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Kinetically-Controlled Displacement by Azide on an Allylic Chloride: Synthesis of a Highly Potent Serotonin-3 Receptor Ligand Prototype

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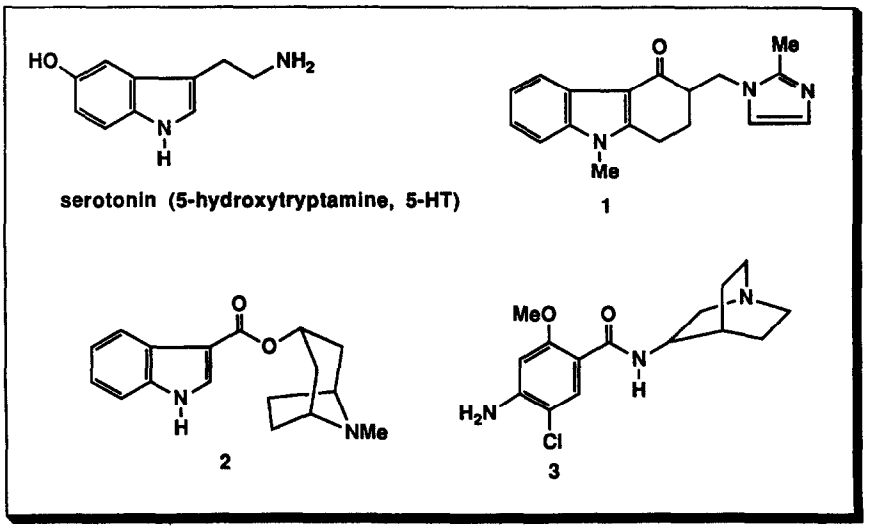
Abstract: *The discovery and selective synthesis of a novel and highly potent serotonin-3 receptor ligand, 4-amino-5-chloro-2-methoxy-N-(1-azabicyclo[2.2.2]-oct-2-enyl-2-methyl) benzamide (4) are described. The key step in the preparation of 4 involves an unusual example of a kinetically controlled displacement to provide a thermodynamically disfavored allylic azide isomer. This azide is a precursor to 2-aminomethyl-1-azabicylo[2.2 2]oct-2-ene (5), a convergent intermediate for the synthesis of analogs related to 4.*

INTRODUCTION

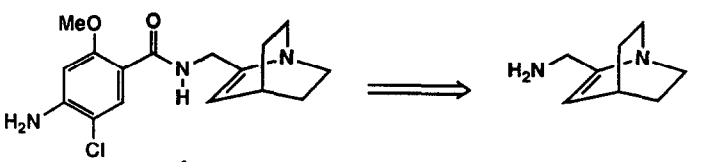
During recent years, there has been intense effort devoted to the identification and functional characterization of serotonin (5-HT) receptor subtypes and the preparation of ligands with potent binding affinity and receptor subtype specificity.[1] Such ligands often contain an aromatic group and nitrogenous basic moiety linked in such a manner as to induce a conformational rigidity or bias which is related to a particular conformation of serotonin, and these features presumably account in part for the specificity of recognition for such compounds at receptor subtypes.

The presence of a serotonin receptor subtype in the periphery, now classified as serotonin-3 (5-HT_3), has been known for some time.[2] More recent data have demonstrated the presence of 5-HT_3 binding sites in brain.[3] Several compounds exhibiting high affinity for this receptor have been identified. Antagonists at this receptor, typified by **1** (ondansetron)[4] and **2** (ICS-205-930),[5] have been shown to be highly effective for the blockade of chemotherapy-induced emesis,[6] an effect suggested to be modulated by 5-HT_3 receptors in the *area postrema*.[7] Perhaps more intriguing have been pharmacological, behavioral and neurochemical results which suggest that 5-HT_3 receptor antagonists may play a useful role in the amelioration of central nervous system disorders[8] such as schizophrenia or anxiety, although these indications remain to be validated clinically. Serotonin-3 receptors also have been shown to modulate cholinergic neurons,[9] suggesting a potential use for 5-HT_3 receptor antagonists in the treatment of memory disorders.

The majority of 5-HT_3 receptor antagonists reported to date, such as **2** and **3** (zacopride),[10] consist of an amino- or hydroxyl-substituted bicyclic amine acylated with a lipophilic aromatic carboxylic acid.

