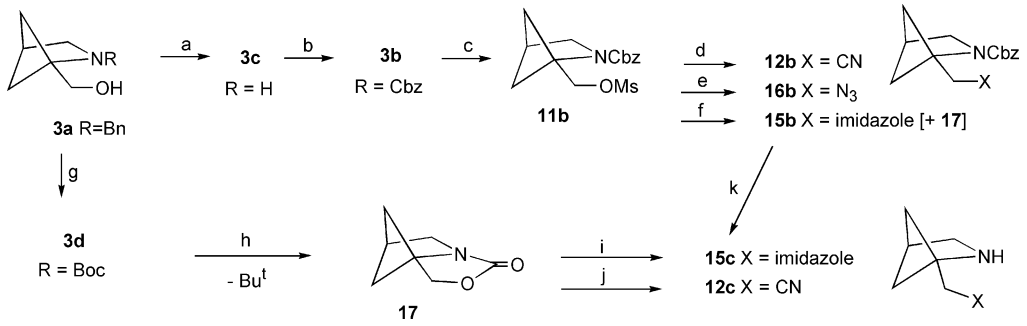
SCHEME 3[a]



[a] Reagents: (a) $MsCl/CH_2Cl_2$ (88%); (b) KCN, 18-crown-6, CH_3CN, 80 °C, 48 h (65%); (c) as (b), 60 °C (78%); (d) (i) H^+/H_2O, (ii) $SOCl_2$, (iii) EtOH (32%); (e) (i) acetoxime, BuLi, (ii) concentrated HCl, 90 °C; (f) imidazole/NEt_3/acetonitrile, 90 °C, 48 h (29%).

SCHEME 4[a]



[a] Reagents: (a) H_2/Pd (100%); (b) BnOCOCl, pH 7−8 (40%); (c) $MsCl/CH_2Cl_2/NEt_3$ (80%); (d) KCN, 18-crown-6, CH_3CN, 80 °C, 48 h (78%); (e) NaN_3, DMF (85%); (f) imidazole/BuLi/CH_3CN (**15b**, 43%; **17**, 6%;); (g) H_2/Pd/C/MeOH, $(Boc)_2O$ (60%); (h) $MsCl/CH_2Cl_2/NEt_3$ (88%); (i) as (f) (40%); (j) as (d) (55%); (k) TMSI, HBF_4, CH_2Cl_2 (90%).

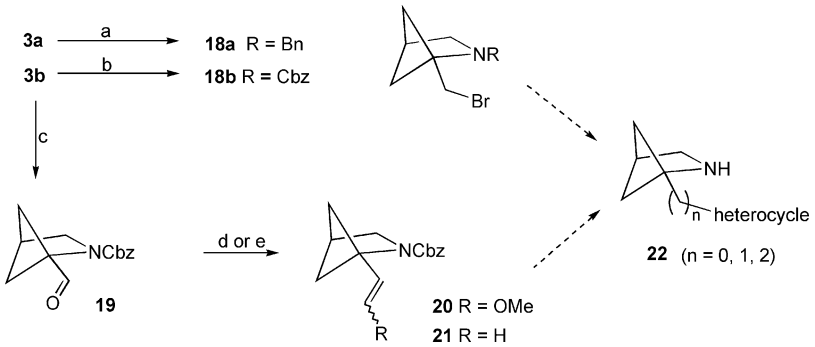
nitrile **12a** in 63% yield (Scheme 3; yields are not optimized). The use of mesylate proved slightly more effective than the conversion via the tosylate **4a**. Acid hydrolysis/esterification of **12a** gave the ester **13a**. Conversion into the methylisoxazole[12a] **14a** was attempted despite the potential for competing pathways based, for example, on enolization of **13a**, and a sample of **14a** was isolated in very low yield (as shown by signals at δ 5.96 and 2.26, corresponding to the lone isoxazole proton and the methyl group, respectively). This is not a practical preparative route but was our first example of a heterocyclic derivative of the title ring system attached to the 1-position by a methylene "spacer". The synthesis of a second example was achieved by treatment of **11a** with imidazole in the presence of triethylamine, giving **15a** directly in 29% yield and demonstrating that the direct displacement approach is also effective using a nitrogen nucleophile. The conditions for the substitution reactions are suggestive of S_N2 reactivity (the methylene bridges of the azabicyclic system clearly offer less steric hindrance than a normal neopentyl system), but we have no further evidence, as yet, concerning the balance between S_N2 and S_N1.

Having established the validity of the basic approach in Scheme 3 in the *N*-benzyl-protected (a) series, we explored the use of *N*-alkoxycarbonyl groups to protect the nitrogen, i.e., the (b) series shown in Scheme 4. The use of *N*-alkoxycarbonyl instead of *N*-benzoyl in the initial photochemical reaction has been used by Piotrowski to produce 1-aryl and 1-pyridyl 2-azabicyclo-[2.1.1]hexane derivatives,[2d] but in our hands the yields of photoadducts using the benzyloxycarbonyl (Cbz) group were poor. We therefore chose to debenzylate **3a** and reprotect the secondary amine **3c** with the Cbz (**3b**) and Boc (**3d**) groups.[13]

Scheme 4 shows the preparation of the *N*-protected derivative **3b** and conversion into the mesylate **11b** together with further substitution reactions. Nucleophilic displacement on **11b** using cyanide ion gave the nitrile **12b** in 78% yield. An X-ray crystal determination confirmed the retention of the 2-azabicyclo[2.1.1]hexane core of **12b**. Spectroscopic comparisons and protonation studies within the *N*-Bn and *N*-Cbz series eliminated any possibility of isomeric 3-azabicyclo[3.1.1]heptane derivatives derived from the hypothetical intermediate **8**. Further chemical interconversions confirmed the absence of rearrangement in both series; for example, reduction of the cyanomethyl derivative **12a** gave a primary amine attached to the 1-position by a bismethylene chain. Treatment of **11b** with azide ion provided the azide **16b** (85% yield), and use of the imidazole anion gave **15b** together with a minor product that was identified as the cyclic carbamate **17** (6% yield). The products **15b** and **17** were also formed (27% and 36%, respectively) using imidazole and triethylamine to displace the mesyl group. Clearly the cyclic carbamate **17** is formed by NGP of the benzyloxycarbonyl oxygen with loss of benzyl, and predictably, it was produced more efficiently under similar reaction conditions via loss of *tert*-butyl from the *N*-Boc-

