2-Amino-2-oxazolines as Subtype Selective α_2 Adrenoceptor Agonists

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Cyclohexylamino oxazoline **1** (AGN 190837), an analogue of **2** (Bay a6781), is a potent α_2 adrenoceptor agonist. On the basis of a design generated by receptor−ligand modeling, a number of cyclohexyl and norbornyl analogues were synthesized wherein the propyl group of **1** was replaced by phenylalkyl subsituents. This resulted in compound **6** being an α_{2c} selective agonist, as well as **7** and **9** being α_{2a}/α_{2c} selective.

Introduction

The α adrenoceptors are members of the diverse family of G-protein coupled receptors which are cell membrane proteins consisting of seven putative transmembrane helices.[1] These receptors have long been targets for drug development because of their importance in controlling many physiological functions both peripherally and centrally.[2] Medetomidine,[3] brimonidine (UK 14,304),[4] and clonidine[5] are examples of α_2 adrenoceptor agonists which have been developed as antihypertensive, antiglaucoma, analgesic, and veterinary anesthetic agents. Recent studies in animals with deletions or overexpression of the genes encoding the different α_2 adrenoceptor subtypes suggest that each of these subtypes mediates discrete physiological functions.[6] In addition, these studies have highlighted the potential for the development of subtype selective therapeutic agents with improved efficacy and/or reduced side effects when compared to existing drugs.

We are interested in designing novel α_2 agonists which are selective for each of the three α_2 adrenoceptor subtypes.[7] These compounds are expected to serve as useful pharmacological tools to delineate the physiological roles of each α_2 subtype. Moreover, an α_2 subtype selective agonist may be useful for the treatment of such conditions as pain, hypertension, and glaucoma with potentially fewer side effects.[6b] Cyclohexylamino oxazoline **1** (AGN 190837),[8] an analogue of **2** (Bay a6781),[9] was used as our design lead because it is a potent α_2 agonist and its alkyl side chain appears to be important for receptor activation (Figure 1). By modeling the molecular interaction of **1** with the human α_{2c} receptor (Figure 2), we have designed and synthesized two new series of compounds which showed interesting binding and functional activities at the cloned human α_2 adrenoceptors.[10] Herein we report our results.

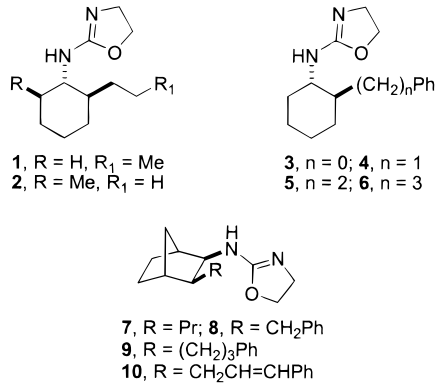

Figure 1. Cyclohexylamino and norbornylamino oxazolines.

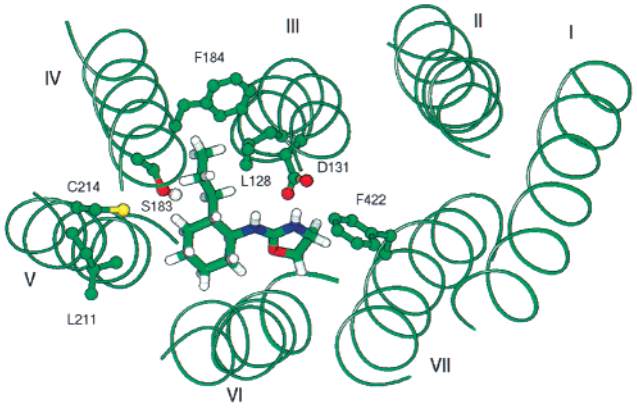

Figure 2. Model of molecular interaction between **1** and the human α_{2c} receptor (extracellular view showing the seven transmembrane helices I−VII arranged in a counterclockwise manner with the side chains of the relevant amino acid residues highlighted).