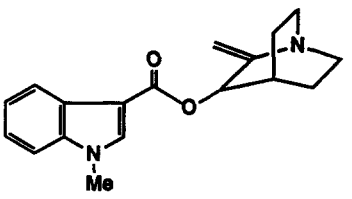


Herein, we report the discovery of a structurally novel and highly potent 5-HT_3 receptor ligand prototype (**4**) and a facile and selective synthesis of its azabicyclic amine precursor **5** which also is a convergent intermediate for synthesis of related serotonergic receptor ligands. Also described is an unusual example of a kinetically controlled displacement to obtain a thermodynamically disfavored allylic azide isomer, which serves as a key intermediate for the preparation of **5**.



RESULTS AND DISCUSSION

Based on the observed 5-HT_3 receptor binding affinity (K_i = 13nM) of the methylene-substituted quinuclidine **6** and known structure-activity relationships, we desired the amide **7** for biological evaluation. The synthesis of **7** is shown in Scheme 1. Reduction of 2-methylene-3-quinuclidinone[11] with sodium borohydride followed by treatment with methanesulfonyl chloride affords the allylic mesylate **10**. Exposure of **10** to tetra-*n*-butylammonium azide (65°C, 2h, CH_3CN) gives a *ca* 2:1 mixture of the azides **11** and **12**. Sequential reduction and acylation with the imidazolide of 4-amino-5-chloro-2-methoxybenzoic acid[12] provides the amides **7** and **4** which are separated by flash column chromatography. The target amide **7** exhibits moderate biological activity (K_i = 35 nM); however, the side product **4** surprisingly was found to exhibit excellent 5-HT_3 receptor binding affinity (K_i = 0.6 nM) [13]



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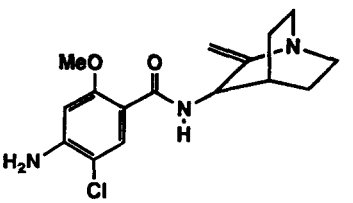

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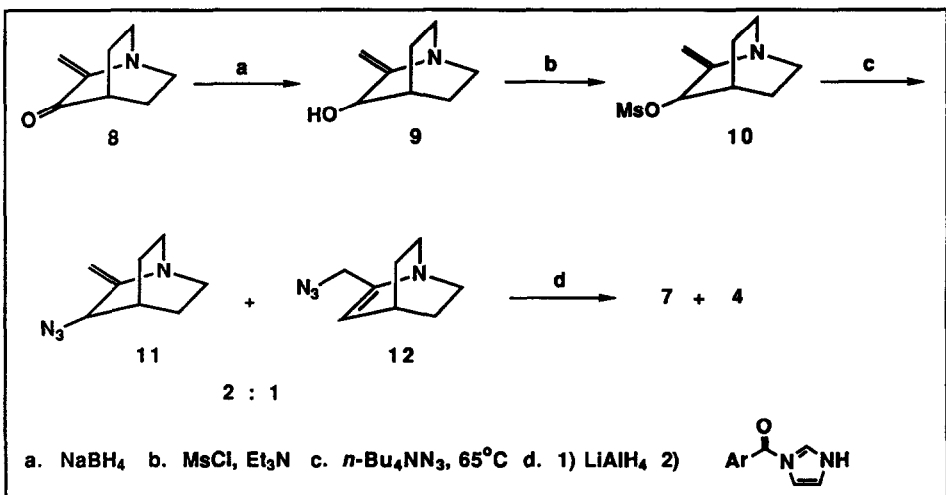
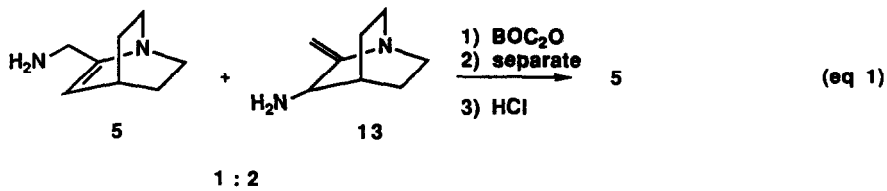
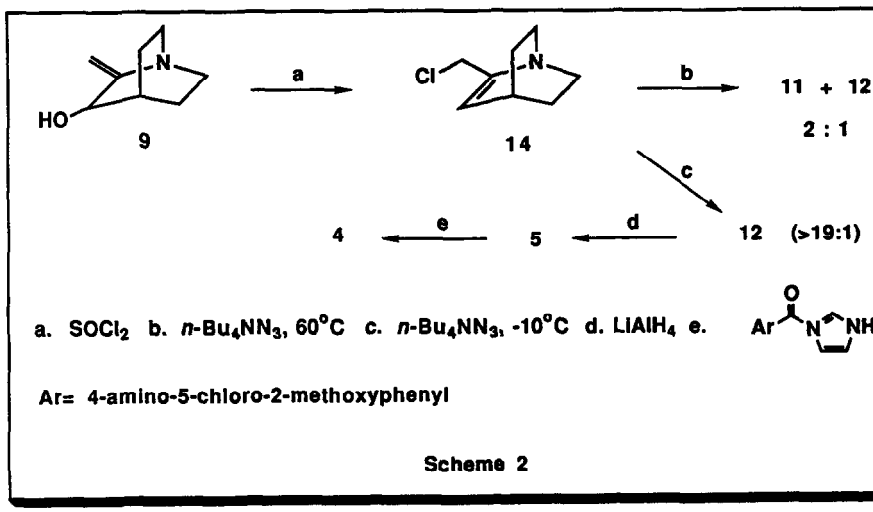