(13) *N*-Boc- and *N*-Cbz derivatives of the parent 2-azabicyclo[2.1.1]-hexane derivatives have been described.[3a,6]

SCHEME 5[a]



[a] (a) $SOBr_2$ (77%); (b) CBr_4/PPh_3 (80%); (c) Swern oxidation (90%); (d) **(20)** methoxymethylenetriphenylphosphorane; (e) **(21)** methylenetriphenylphosphorane 63%.

protected derivative **3d**. This observation raises the possibility of wider involvement of the carbonyl of the Cbz protecting group in other displacements in Scheme 4, although the fact that corresponding reactions in the *N*-Bn and *N*-Cbz series require similar temperatures and reaction times weakens the case for wider NGP by the carbonyl group. More detailed kinetic investigations will be required to clarify this issue. Nucleophilic attack at the 1-methylene position of **17** by the imidazolyl anion required more vigorous conditions than for the mesylate **11b** but provided the *N*-deprotected compound **15c** directly (with concomitant decarboxylation) in good yield; the identical secondary amino-compound **15c** was also formed by *N*-deprotection of **15b** using TMSI. Similar treatment of **17** with cyanide ion gave **12c**. The value of **17** as a convenient direct source of *N*-deprotected 1-functionalized derivatives of the 2-azabicyclo[2.1.1]hexane ring system is under continuing study.

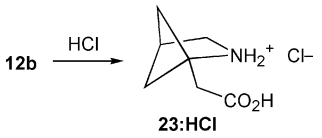
The potential for synthesis of a wider range of derivatives of this ring system is illustrated in Scheme 5. The bromo-derivative **18a** was isolated from treatment of **3a** with thionyl bromide (77%) and **18b** was accessible from **3b** using CBr_4/PPh_3 (80%); these compounds will form the basis for coupling chemistry. Swern oxidation of **3b** provided the aldehyde **19**, which was converted into the mixture of vinyl ethers **20** and the alkene **21** using established Wittig methodology.[14] The vinyl ethers **20** are precursors of systems containing pendant heterocycles including diazenes[14] and were isolated in acceptable purity, although they were not amenable to chromatographic purification.[16] Pyridyl derivatives **22** should be accessible from the alkenes using reductive Heck chemistry[15] and from halo-derivatives (e.g., **18**) via coupling reactions. These intermediates are currently forming the basis for the synthesis of target compounds having a wider range of nitrogen heterocycles attached to the 1-position by methylene chains of varying lengths. Such derivatives should allow systematic investigation of the effects of the key N−N distances (secondary N/heterocyclic N) and orientation on nAChR subtype selectivity.

(14) For typical procedures, see ref 12c. For the preparation of **20** we used potassium *tert*-butoxide in place of LDA.

(15) See refs 10b and 11 for typical reductive Heck procedures and references to the work of other groups.

(16) The purity of **20** was estimated to be greater than 90% by NMR. The spectra were complicated further owing to the presence not only of *cis*/*trans* isomers but also of slow rotation about the C-N bond. Spectra of many *N*-alkoxycarbonylamines in this work showed the effects of slow rotation (cf. ref 11).

The recent interest in 2,4-methanoproline[1] led us to synthesize the novel homologue, the β-amino acid **23**, by hydrolysis of the 1-cyanomethyl derivative **12b**. The crude hydrochloride salt **23**·HCl was isolated directly in good yield and ion-exchange chromatography provided the crystalline amino acid **23**. Derivatization and further chemistry of **23** is under continuing study.



Conclusions

Nucleophilic substitution has been successfully demonstrated (without rearrangement) at a methylene group attached to the 1-position of the 2-azabicyclo[2.1.1]hexane ring system and has led to the isolation of a broad selection of novel substituted derivatives. The work has demonstrated that a wide range of 1-substituted intermediates having different chain lengths are accessible, including heterocyclic derivatives that have significance as potential ligands for the nAChR. The methodology will also be applicable to precursors bearing substituents in the azabicyclic core.

Experimental Section

NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard. Routine mass spectra were measured using electrospray, and accurate mass measurements were made using FAB. All reactions were performed in oven-dried glassware under dry nitrogen (or argon where stated). Commercially available solvents were purified and dried, when necessary, prior to use. "Ether" refers to diethyl ether and "petrol" to petroleum ether, bp 40−60 °C, unless indicated otherwise.

Flash chromatography was carried out using silica gel (60) unless stated otherwise. Thin-layer chromatography was conducted on silica 60-254 plates. Chromatography solvents were routinely saturated with ammonia gas for amine (and *N*-protected amine) separations.

***N*-Benzoyl-*N*-allyldehydroalanine Ethyl Ester, 1.** Allylamine (9.38 mL, 125 mmol) was added dropwise to a stirred solution of ethyl pyruvate (13.7 g, 125 mmol) in toluene (150 mL), and stirring was continued for 3 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with toluene (3 × 150 mL). The combined organic layers were dried with $MgSO_4$ and filtered. Distilled triethylamine (19.5 mL, 140 mmol) was added under nitrogen,

followed by dropwise addition of benzoyl chloride (16.3 mL, 140 mmol) over 15 min. After the mixture stirred overnight, the triethylamine hydrochloride was filtered off, and the solvent was evaporated to give crude **1** (42.91 g). A sample (18.36 g) was chromatographed (3:7 ether/petrol; R_f 0.19), yielding **1** as a pale yellow oil (6.53 g, 47%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 3H), 4.07 (q, J = 7.0 Hz, 2H), 4.31 (bd, J = 6.0 Hz, 2H), 5.20 (ddt, J = 10.0, 1.5, 1.0 Hz), 5.24 (ddt, J = 17.0, 1.5, 1.5 Hz), 5.51 (bs, 1H), 5.92 (ddt, J = 17.0, 10.0, 6.0 Hz, 1H), 6.07 (bs, 1H), 7.26−7.52 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.8 (CH_3), 51.8, 61.4, 117.8, 121.8 (CH_2), 127.9, 130.0, 132.8 (CH), 135.6 (C), 140.6 (C), 163.7, 170.6 (C). ν_{max} ($CDCl_3$): 1702 1652, 1625, cm^{-1}. m/z: 260.12865; $C_{15}H_{18}NO_3$ [MH^+] requires 260.12867.