Model Construction

The three-dimensional model of the human α_{2c} receptor used in this study was built using a homology modeling procedure similar to that of Hibert,[11] with bacteriorhodopsin as the template. Energy minimization and constrained molecular dynamics were used for the refinement of the receptor model. On the other hand, the 3D structure of ligand **1** was built and optimized using the Insight II/Discover program (Biosym Technologies, San Diego). It was docked into the α_{2c} receptor model using the following computational process: af-

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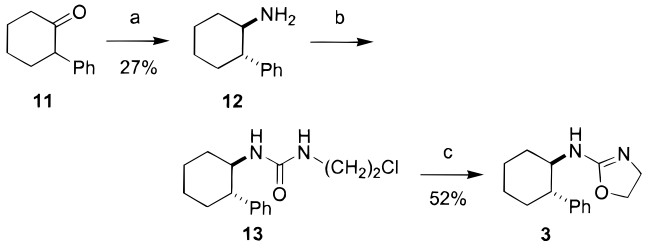
Scheme 1. Synthesis of Oxazoline **3**[a]



[a] Reagents: (a) NH_4OAc, $NaCNBH_3$; (b) $Cl(CH_2)_2NCO$; (c) boiling H_2O, or CH_3CN, KF/alumina.

finity grid maps, generated by the method of Goodford,[12] were used to define the targeted binding site and to calculate binding energies; the exploration of the position and orientation of the ligand was carried out using Monte Carlo simulated annealing.[13]

Molecular Design

It is generally accepted that the carboxylate anion of the Asp residue on the transmembrane helix III of α_2 receptors forms a salt bridge with the protonated nitrogen of a substrate such as oxazoline **1**.[14] However, while catecholamines (e.g., norepinephrine) activate the receptors by hydrogen bonding between the aromatic hydroxyl groups and the Ser and/or Cys residues on transmembrane helix V, **1** lacks a hydroxyl group and therefore is likely to activate the receptors by some other mechanism. By docking **1** in a computer-generated model of the human α_{2c} receptor (Figure 2), we found that the propyl side chain of **1** orients itself between transmembrane helices III and IV. It has previously been reported that *p*-azidoclonidine, when photoactivated, labeled the fourth transmembrane helix of the α_{2c} receptor.[15] Therefore, we hypothesized that the propyl side chain of **1** may be involved in the activation of the receptors. By aligning the amino acid sequences of the three human α_2 receptor subtypes, we observed that both helices III and IV are conserved in the area of the binding pocket. However, while the α_{2a} and α_{2c} subtypes have a Phe on transmembrane helix IV, the α_{2b} subtype has a Leu at the corresponding location. As such, modifying the side chain of **1** so that it selectively interacts with the Phe of α_{2a} and α_{2c} but not with the Leu of α_{2b} might yield subtype selective ligands. Hence, our plan was to prepare compounds **3**−**6** (Figure 1) wherein the phenyl group is gradually extended out in an attempt to reach the Phe on helix IV. In addition, we also prepared norbornyl analogues **7**−**10** (Figure 1) to determine if the six-membered ring conformation would affect affinity and potency.

Synthesis

The synthesis of compound **3** is outlined in Scheme 1. Reductive amination of 2-phenylcyclohexanone (**11**) gave, after chromatographic purification, *trans*-amine intermediate **12** which was then converted to urea **13**. Subsequent cyclization in either boiling water or acetonitrile containing KF/alumina[7a] afforded **3**.

The amine precursors to **4**−**6** were prepared according to Scheme 2. Treatment of cyclohexene oxide (**14**) with Grignard reagents[17] gave *trans*-alcohol **15**. Tosylation of **15** led to *cis*-tosylate **16** which was then converted to azide **17** with overall retention of configuration. Subsequent hydrogenation afforded *trans*-amine **18** which was cyclized to the final products according to the method depicted in Scheme 1.

The synthesis of the amine precursors to norbornyl **7**−**10** is depicted in Scheme 3 whereby norcamphor (**19**) was alkylated with the appropriate halides, and the resulting *exo*-ketone **20** was then reduced with lithium aluminum hydride to give a mixture of two isomeric alcohols from which *trans*-alcohol **21** could be isolated after flash chromatography. Conversion to azide **22** was accomplished with inversion of configuration by using diphenylphosphoryl azide. Subsequent transformation to the final products followed the above-mentioned processes.