8 9 10 11 12

Scheme 1

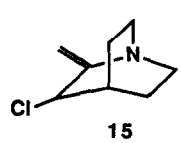
The unexpectedly potent receptor binding affinity of compound **4** necessitated the development of an efficient preparation of the precursor amine **5**. It was found that the 1:2 mixture of **5** and **13** could be converted to a corresponding mixture of *tert*-butyl carbamates which are separable by flash column chromatography. Subsequent acidic cleavage of the carbamate moiety affords the pure amine **5** (equation 1). However, the inefficiency of this isomer separation as well as the problem that the desired isomer is the minor component of the mixture prompted further study of the synthetic route, in particular the nature of the azide displacement reaction. Initially, it was not known whether the 2:1 mixture of azides **11** and **12** represents a slight kinetic preference for S_N2 *versus* S_N2' displacement by azide or a thermodynamic ratio. This issue was clarified, as shown in Scheme 2.





Scheme 2

Treatment of allylic alcohol **9** with thionyl chloride furnishes the primary chloride **14**. No evidence suggesting isomerization between **14** and **15** was observed at any point during the course of this study, although **14** slowly dimerizes, even at 0°C, to give the symmetrical *bis*-tetraalkylammonium salt **16**. The structure of **16** was verified by single crystal x-ray analysis.[18]



15

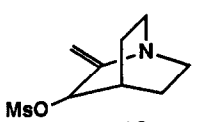
16

Heating **14** with tetra-*n*-butylammonium azide, under conditions analogous to those employed with the methylsulfonate ester substrate **10** (Scheme 1) affords a similar 2:1 mixture of allylic azides **11** and **12**, the undesired secondary isomer predominating. This result suggests that

the product mixture does in fact reflect a thermodynamic ratio. Indeed, it was found that treatment of **14** with tetra-*n*-butylammonium azide at low temperature (-10 - 0°C) affords smoothly the primary azide **12** (>19:1), demonstrating a clear kinetic preference for the S_N2-derived product. Furthermore, the isomerization of **12** to give an equilibrium mixture of **11** and **12** (2:1) can be followed by ^1H HMR spectroscopy. At room temperature in $CDCl_3$, equilibrium is attained after a period of *ca.* 2 days. These results are similar to observations first reported by Winstein[14] involving the equilibration of simple allylic azides. The rearrangement is thought to involve an intramolecular, partially concerted mechanism.[14] In practice, **12** is reduced ($LiAlH_4$) immediately upon isolation to provide the desired primary amine **5**. Acylation of **5** affords the amide **4**. The structure of this novel 5-HT_3 receptor ligand prototype was confirmed by single crystal x-ray analysis.[18]

Subsequent to the initial report[14] concerning the facile equilibration of allylic azides, studies involving compounds containing this functionality have been reported, and their propensity for such isomerization has become well recognized.[15] Interesting synthetic transformations involving the reaction of such equilibrating mixtures to provide single products, due to the enhanced reactivity of one of the regioisomeric azides, have been reported.[16] However, the sequence **14** → **12** → **5** appears to be the first demonstrated example of an allylic azide obtained selectively under kinetic conditions with sufficient isomeric stability to serve as a practical synthetic intermediate.