2-Benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylic Acid Ethyl Ester, 2. These methods were based on the work of Pirrung[2a] and Clardy.[2b,c] Compound **1** (1.0−1.5% in dry benzene containing 0.2% acetophenone) was photolyzed in quartz tubes in a Rayonet reactor (254 nm, 40 h) to give crystalline **2**, mp 105.5−106.5 °C, in 65% yield after chromatography (1:1 ether/petrol). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (t, J = 7.0 Hz, 3H), 1.81 (dd, J = 5.0, 2.0 Hz, 2H), 2.19 (m, 2H), 2.81 (m, 1H), 3.56 (bs, 2H), 4.28 (q, J = 7.0 Hz, 2H), 7.36−7.52, 7.71−7.79 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.4 (CH_3), 35.7 (CH), 42.2, 55.5, 61.4 (CH_2), 70.7 (C), 128.7, 128.8, 131.7 (CH), 135.0 (C), 168.8, 174.2 (C═O). ν_{max} ($CDCl_3$): 1733, 1652 cm^{-1}. m/z: 260.12862; $C_{15}H_{18}NO_3$ [MH^+] requires 260.12867. Further crystallization from ether gave an analytical sample, mp 106.5−107 °C. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 68.48; H, 6.61; N, 5.40. Found: C, 68.42; H, 6.65; N, 5.43. X-ray crystallographic data for **2** are recorded in Supporting Information.

Photolysis of a 1.5% solution of **1** in acetone (254 nm, 60h) followed by filtration through silica (7:3 petrol/ether) gave material, mp 106−107 °C, in ca. 40% yield; although the yield was lower, this method was readily adaptable to production of **2** on a multigram scale because yields were more consistent and the chromatographic separation was simpler.

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)methanol, 3a. The ester **2** (2.32 g, 8.95 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.358 g, 35.78 mmol) in dry THF (40 mL). The mixture was heated at 68 °C for 36 h, cooled, and quenched with water-saturated ether. The slurry was filtered through Celite, and the solvent was removed under reduced pressure prior to chromatographic purification. The less polar impurities were eluted with ether and the product was then flushed off the column with 9:1 ether: methanol (saturated with NH_3, R_f 0.10) to give crystalline **3a** (1.75 g, 96%), mp 58−59 °C after recrystallization from petrol. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.62 (bs, 4H), 2.60 (bs OH), 2.66 (bs, 1H), 2.67 (bs, 2H), 3.69 (bs, 2H), 3.79 (bs, 2H), 7.20−7.44 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.2 (CH), 38.2 (CH_2), 55.8 (CH_2), 57.9 (CH_2), 61.9 (CH_2), 74.3 (C), 127.4, 128.8, 129.0 (CH), 139.8 (C). m/z: 204.13884; $C_{13}H_{18}NO$ [MH^+] requires 204.13885. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.06; H, 8.41; N, 6.88.

1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 3b. Following the procedure of Cox,[17] **3c** (0.908 g, 8.03 mmol) was dissolved in distilled water (10 mL) and cooled to 0 °C. Aqueous sodium hydroxide (12 M, 2.5 mL) was added dropwise, and when addition was halfway through (pH 12), the simultaneous addition of benzyl chloroformate (2.97 mL, 20.81 mmol) was begun. Addition of the sodium hydroxide was finished just after that of the benzyl chloroformate, and stirring was continued at 0 °C for 15 min and then at room temperature for 24 h. Distilled water (10 mL) was added to the reaction mixture. The organic layer was run off, and the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.17) gave **3b** (0.884 g, 45%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.57 (dd, J = 4.8, 1.8 Hz, 2H), 1.79 (m, 2H), 2.77−2.79 (m, 1H), 3.46 (s, 2H), 3.95 (d, J = 7.0 Hz, 2H), 4.60 (bs, 1H), 5.14 (s, 2H), 7.26−7.38 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.7 (CH), 42.1, 52.4, 61.9, 67.1 (CH_2), 74.9 (C), 128.2, 128.4, 128.9 (CH), 137.0 (C), 156.0 (C═O). ν_{max} ($CDCl_3$): 3420, 1684 cm^{-1}. m/z: 248.12867; $C_{14}H_{18}NO_3$ [MH^+] requires 248.12866.

(2-Azabicyclo[2.1.1]hex-1-yl)-methanol, 3c. Compound **3a** (768 mg, 3.78 mmol) in dry methanol (20 mL) was hydrogenated using 10% Pd/C (250 mg) at room temperature for 24 h. Ammonia gas was bubbled through the solution, which was filtered through Celite. The solid was washed with methanol saturated with NH_3 (100 mL), and the combined methanol extracts were evaporated under reduced pressure to yield **3c** (427 mg, 100%) as a yellow oil. (R_f 0.10 in 6:4 ether/methanol saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.53 (dd, J = 4.4, 1.8 Hz, 2H), 1.86 (m, 2H), 2.79 (m, 1H), 3.05 (m, 2H), 3.74 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.1 (CH), 39.8, 48.5, 62.2 (CH_2), 70.6 (C). ν_{max} ($CDCl_3$): 3375, 1650, 1638 cm^{-1}. m/z: 114.09181; $C_6H_{12}NO$ [MH^+] requires 114.09189.