Table 1. Binding and Functional Activities at Cloned Human α_2 Adrenoceptors[a]

	α_{2a}		α_{2b}		α_{2c}	
compd	pK_i	pEC_{50} (IA)	pKi	pEC_{50} (IA)	pKi	pEC_{50} (IA)
1	8.53	8.79 (1.0)	8.23	8.03 (1.0)	7.61	8.39 (1.0)
3	7.74	NA	7.65	NA	7.28	NA
4	7.68	NA	7.39	NA	7.18	NA
5	8.84	NA	8.16	NA	7.97	NA
6	7.82	NA	7.49	NA	7.49	7.57 (0.9)

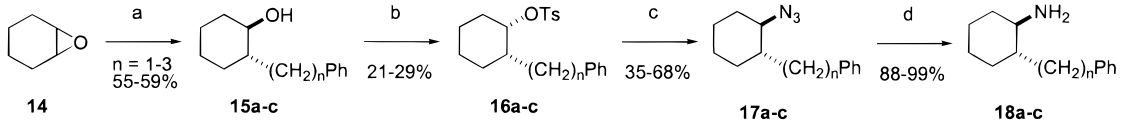
[a] SEM's are typically within ±3% of the mean pK_i or pEC_{50} values.

Results and Discussion

Equilibrium competition binding assays using [^{3}H]-rauwolscine were preformed with membrane preparations from cultured LM(tk$^-$) cells stably transfected with cloned human α_2 adrenoceptor subtypes, except for α_{2b} which was expressed in Y-1 cells.[18] Estimates of equilibrium inhibition constants (expressed as pK_i) were determined by nonlinear regression analysis. The agonist potency (expressed as pEC_{50}) was measured as a function of the ability to inhibit forskolin-stimulated synthesis of cyclic adenosine monophosphate (cAMP).[19] Intrinsic activity (IA) is the fraction of maximum inhibition produced by each test compound relative to norepinephrine (IA = 1.0). The tables summarize the binding and functional activities of the test compounds (NA = not active; a compound is considered not active when IA < 0.3). None of the compounds were evaluated for antagonist activity.

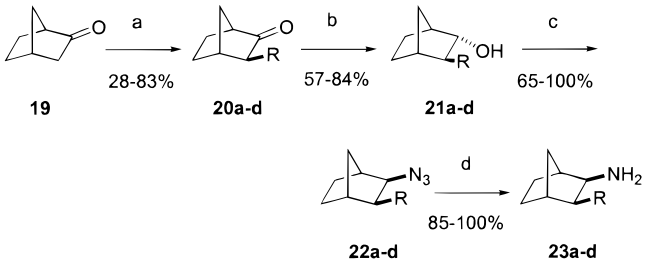
Compound **1** (AGN 190837) clearly binds with high affinity and activates all three α_2 adrenoceptors (Table 1). In contrast, **3** and **4** bind to the receptors but do not seem to activate them. Interestingly, compound **5** with a longer ethyl chain has gained some affinity but still

Scheme 2. Synthesis of Cyclohexylamines[a]



[a] Reagents: (a) $Ph(CH_2)_nMgX$; (b) $Zn(OTs)_2$, PPh_3, DEAD; (c) NaN_3, DMF; (d) H_2 or PMe_3/H_2O.

Scheme 3. Synthesis of Norbornylamines[a]



[a] Reagents: (a) $LiN(SiMe_3)_2$, RX; (b) $LiAlH_4$; (c) $(PhO)_2PON_3$, PPh_3, DEAD; (d) H_2 or PMe_3/H_2O.

Table 2. [a]Binding and Functional Activities at Cloned Human α_2 Adrenoceptors

	α_{2a}		α_{2b}		α_{2c}	
compd	p*Ki*	pEC_{50} (IA)	p*Ki*	pEC_{50} (IA)	p*Ki*	pEC_{50} (IA)
7	7.55	7.96 (0.9)	7.04	6.25 (0.4)	6.91	7.67 (0.9)
8	7.86	NA	7.39	NA	7.10	7.86 (0.5)
9	7.51	7.46 (0.98)	6.85	NA	6.91	7.22 (0.92)
10	7.80	7.15 (0.5)	6.99	NA	7.07	8.70 (0.45)

[a] SEM's are typically within ±3% of the mean pK_i or pEC_{50} values.

does not activate the receptors. However, compound **6** with a phenylpropyl side chain selectively activates only the α_{2c} receptor with an IA close to 1. This appears to support our hypothesis that the benzene ring on **6** is able to reach and selectively interacts with the Phe moiety on helix IV of the α_{2c} receptor but not the corresponding Leu of α_{2b}. Meanwhile, it is possible that the α_{2a} receptor is not activated because its binding pocket has a conformation different from that of α_{2c} such that compound **6** does not bind to the two receptors in the same manner.