A final aspect of this study which required clarification involves the preferential site of kinetic attack of azide on the secondary mesylate **10**. Treatment of **10** with tetra-*n*-butylammonium azide at *ca.* 0°C affords a mixture of **11** and **12** and recovered **10** (*ca.* 1:2:1) after a period of 5h (equation 2). The predominance of the thermodynamically less favored isomer **12** indicates a preference for the S_N2' site of attack in this system. It is likely that this product ratio reflects the approximate selectivity for the S_N2 *versus* S_N2' attack of azide for this system (at 0°C), since the previous results (Scheme 2, **14**→**12**) indicate that equilibration under these conditions should be minimal. Upon standing at room temperature, this product equilibrates to a mixture containing a 2:1 ratio of **11** and **12**, analogous to the product composition obtained when the reaction is carried out at 60°C.



10

n-Bu_4NN_3

-10-0°C

5h

11 + **12** + **10**

1 : 2 : 1

(eq 2)

In summary, a selective synthesis of the azabicyclic allylic amine **5** is described. The key step involves a kinetic displacement of the allylic chloride **14** with azide, avoiding a facile equilibration of the primary allylic azide **12**. Compound **5** is a precursor to a novel and highly potent (K_i = 0.6nM) serotonin-3 receptor ligand prototype, and the route thus makes available the

compound for further pharmacological profiling as well as providing a ready source of the convergent intermediate amine for the preparation of related analogs.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. Thin layer chromatographic analysis was performed using Analtech silica gel GF (250μ) TLC plates, and compound visualization was effected using a UV lamp (254 nM) or a 2-5% solution of concentrated sulfuric acid in ethanol. ^{1}H NMR spectra were determined on a Varian XL-300 spectrometer operating at 299.9 MHz or a Bruker AM300 spectrometer operating at 300.1 MHz. Significant ^{1}H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. ^{13}C NMR spectra were determined on a Varian XL-300 or a Bruker AM300 spectrometer (75 MHz). Mass spectra were obtained with an A.E.I. MS-30 mass spectrometer or a Finnigan 4510 instrument. Column chromatography was done with J. T. Baker silica gel for flash column chromatography (40 μM average particle diameter) or Silica Woelm 32-63 (particle size 32-63 μM). Elemental analyses were performed by the Microanalytical Laboratory, operated by the Analytical Department, Pfizer Central Research, Groton, CT.

3-Hydroxy-2-methylene-1-azabicyclo[2.2.2]octane (9). Under a nitrogen atmosphere, in a round-bottom flask were placed 31 g (0.23 mol) of 2-methylene-3-quinuclidinone[11,17] and 400 mL of MeOH, and the system was cooled in an ice bath. To the stirring solution was added 4.3 g (0.11 mol) of sodium borohydride in portions over a period of 10 min, and the mixture was stirred for a period of 30 min. To the system was added cautiously 10mL of saturated aqueous $NaHCO_3$ in 1 mL portions. Additional (30 mL) saturated aqueous $NaHCO_3$ was added to the stirring reaction mixture over a period of 50 min, the mixture was allowed to come to room temperature, and Na_2SO_4 was added to the system. The mixture was stirred for 30 min, filtered and the filtrate was concentrated with a rotary evaporator. Toluene was added to the system, and the mixture was concentrated. The residue was dissolved in CH_2Cl_2 and the solution dried (Na_2SO_4), filtered and concentrated to afford 35.8 g of oil. The crude material was purified by flash column chromatography to obtain 12.7 g (40% yield) of **9**: mp 90-92°C; IR($CHCl_3$) 3580, 3250, 2940, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 1H), 1.46 (m, 1H), 1.62 (m, 1H), 1.86 (m, 2H), 2.68 (m, 1H), 2.88 (m, 3H), 4.17 (d, 1H, J = 2), 4.96 (d, 1H, J = 2), 5.08 (d, 1H, J = 2), mass spectrum, m/z 139 (parent). ^{13}C NMR ($CDCl_3$) δ 18.7(t), 24.9 (t), 31.3 (d), 48.0 (t), 49.7 (t), 69.7 (d), 108 (t), 159 (s) HRMS, calcd for $C_8H_{13}NO$: 139 0998. Found: 139.0998. Anal. Calcd for $C_8H_{13}NO$: C, 69.03, H, 9 41, N, 10.06. Found: C, 68.63, H, 9.24, N, 10.09