1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid *tert*-Butyl Ester, 3d, from 3a. Compound **3a** (60 mg, 0.295 mmol) was stirred in dry methanol (1 mL) with (10%) Pd/C (250 mg) and Boc_2O (45 mg, 0.206 mmol) at room temperature for 24 h. The mixture was filtered through Celite, and the solid was washed with ethyl acetate saturated with NH_3 (30 mL) and methanol saturated with NH_3 (30 mL). The combined organic layers were evaporated under reduced pressure, and the product was chromatographed (7:3 petrol/ether saturated with NH_3, R_f 0.58) to give **3d** (38 mg, 60% yield) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.56 (dd, J = 4.6, 1.8 Hz, 2H), 1.76 (m, 2H), 2.75 (m, 1H), 3.37 (s, 2H), 3.93 (d, J = 7.0 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.0 (CH_3), 34.7 (CH), 42.2, 52.9, 62.2 (CH_2), 74.6 (C), 80.3 (C), 156.2 (C). m/z: 214.14432; $C_{11}H_{20}NO_3$ [MH^+] requires 214.14429.

Toluene-4-sulfonic Acid (2-Benzyl-2-azabicyclo[2.1.1]-hex-1-ylmethyl) Ester, 4a. A solution of the alcohol **3a** (2.03 g; 10 mmol) in dry pyridine (50 mL) was cooled in an ice bath, and tosyl chloride (3.81 g; 20 mmol) was added portionwise so that the temperature did not exceed 10 °C. The mixture was left overnight at 4 °C, poured into ice water, and basified with aqueous NH_3. The resulting yellowish solid was slurried and filtered twice more with ice water (2 × 100 mL). The solid was dried under vacuum to afford the tosylate **4a** (3.08 g; 86%), which was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.52 (m, 2H), 1.68 (m, 2H), 2.43 (s, 3H), 2.65 (m, 3H), 3.58 (bs, 2H), 4.18 (s, 2H), 7.2−7.3 (m, 7H), 7.75 (d, J = 8 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.0 (CH_3), 37.2 (CH), 38.4, 56.9, 58.1, 69.8 (CH_2), 70.9 (C), 127.2, 128.3, 128.6, 128.9, 130.2 (CH), 133.3, 139.9, 145.2 (C). ν_{max} (CH_2Cl_2): 1598 cm^{-1}. m/z: 358.14769; $C_{20}H_{24}NO_3S$ [MH^+] requires 358.14764. X-ray crystallographic data for **4a** are recorded in Supporting Information.

2-Benzyl-1-methyl-2-azabicyclo[2.1.1]hexane, 5. A solution of **4a** (3.00 g, 8.4 mmol) in dry THF (80 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.60 g, 40 mmol) in dry THF (120 mL) and heated overnight under reflux. After careful decomposition of the excess $LiAlH_4$ using water-saturated ether, the mixture was filtered, dried with $MgSO_4$, and evaporated under vacuum to yield **5** as a pale yellow oil (1.44 g, 91%). An analytical sample was obtained by chromatography on alumina (ether). ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.41−1.62 (m, 4H), 2.55 (brs, 1H), 2.59 (brs, 2H), 3.60 (s, 2H), 7.13−7.44 (m, 5H). ^{13}C NMR (15 MHz, $CDCl_3$): δ 17.7 (CH_3), 36.6 (CH), 40.8, 56.0, 57.9 (CH_2), 70.1 (C), 126.8,

(17) Cox, C. D. PhD Thesis, University of Leicester, 2000. We thank Caroline Cox for a synthesis of **18b** and the corresponding iodo-derivative. Details of coupling investigations will be reported in due course. We also acknowledge her additional assistance with the optimization of yields for compounds **2**, **3a**, and **4a**.

128.4, 128.9 (CH), 140.6 (C). Anal. Found: C, 83.04; H, 9.17; N, 7.36. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48.

1-Methyl-2-azabicyclo[2.1.1]hexane Hydrochloride, 6·HCl, and Picrate Salt of 6. A solution of **5** (0.48 g, 2.57 mmol) in ethanol (15 mL) was hydrogenated over 10% Pd/C (0.14 g) for 24 h. The reaction mixture was filtered through Celite, and dry HCl gas was passed through the cooled filtrate. Removal of solvent left a dark oil, which was dissolved in the minimum of CH_2Cl_2 and treated with ether to precipitate the hydrochloride salt. This was filtered and dried under vacuum to afford **6**·HCl, which was used without further purification. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.83 (brs, 4H), 2.78 (brs (1H), 3.30−3.48 (m, 2H), 9.88 (brs, exch. 2 × NH). Solutions of the free amine **6** were prepared as required by dissolution of the salt in water and basification with 2 M aqueous NaOH. The free amine was then extracted into ether (or an alternative solvent such as a low-boiling chlorofluorocarbon) and dried by passage through a short column of $MgSO_4$. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.83 (brs, 4H), 2.78 (brs, 1H), 3.30−3.48 (m, 2H), 9.88 (brs, NH). The hydrochloride **6**·HCl was hygroscopic, and a solution of **6** in ether was used to prepare an analytical sample of **6** as the picrate salt. A solution of the free amine was concentrated carefully under reduced pressure and treated with a dry, saturated solution of picric acid in ether until no further precipitate appeared. The supernatant was removed from the precipitate, which was washed with a small aliquot of cold, dry ether. The precipitate was recrystallized from 80% ethanol/water, filtered, and dried under vacuum to afford the picrate salt of **6** as a yellow crystalline solid, mp 166−172 °C (dec). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22 (bd, J = 4 Hz, 2H), 1.38 (s, 3H), 1.55 (bd, 2H), 2.03 (brs, NH), 2.64 (m, 1H), 2.97 (brs, 2H). Anal. Found: C, 44.09; H, 4.32; N, 17.02. $C_{12}H_{14}N_4O_7$ requires C, 44.18; H, 4.33; N, 17.17.