2-Chloromethyl-1-azabicyclo[2.2.2]oct-2-ene (14). Under a nitrogen atmosphere, in a round-bottom flask were placed 2.0 g (14 mmol) of **9** and 5mL of CH_2Cl_2, and the system was immersed in an ice bath To the system was added 5.2 mL (72 mmol) of thionyl chloride dropwise over a period of 5 min. The ice bath was allowed to expire, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated with a rotary

evaporator, and 2*N* aqueous NaOH was added to the system. To the system was added water, and the mixture was extracted with two portions of CH_2Cl_2. The combined organic fractions were dried, filtered and concentrated to afford 1.9 g (84% yield) of **14** as a yellow oil. This material was used in subsequent transformations without purification. An analytical sample was prepared by flash column chromatography: IR ($CHCl_3$) 2920, 2840, 1460, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (m, 2H), 1.56 (m, 2H), 2.56 (m, 3H), 2.94 (m, 2H), 3.96 (s, 2H), 6.48 (d, 1H, J = 6); ^{13}C NMR ($CDCl_3$) δ 27.4(d), 28.6 (t), 44.9 (t), 49.4 (t), 132 (d), 150 (s). HRMS calcd for $C_8H_{12}NCl$:157.0658. Found: 157.0644. Anal. Calcd for $C_8H_{12}ClN \bullet 1/2\ H_2O$: C, 57.65, H, 7.86, N, 8.40. Found: C, 57.92, H, 7.92, N, 8.17.

Upon extended storage, **14** dimerized to afford **16** as a white solid. Crystals of **16** were obtained for x-ray analysis by slow evaporation from ethyl acetate/$CHCl_3$; mp 254-257°C; IR (KBr) 3400, 2920, 1460 cm^{-1}; ^1H NMR (DMSO -d_6) δ 1.84 (m, 4H), 2.15 (m, 4H), 3.22 (m, 2H), 3.39 (m, 2H), 3.6 (m, 2H), 3.82 (m, 2H), 4.02 (m, 2H), 4.91 (d, 2H, J = 15), 5.59 (d, 2H, J = 15), 7.39 (d, 2H, J = 6); ^{13}C NMR (CD_3OD) δ 24.7 (t), 25.1 (t), 28.3 (d), 56.4 (t), 60.7 (t), 62.4 (t), 133 (s), 142 (d). HRMS calcd for $C_{16}H_{24}N_2Cl_2$: 314.1311. Found: 314.1299 Anal. Calcd for $C_{16}H_{24}N_2Cl_2 \bullet 1.5\ H_2O$; C, 56.14, H, 7.94, N, 8.18. Found: C, 56.29, H, 7.97, N, 8.14.

2-Aminomethyl-1-azabicyclo[2.2.2]oct-2-ene (5). Under a nitrogen atmosphere, in a round-bottom flask immersed in an ice/acetone bath were placed 3.0 g (19 mmol) of the allylic chloride **14**, 30 mL of CH_3CN, 2.65 mL (19 mmol) of triethylamine and 10 g (35 mmol) of tetra-*n*-butylammonium azide, and the reaction mixture was stirred for two h. The temperature of the cold bath gradually rose to -5°C. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$ and extracted with cold ethyl acetate. The ethyl acetate solution was washed with three portions of cold aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to obtain 8 g of crude product. This material was dissolved in cold ether/ethyl acetate and washed with five portions of cold aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated (rotary evaporator, cold water bath) to obtain 1.8 g (58% yield) of the allylic azide **12** as a yellow oil which was used immediately for the next transformation: IR ($CHCl_3$) 2920, 2880, 2100, 1660, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (m, 2H), 1.50 (m, 2H), 2.28 (m, 2H), 2.94 (m, 2H), 3.26 (m, 1H), 3.65 (s, 2H), 6.37 (d, 1H, J = 7); ^{13}C NMR ($CDCl_3$) δ 27.0 (d), 28.6 (t), 49.0 (t), 53.1 (t), 132 (d), 148. HRMS calcd for $C_8H_{12}N_4$. 164.1061. Found: 164.1025. Anal. (mixture of isomers **11** and **12**) Calcd for $C_8H_{12}N_4 \bullet 0.25H_2O$: C, 56.95; H, 7.47; N, 33.20. Found: C, 57.13; H, 7.28; N, 32.90. The equilibration of **12** to give a *ca.* 2:1 mixture of **11** and **12**, respectively occurs over a period of *ca.* 2 days (room temperature, $CDCl_3$) and may be monitored by ^1H NMR spectroscopy.