1-Methanesulfonic Acid (2-Benzyl-2-azabicyclo[2.1.1]-hex-1-ylmethyl) Ester, 11a. Methanesulfonyl chloride (0.726 mL, 9.39 mmol) was added dropwise to a solution of the alcohol **3a** (1.74 g, 8.53 mmol) in dry CH_2Cl_2 (15 mL) followed by dry triethylamine (2.38 mL, 17.06 mmol). The reaction was heated at 30 °C for 20 h, filtered to remove triethylamine hydrochloride, and washed with distilled water (2 × 25 mL) and finally with saturated $NaHCO_3$ (30 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to yield **11a** (2.10 g, 88%) as a brown oil, which was used without further purification. (R_f 0.29 in ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.61 (dd, J = 4.6, 1.4 Hz, 2H), 1.71 (m, 2H), 2.65 (s, 3H), 2.92 (s, 3H), 3.65 (s, 2H), 4.38 (s, 2H), 7.1−7.4 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.7 (CH), 37.4 (CH_3), 38.1 (CH_2), 56.4 (CH_2), 57.6 (CH_2), 68.4 (CH_2), 70.8 (C), 126.9, 128.2, 128.5 (CH), 139.3 (C). ν_{max} ($CDCl_3$): 3430, 1638, 1628 cm^{-1}. m/z: 282.11639 (MH^+); $C_{14}H_{20}NO_3S$ [MH^+] requires 282.11644.

1-Methanesulfonyloxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 11b. Compound **3b** (606 mg, 2.45 mmol) in CH_2Cl_2 (10 mL) was treated with methanesulfonyl chloride (0.209 mL, 2.695 mmol) and dry triethylamine (0.683 mL, 4.9 mmol) using the procedure for **11a** and gave **11b** (0.670 g, 81%) as a pale yellow oil (R_f 0.76 in 4:1 petrol/ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.47 (dd, J = 4.0, 1.7 Hz, 2H), 1.94 (m, 2H), 2.74 (m, 1H), 2.92 (s, 3H), 3.42 (s, 2H), 4.76 (s, 2H), 5.02 (s, 2H), 7.2−7.4 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.7 (CH), 37.3 (CH_3), 41.5, 52.2, 66.6, 68.6 (CH_2), 69.7 (C), 127.9, 128.0, 128.5 (CH), 136.3 (C), 155.6 (C). ν_{max} ($CDCl_3$): 1750, 1685, 1636 cm^{-1}. m/z: 326.10622; $C_{15}H_{20}NO_5S$ [MH^+] requires 326.10620.

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-acetonitrile, 12a. Potassium cyanide (1.47 g, 22.51 mmol) and 18-crown-6 (0.238 g, 0.90 mmol) were added to a solution of mesylate **11a** (1.58 g, 5.63 mmol) in dry acetonitrile (8 mL). The mixture was heated at 60 °C for 72 h, cooled, triturated with ether, and filtered, and the solvent was removed under reduced pressure. Chromatography (4:1 petrol/ether saturated with NH_3, R_f 0.77) gave **12a** (0.778 g, 65%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.68 (dd, J = 4.6, 1.6 Hz, 2H), 1.79 (m, 2H), 2.70 (bs, 5H), 3.64 (s, 2H), 7.22−7.47 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.0 (CH_2), 36.5 (CH), 39.4 (CH_2), 55.9 (CH_2), 57.9 (CH_2), 68.4 (C), 117.4 (CN), 127.0, 128.3, 128.5 (CH), 139.2 (C). m/z: 213.13917; $C_{14}H_{17}N_2$ [MH^+] requires 213.13918.

1-Cyanomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 12b. The mesylate **11b** (350 mg, 1.08 mmol) in dry acetonitrile (5 mL) was reacted with KCN (280 mg, 4.30 mmol) and 18-crown-6 (4.4 mg, 0.165 mmol). After 48 h of heating at 60 °C and workup as described for **12a**, the solid product was chromatographed (7:3 petrol/ether saturated with NH_3, R_f 0.23) to give **12b** (215 mg, 78%); a small sample was recrystallized from ether for CHN analysis and X-ray determinations, mp 86.5−88.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.51 (dd, J = 4.7, 1.95 Hz, 2H), 1.92 (m, 2H), 2.72−2.75 (m, 1H), 3.24 (s, 2H), 3.42 (s, 2H), 5.04 (s, 2H), 7.12−7.29 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.6 (CH_2), 34.1 (CH), 42.9, 52.3, 66.5 (CH_2), 68.2 (C), 117.2 (CN), 127.6, 127.9, 128.4 (CH), 136.3 (C), 155.8 (C). m/z: 257.12900; $C_{15}H_{17}N_2O_2$ [MH^+] requires 257.12905. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.39; H, 6.54; N, 11.13. X-ray crystallographic data for **12b** are recorded in Supporting Information.

(2-Azabicyclo[2.1.1]hex-1-yl)-acetonitrile, 12c. The carbamate **17** (20 mg, 0.144 mmol) was reacted with KCN (37 mg, 0.57 mmol) and 18-crown-6 (6 mg, 0.023 mmol) in dry acetonitrile (3 mL) and heated at 80 °C for 168 h. After workup as described for **12a**, chromatography (9:1 ether/methanol saturated with NH_3, R_f 0.14) yielded **12c** as a yellow oil (12 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (dd, J = 4.38, 1.77 Hz, 2H), 1.79 (m, 2H), 2.10 (bs, NH), 2.79 (m, 2H), 2.81 (m, 1H), 3.07 (s, 2H). ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 22.0 (CH_2), 37.2 (CH), 41.8, 49.3 (CH_2), 64.9, 116.9 (C). m/z: 123 (MH^+).