Under a nitrogen atmosphere, in a round-bottom flask were placed 22 mL (22 mmol) of 1*M* lithium aluminum hydride in THF, and the system was cooled in a dry ice/acetone bath. To the system was added dropwise, over a period of *ca.* 2 min, a solution of 1.8 g (11 mmol) of **12** in 7 8 mL of THF, and the cold bath was replaced with an ice/acetone bath. The reaction mixture was stirred for 30 min., the cold bath was removed and the mixture was stirred for an additional 30 min. The system was immersed in an ice/acetone bath, and 10 mL of 2*N* aqueous NaOH was added slowly and cautiously to the mixture. The system was removed from the cold bath, and the reaction mixture was stirred for 10 min. Sodium sulfate was added to the mixture, and after 15

min the solids were removed by suction filtration. The filtrate was concentrated with a rotary evaporator to obtain 1.67 g of crude amine **5** as a colorless oil which was used in subsequent transformations without further purification: IR ($CHCl_3$) 3650, 2940, 2000, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (m, 2H), 1.50 (m, 2H), 2.48 (m, 3H), 2.90 (m, 2H), 3.21 (s, 2H), 6.17 (d, 1H, J = 7); ^{13}C NMR ($CDCl_3$) δ 26.7(d), 29.0 (5), 44.4 (t), 49.2 (t), 126 (d), 154 (s). Mass spectrum, m/z 138 (parent). HRMS calcd for $C_8H_{14}N_2$: 138.1154. Found 138.1146.

4-Amino-5-chloro-2-methoxy-*N*-(1-azabicyclo[2.2.2]-oct-2-enyl-2-methyl) Benzamide (4). Under a nitrogen atmosphere, in a round-bottom flask were placed 363 mg (1.8 mmol) of 4-amino-5-chloro-2-methoxybenzoic acid and 2 mL of THF. To the system was added 586 mg (3.6 mmol) of carbonyl diimidazole. The reaction mixture was stirred for 25 min, partitioned between $CHCl_3$ and water and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated with a rotary evaporator. To the system was added 250 mg (1.8 mmol) of the amine **5** in 2 mL of THF, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between $CHCl_3$ and saturated aqueous sodium $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated, and the crude product was purified by flash column chromatography (60 g of silica gel) using 1:12.5 MeOH/$CHCl_3$ as the eluant to obtain 273 mg (47% yield) of **4** as a white solid: mp 202-204°C; IR ($CHCl_3$) 3750, 2940, 1640, 1620, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.58 (m, 2H), 2.54 (m, 3H), 2.92 (m, 2H), 3.86 (s, 3H), 3.99 (d, 2H, J = 6), 6.24 (s, 1H), 6.28 (d, 1H, J = 6), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9 (d), 28.8 (t), 41.9 (t), 49.1 (t), 56.0 (q), 97.8 (d), 111, 128 (d), 133 (d), 147, 149 (s), 158 (s), 164 (s). Mass spectrum, m/z 321 (parent). HRMS calcd for $C_{16}H_{20}N_3O_2{}^{35}Cl$: 321.1244. Found: 321.1198. Anal. Calcd for $C_{16}H_{20}N_3O_2Cl \cdot 0.5\ H_2O$: C, 58.08; H, 6.39; N, 12.70. Found C, 58.33; H, 6.19; N, 12.68. Crystals for x-ray analysis were obtained by slow evaporation (room temperature) from ethyl acetate/$CHCl_3$.