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl) Acetic Acid Ethyl Ester, 13a. The nitrile **12a** (0.691 g, 3.25 mmol) was heated in 8 N HCl (5 mL) at 90 °C for 96 h. After cooling and evaporation to dryness under reduced pressure, thionyl chloride (4 mL, 54.37 mmol) was added. The mixture was heated to 40 °C for 5 h and evaporated to dryness, and absolute ethanol (5 mL) was added. The mixture was stirred at room temperature for 15 min and evaporated to dryness, and the solid remaining was dissolved in 1 N HCl (5 mL). After washing with ethyl acetate (2 × 5 mL), the aqueous layer was basified with ammonium hydroxide and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.43) gave **13a** (0.296 g, 35%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 3H), 1.66 (dd, J = 4.6, 1.6 Hz, 2H), 1.70 (m, 2H), 2.68 (s, 2H), 3.66 (s, 2H), 3.73 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 7.18−7.45 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (CH_3), 36.4 (CH), 37.2 (CH_2), 39.6 (CH_2), 57.4 (CH_2), 60.3 (CH_2), 69.7 (C), 128.1, 128.2, 128.6 (CH), 140.0 (C), 171.1 (C=O). ν_{max} ($CDCl_3$): 1732 cm^{-1}. m/z: 260.16500; $C_{16}H_{22}NO_2$ [MH^+] requires 260.16505.

2-Benzyl-1-(3-methylisoxazolyl-5-ylmethyl)-2-azabicyclo[2.1.1]hexane, 14a. Butyllithium (1.57 M solution; 800 μL) was added to acetone oxime (13.2 mg, 0.18 mmol) in THF (580 μL). The solution was heated at 60 °C for 5 min in a sealed reacti-vial. A solution of the ester **13a** (40 mg, 0.15 mmol) in THF (240 mL) was injected, and the mixture was stirred at 60 °C for 45 min. Concentrated HCl (800 mL) was added, and the solution was heated in the sealed reacti-vial at 100 °C for 3 h. After neutralization with aqueous $NaHCO_3$ and extraction with ethyl acetate (3 × 8 mL), the organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvent removed under reduced pressure to yield a brown oil, which was chromatographed (7:3 ether/petrol, R_f 0.35) to give an impure sample of **14a** (10 mg) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44−1.63 (m, 4H), 2.26 (s, 3H), 2.58−

2.63 (m, 3H), 3.10 (s, 2H), 3.68 (s, 2H), 5.96 (s, 1H), 7.2−7.4 (m, 5H). *m/z*: 269 (MH^+). Yields from later attempts to produce **14a** were low and variable, and alternative approaches to this compound are under study.

2-Benzyl-1-imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15a. The mesylate **11a** (100 mg, 0.355 mmol) was dissolved in dry acetonitrile (3 mL), and imidazole (24 mg, 0.355 mmol; dried by azeotropic distillation with benzene prior to use) was added, followed by dry triethylamine (54 μL, 0.39 mmol). After heating at 90 °C for 48 h, the mixture was cooled and basified with gaseous NH_3 before removal of the solvent under reduced pressure. The crude product was purified by flash chromatography (4:1 petrol/ether saturated with NH_3, R_f 0.45) to give **15a** (26 mg, 29%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.49 (m, 2H), 1.60 (dd, J = 4.6, 1.5 Hz, 2H), 2.63 (m, 1H), 2.69 (s, 2H), 3.74 (s, 2H), 4.19 (s, 2H), 6.95 (s, 1H), 7.06 (s, 1H), 7.26−7.40 (m, 5H), 7.50 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.0 (CH), 38.2 (CH_2), 47.7 (CH_2) 55.9 (CH_2), 57.9 (CH_2), 72.5 (C), 119.9, 127.1, 128.4, 128.5, 129.1 137.7 (CH), 139.2 (C). ν_{max} ($CDCl_3$): 1676 cm^{-1}. *m/z*: 254.16572 (MH^+); $C_{16}H_{20}N_3$ [MH^+] requires 254.16573.

A similar reaction using butyllithium instead of triethylamine (following the procedure described below for **15b**) gave **15a** in improved yield (35%).

Reaction of Mesylate 11b with Imidazole; Formation of 1-Imidazol-1-ylmethyl-2-aza-bicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 15b and 17. Imidazole (199 mg, 2.92 mmol) was dried by azeotropic distillation with benzene. Butyllithium (1.57 M in hexanes, 1.434 mL) in dry acetonitrile (5 mL) was then added, and the mixture was stirred for 15 min, forming a white precipitate. The mesylate **11b** (733 mg, 2.25 mmol) in dry acetonitrile (8 mL) was added dropwise, and the mixture was heated at 40 °C for 96 h. After basification with gaseous NH_3 and removal of solvent under reduced pressure, the mixture was introduced onto silica and washed with ether. Further elution (CH_2Cl_2) gave the cyclic urethane **17** (19 mg, 6% yield), and elution with 5% methanol/CH_2Cl_2 (saturated with NH_3) gave the imidazole derivative **15b** (285 mg, 43%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.46 (dd, J = 4.5, 1.7 Hz, 2H), 1.68 (m, 2H), 2.70 (m, 1H), 3.48 (s, 2H), 4.76 (s, 2H), 5.13 (s, 2H), 7.09 (bs, 2H), 7.25−7.33 (m, 5H), 7.55 (bs, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 33.8 (CH), 41.8, 47.7, 52.8, 66.7 (CH_2), 73.0 (C), 127.2, 127.8, 128.1, 128.3, 128.5, 128.9 (CH), 136.6 (C), 156.4 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m/z*: 298.15555; [MH^+] requires 298.15544.