2-Methylene-3-methylsulfonyloxy-1-azabicyclo[2.2.2] octane (10). Under a nitrogen atmosphere, in a round-bottom flask were placed 1.0 g (7.2 mmol) of the alcohol **9** and 10 mL of THF. To the system (cooled in an ice/acetone bath) was added 1.95 mL (14.0 mmol) of triethylamine followed by 0.61 g (5.3 mmol) of methanesulfonyl chloride over a period of *ca.* 5 min. The mixture was gradually warmed to room temperature and stirred overnight. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$, the layers were separated and the aqueous phase was extracted with three portions of $CHCl_3$. The combined $CHCl_3$ fractions were dried (Na_2SO_4), filtered and concentrated (rotary evaporator). The crude material was purified by flash column chromatography (60 g of silica gel) using 7:93 MeOH/$CHCl_3$ as the eluant to obtain 0.90 g (58% yield) of the mesylate **10**: ^1H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.68 (m, 1H), 1.84 (m, 1H), 2.28 (m, 1H), 2.76 (m, 1H), 2.94 (m, 3H), 3.04 (s, 3H), 5.08 (d, 1H, J = 5), 5.14 (s, 1H), 5.24 (d, 1H, J = 5); ^{13}C NMR ($CDCl_3$) δ 18.3 (t), 24.1 (t), 29.4 (d), 38.9 (q), 48.2 (t), 48.6 (t), 78.4 (d), 113 (t), 152 (s).

Mixture of 3-Azido-2-methylene-1-azabicyclo[2.2.2]octane (11) and 2-Azidomethyl-1-azabicyclo [2.2.2] oct-2-ene (12). Under a nitrogen atmosphere were placed 5.3 g (24 mmol) of the mesylate **10** and 65 mL of CH_3CN. To the system was added 13.7 g (48 mmol) of tetra-*n*-butylammonium azide, and the reaction mixture was stirred at 55°C for 90 min and at room

temperature overnight. The reaction mixture was partitioned between saturated $NaHCO_3$ and $CHCl_3$, the layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined $CHCl_3$ fractions were dried (Na_2SO_4), filtered and concentrated with a rotary evaporator. The crude material was purified by flash column chromatography (560 g of silica gel) using 1:9 MeOH/$CHCl_3$ as the eluant to obtain 5.5 g of colorless oil. This material was dissolved in $CHCl_3$ and extracted with dilute aqueous HCl. The aqueous extract was adjusted to a pH of *ca.* 7.5 and extracted with three portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered and concentrated to afford 3.46 g of a mixture (*ca.* 2:1) of the azides **11** and **12**, respectively. The spectral properties of **12** are described above. Key peaks in the ^1H NMR spectrum of **11** that may be discerned from the spectrum of the mixture: ($CDCl_3$), δ 4.10 (m, 1H), 4.96 (s, 1H), 5.26 (s, 1H).

3-Amino-2-methylene-1-azabicyclo[2.2.2]octane (13). Under a nitrogen atmosphere, in a round-bottom flask were placed 50 mg (0.36 mmol) of a mixture of the amines **5** and **13** (prepared by $LiAlH_4$ reduction of the corresponding mixture of azides **11** and **12**, using a procedure analogous to that described for the reduction of the isomerically pure azide **12**), 80 mg (0.36 mmol) of di-*tert*-butyldicarbonate and 0.5 mL of CH_2Cl_2, and the reaction mixture was stirred at room temperature for three days. The mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated with a rotary evaporator. The crude material was subjected to flash column chromatography (15 g of silica gel) to obtain 46 mg of the *t*-butoxycarbonyl (BOC) derivative of **13** and 13 mg of the *t*-butoxycarbonyl derivative of **5**. BOC-**13**: ^1H NMR ($CDCl_3$) δ 1.44 (m, 10H), 1 6 (m, 2H), 2.16 (m, 1H), 2.52 (m, 3H), 2.92 (m, 2H), 3.70 (m, 2H), 6.28 (d, 1H, J = 7). Mass spectrum, m/z 248 (parent). BOC-**5**: ^1H NMR ($CDCl_3$) δ 1.44 (m, 10H), 1.6 (m, 2H), 2.16 (m, 1H), 2.52 (m, 3H), 2.92 (m, 2H), 3.70 (m, 2H), 6.28 (d, 1H, J = 7). Mass spectrum, m/z 248 (parent).