In another experiment, dry imidazole (48 mg, 0.699 mmol) in dry acetonitrile (4 mL) was added to **11b** (175 mg, 0.538 mmol) in dry acetonitrile (5 mL), followed by dry triethylamine (0.112 mL, 0.807 mmol). After heating at 60 °C for 96 h, the mixture was worked up and chromatographed as above to give the cyclic urethane **17** (27 mg, 36%) and **15b** (69 mg, 0.232 mmol, 27%). An improved method and spectral data for **17** are given below.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15c, from 17. Compound **17** (34 mg, 0.24 mmol) in dry DMF (3 mL) was added to a solution of the imidazolyl anion [prepared from imidazole (34 mg, 0.24 mmol) and butyllithium (1.57 M, 0.202 mL) in dry DMF (2 mL) as described in the previous procedure]. The mixture was heated at 90 °C for 144 h and chromatographed (9:1 CH_2Cl_2/methanol saturated with NH_3) to give some unchanged **17** and **15c** (22 mg, 55% yield, 69% conversion) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (dd, J = 4.4, 1.8 Hz, 2H), 1.75 (m, 2H), 2.85 (m, 1H), 3.10 (s, 2H), 4.38 (s, 2H), 6.87 (bs, 1H), 6.98 (bs, 1H), 7.55 (bs, 1H). Shifts varied and showed broadening, possibly associated with traces of moisture and slow rotation of the imidazole ring. ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 37.0 (CH), 40.7, 48.7, 49.4 (CH_2), 69.8 (C), 119.4, 129.2, 137.2 (CH). *m/z*: 163.11095; $C_9H_{13}N3$ [MH^+] requires 163.11092.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15c, from 15b. To **15b** (57 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL) was added TMSI (136 μL, 0.96 mmol). After 7 min of stirring, HF−ether complex (29 μL, 0.38 mmol) was added, and stirring was continued for a further 6 min. Water (200 μL) was added, and the solvent was removed under reduced pressure. Additional water (0.5 mL) was added, and the solution was washed with petrol (2 × 2 mL). The aqueous solution was neutralized with solid K_2CO_3 and extracted with CH_2Cl_2 (5 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography (95:5 CH_2Cl_2/methanol saturated with NH_3, R_f 0.14) gave **15c** (27 mg, 87%) as a yellow oil.

1-Azidomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 16b, from 11b. Sodium azide (146 mg, 2.25 mmol) was added to a solution of **11b** (183 mg, 0.56 mmol) in dry DMF (4 mL), and the mixture was heated at 40 °C for 48 h. After washing with aqueous NH_4Cl (2 × 5 mL) and distilled water (2 × 4 mL), the organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to yield **16b** (130 mg, 85%) as a yellow oil, which was not purified further (R_f 0.74 in ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.51 (dd, J = 4.6, 1.84 Hz, 2H), 1.93 (m, 2H), 2.76 (m, 1H), 3.48 (s, 2H), 4.02 (s, 2H), 5.13 (s, 2H), 7.27−7.37 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.2 (CH), 41.7, 51.6, 52.3, 66.4 (CH_2), 72.2 (C), 127.7, 127.9, 128.7 (CH), 136.7 (C), 155.6 (C). ν_{max} (CH_2Cl_2): 2090, 1690 cm^{-1}. *m/z*: 273.13515; $C_{14}H_{17}N_4O_2$ [MH^+] requires 273.13522.

3-Oxa-5-aza-tricyclo[5.1.1.0^{1,5}]nonan-4-one, 17, from 3d. Methanesulfonyl chloride (0.340 mL, 4.39 mmol) was added dropwise to **3d** (0.891 g, 4.39 mmol) in dry CH_2Cl_2 (10 mL) followed by dry triethylamine (1.16 mL, 8.36 mmol), and the mixture was heated at 30 °C for 24 h. Triethylamine hydrochloride was filtered off and washed with dry CH_2Cl_2 (10 mL). The organic extracts were washed with distilled water (2 × 10 mL) and saturated $NaHCO_3$ (20 mL), dried with anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.17) yielded **17** (0.509 g, 88%) as a cream solid, mp 29.5−31.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.62 (dd, J = 4.7, 1.8 Hz, 2H), 1.93 (m, 2H), 2.88−2.91 (m, 1H), 3.25 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 40.1 (CH), 42.6, 47.0, 66.4 (CH_2), 73.9 (C), 156.7 (C). ν_{max} (CH_2Cl_2): 1745 cm^{-1}. *m/z*: 140.07115; $C_7H_{10}NO_2$ [MH^+] requires 140.07109.

2-Benzyl-1-bromomethyl-2-azabicyclo[2.1.1]hexane, 18a. Thionyl bromide (34 mg, 13μL, 164 mmol) was added to a solution of **3a** (28.0 mg, 138 mmol) in $CDCl_3$ (1 mL) in an NMR tube, which was shaken and left for 17 h. NH_3(g) was bubbled through the reaction mixture until the pH was alkaline, the ammonium bromide salt was filtered off, and the solvent was removed under reduced pressure. Chromatography (3:1 petrol/ether R_f 0.29) gave **18a** (28.3 mg, 106 mmol, 77%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.68 (bs, 4H), 2.63 (bs, 1H), 2.68 (bs, 2H), 3.63 (bs, 4H), 7.20−7.48 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.9 (CH), 32.8, 39.2, 39.2, 55.6, 57.7 (CH_2) 71.6 (C), 126.8, 128.2, 128.8 (CH), 139.5 (C). *m/z*: 266.05444 & 268.05252; $C_{13}H_{17}N^{79}Br$ [MH^+] requires 266.05452.

1-Bromomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 18b. Triphenylphosphine (212 mg, 0.81 mmol) was added to a solution of **3b** (50 mg, 0.20 mmol) in dry CH_2Cl_2 (5 mL) followed by slow addition of CBr_4 (288 mg, 0.87 mmol). After heating at 25 °C for 10 min, the mixture was stirred at room temperature for 24 h. The mixture was filtered, and the solids were washed successively with dry CH_2Cl_2 (50 mL) and ether (20 mL). Chromatography (1:1 petrol/ether saturated with NH_3, R_f 0.23) gave **3b** (50 mg, 80%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.50 (dd, J = 4.7, 2.0 Hz, 2H), 1.90−194 (m, 2H), 2.65−2.68 (m, 1H), 3.44 (s, 2H), 4.05 (s, 2H), 5.06 (s, 2H), 7.24−7.26 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 32.7 (CH_2), 33.4 (H), 42.8, 53.2, 66.5 (CH_2), 72.6 (C), 127.8, 127.9, 128.4 (CH), 136.7, 155.8 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m/z*: 310.04427 and 312.04235; $C_{14}H_{17}NO_2{}^{79}Br$ [MH^+] requires 310.04422. Treatment of **3b** with

$SOBr_2$ following the procedure of Cox[17] also produced **18**, but the method above was more successful.