Under a nitrogen atmosphere, in a round-bottom flask were placed 29 mg (0.12 mmol) of BOC-**13** and 0.8 mL of dioxane saturated with HCl The mixture was stirred at room temperature for 90 min and concentrated with a rotary evaporator to obtain 34 mg of the hydrochloride salt of **13** as a white solid: IR (KBr) 2860, 2000, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.92 (m, 3H), 2.10 (m, 1H), 2.44 (m, 1H), 3.24 (m, 1H), 3.46 (m, 3H), 4.30 (m, 1H), 5.93 (s, 1H), 6.03 (s, 1H). Mass spectrum, m/z 238 (parent). HRMS calcd for $C_8H_{14}N_2O_2$: 138.1154. Found: 138.1146.

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REFERENCES

1 Peroutka, S. J *Ann. Rev. Neurosci.* **1988**, *11*, 45 and references therein.

2 Gaddum, J. H.; Picarelli, Z. P. *Br. J. Pharmacol. Chemother.* **1957**, *12*, 323.

3. Kilpatrick, G. J ; Jones, B. J.; Tyers, M B. *Nature* **1987**, *330*, 746.

4. Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C.C.; Tyers, M. B. *Br. J. Pharmacol.* **1988**, *94*, 397.
5. Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* **1985**, *316*, 126.
6. (a) Cunningham, D.; Pople, A.; Ford, H. T.; Hawthorn, J.; Gazet, J. C.; Challoner, T. *Lancet*, **1987**, *i*, 1461; (b) Cubeddu, L. X.; Hoffmann, I.S.; Fuenmayor, N. T.; Finn, A. L. *N. Engl. J. Med.* **1990**, *322*, 810; (c) Marty, M.; Pouillart, P.; Scholl, S.; Droz, J. P.; Azab, M.; Brion, N.; Pujade-Lauraine, E.; Paule, B.; Paes, D.; Bons, J. *ibid.* **1990**, *322*, 816.
7. Higgins, G. A.; Kilpatrick, G. J.; Bunce, K. T.; Jones, B. J.; Tyers, M. B. *Br. J. Pharmacol.* **1989**, *97*, 247 and references therein.
8. For a review of this area, see Tricklebank, M.D. TiPS **1989**, *10*, 127.
9. Barnes, J. M.; Barnes, N. M.; Costall, B.; Naylor, R. J.; Tyers, M. B. *Nature* **1989**, *338*, 762.
10. Smith, W. W.; Sancilio, L. F.; Owera-Atepo, J. B.; Naylor, R. J.; Lambert, L. *J. Pharm. Pharmacol.* **1988**, *40*, 301.
11. Hansen, A. R.; Bader, H. *J. Het. Chem.* **1966**, *3*, 109.
12. Murakami, M.; Inukai, N.; Koda, A.; Nakano, K. *Chem. Pharm. Bull.* **1971**, *19*, 1696 and references therein.
13. Receptor binding affinities (K_i values) were determined by displacement of [^{3}H]-**2** binding to NG-108-15 cells; (a) Hoyer, D., Neijt, H. C. *Eur. J. Pharmacol.* **1987**, *143*, 291; (b) Neijt, H. C.; Karpf, A.; Schoeffter, P.; Engel, G.; Hoyer, D. *Arch. Pharmacol.* **1988**, *337*, 493.
14. Gagneux, A.; Winstein, S.; Young, W. G. *J. Amer. Chem. Soc.* **1960**, *82*, 5956.
15. For examples, see (a) Murahashi, S. I.; Taniguichi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292; (b) Guthrie, R. D ; Irvine, R. W. *Carbohydrate Res.* **1980**, *82*, 207 and references therein.
16. For examples, see (a) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005; (b) Murahashi, S. I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227.
17. Morgan, T. K., Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem* **1987**, *30*, 2259.
18. Experimental details containing positional thermal parameters of atoms, bond lengths, bond angles and torsion angles for compounds **4** and **16** are available from the authors.