1-Formyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 19. DMSO (0.097 mL, 1.38 mmol) in dry CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (0.060 mL, 0.69 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The mixture was stirred for 30 min at −78°C after completion of the addition. A solution of **3b** in dry CH_2Cl_2 (5 mL) was added dropwise, and the mixture was stirred for a further 15 min at −78°C. Triethylamine (0.230 mL, 1.65 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise, and the reaction mixture was warmed to room temperature with stirring for 90 min. CH_2Cl_2 (2 mL) was added, and the mixture was washed with water (2 × 10 mL) and saturated aqueous $NaHCO_3$ (5 × 15 mL). The organic extracts were dried with anhydrous $MgSO_4$ and filtered, and the solvent removed under reduced pressure to yield **19** (60 mg, 90%) as a pale yellow oil (R_f 0.82 in ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.65 (dd, J = 4.7, 1.95 Hz, 2H), 2.12 (m, 2H), 2.82 (m, 1H), 3.43 (s, 2H), 5.16 (s, 2H), 7.30−7.36 (m, 5H), 9.87 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.0 (CH), 41.5, 52.3, 67.5, (CH_2), 76.3 (C), 128.0, 128.2, 128.5 (CH), 136.1 (C), 194.0 (C). ν_{max} (CH_2Cl_2): 1735, 1680 cm^{-1}. *m*/*z*: 246.11302; $C_{14}H_{16}NO_3$ [MH^+] requires 246.11296.

1-(2-Methoxy-vinyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 20. Potassium *tert*-butoxide (143 mg, 1.28 mmol) was stirred in dry THF (2 mL) at 0 °C under an argon atmosphere. (Methoxymethyl)triphenylphosphonium chloride (437 mg, 1.28 mmol) was then added, followed by dry THF (2 mL). The bright red mixture was stirred for 2 h at 0 °C under argon. Compound **19** in dry THF (4 mL) was added at 0 °C, and the mixture was stirred for 20 h under argon. Water-saturated ether (6 mL) was added at room temperature, and the mixture was stirred for 10 min followed by more water (4 mL) and stirring (10 min). The organic layer was separated, and the aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous $MgSO_4$, and filtered, and the solvent removed under reduced pressure to yield the mixture of *cis* and *trans* stereoisomers **20** as an orange oil that still contained some triphenylphosphine oxide. The crude product was unstable and was not purified by chromatography. ^{1}H NMR (250 MHz, $CDCl_3$): δ (both stereoisomers showed slow N-CO rotation) 1.61 (dd, J = 4.93, 3.10 Hz, 2H), 1.83 (m, 2H), 2.96 (m, 1H), 3.32 (s, 2H), 3.41 (s, 3H), 5.12 (m, 1H), 5.19 (m, 2H), 5.48 (d, J = 13.1 Hz, 1H), 5.91 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 12.9 Hz, 1H), 6.50 (m, 1H), 7.17−7.31 (m, 5H, Ph). *m*/*z*: 273 (MH^+).

1-Vinyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 21. Potassium *tert*-butoxide (0.123 g, 1.09 mmol) was stirred in dry THF (2 mL) under argon at 0 °C. Methyltriphenylphosphonium bromide (0.390 g, 1.09 mmol) was added, followed by dry THF (2 mL). The bright yellow mixture was stirred for 2 h at 0 °C under argon. A solution of **19** in dry THF (3 mL) was added at 0 °C, and the mixture was stirred for 20 h under argon. The workup procedure followed that described for **20**, but the product was chromatographed (1:1 petrol/ether saturated with NH_3, R_f 0.59) to give **21** (0.16 g, 63%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.56 (dd, J = 4.9, 3.1 Hz, 2H), 1.82 (m, 2H), 2.64 (m, 1H), 3.41 (s, 2H), 5.05 (m, 4H), 6.50 (m, 1H), 7.18−7.31 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 30.0 (CH), 43.6, 52.2, 66.2 (CH_2), 74.1 (C), 114.9 (CH_2), 127.7, 128.1, 128.3 (CH), 135.5 (CH), 137.1 155.9 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m*/*z*: 243.12593; $C_{15}H_{17}NO_2$ [MH^+] requires 243.12592.

(2-Azabicyclo[2.1.1]hex-1-yl)-acetic Acid, 23. The nitrile **12b** (40 mg, 0.156 mmol) was dissolved in 8 N HCl (8 mL), and the mixture was heated to 90 °C for 72 h. The reaction was monitored using mass spectroscopy, and when hydrolysis was complete, the product was evaporated to dryness under reduced pressure to give **23**·HCl as a white residue in quantitative yield. ^{1}H NMR (300 MHz, D_2O): δ 1.60 (dd, J = 6.0, 2.0 Hz, 2H), 2.04 (m, 2H), 2.86 (m, 1H), 3.00 (s, 2H), 3.38 (s, 2H). ^{13}C NMR (75.8 MHz, D_2O): δ 34.5 (C_7), 36.0 (C_4), 39.9 ($C_{5/6}$), 49.8 (C_3), 69.6 (C_1), 173.1 (C═O). A small amount of **23**·HCl was passed down a Dowex ion exchange column to give a sample of **23,** which crystallized as fine needles (dec 42−45 °C). ^{1}H NMR (300 MHz, D_2O): δ 1.54 (dd, J = 6.1, 2.3 Hz, 2H), 1.97 (m, 2H), 2.72 (m, 1H), 2.84 (s, 2H), 3.35 (s, 2H). *m*/*z*: 142.08680; $C_7H_{12}NO_2$ [MH^+] requires 142.08689.

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Supporting Information Available: Spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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