Data for norbornyl analogue **7** (Table 2) show that although addition of the methylene bridge lowers affinity, it actually improves selectivity relative to **1** because **7** activates only the α_{2a} and α_{2c} receptors and is at best a partial agonist at α_{2b}. At this point, we cannot rationalize how compound **7** activates the receptors, but it is likely that **1** and **7** do not bind to the receptors identically so that the methylene bridge of **7** led to a binding conformation which resulted in selective activation of only two subtypes.

Benzyl derivative **8** resembles compound **4** in both affinity and lack of the ability to activate the receptors although it may be a partial agonist at α_{2c}. However, compound **9**, like compound **7**, selectively activates only the α_{2a} and α_{2c} receptors. This may mean that the methylene bridge of **9** allows the molecule to bind in such a way that it can interact with the Phe residue of both α_{2a} and α_{2c} equally well, in contrast to compound **6** which activates only α_{2c}. Restraining the side chain of **9** with a double bond as in **10** reduces the ability of the ligand to activate the receptors although affinity is not significantly affected.

Summary

Therefore, given these data, it is conceivable that the Phe on transmembrane helix IV interacts with the aromatic rings on **6** and **9** resulting in selective activation of the α_{2a} and/or α_{2c} receptors. However, the Phe is probably only one of two or more elements by which the receptors are activated because compound **7**, without an aromatic ring, also shows functional selectivity. Further experiments, including the use of mutagenesis and/or docking of **1** in molecular models of the α_{2a} and α_{2b} receptors, are necessary to provide better understanding of the role Phe plays in the activation of the α_2 receptors. Moreover, these new selective ligands may be useful for helping elucidate the functions of the α_2 receptor subtypes.

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp apparatus in open capillary tubes. ^{1}H NMR spectra were recorded on a GE QE Plus 300 MHz spectrometer with $CDCl_3$ as internal standard unless otherwise noted. Mass spectra were obtained by Oneida Research Services, Inc. Elemental analyses were performed at Robertson Microlit Laboratories, Inc.

***trans*-2-(2-Phenylcyclohexyl)amino-2-oxazoline (3).** A mixture of *trans*-2-phenylcyclohexylamine (**12**, 0.1 g, 0.57 mmol) and 2-chloroethyl isocyanate (0.06 mL, 0.68 mmol) in THF (5 mL) was stirred at room temperature overnight. After removal of the solvent, water (10 mL) was added, and the solution was refluxed for 4 h. It was cooled to room temperature and basified to pH 8 with saturated $NaHCO_3$ solution. The aqueous solution was extracted with ethyl acetate to give the crude product (0.12 g). Flash chromatography over silica gel (10:2:1 ethyl acetate−methanol−triethylamine) afforded pure product (0.072 g, 52% yield): ^{1}H NMR (CD_3OD) δ 1.22−1.51 (6H, m), 1.70−1.81 (3H, m), 2.08 (1H, m), 2.42 (1H, dt, J = 11.2, 3.5 Hz), 3.34−3.53 (3H, m), 3.96 (1H, t), 7.05−7.19 (5H, m). The oxazoline in ethanol was treated with 1 equiv of fumaric acid to give a fumarate salt as white crystals (56% yield): mp 130−131.5 °C; ^{1}H NMR (CD_3OD) δ 1.37−1.48 (3H, m), 1.61 (1H, m), 1.65−1.90 (3H, m), 2.04−2.08 (1H, m), 2.49 (1H, m), 3.47−3.57 (3H, m), 4.48 (2H, m), 6.63 (2H, s), 7.17−7.29 (5H, m). Anal. ($C_{15}H_{20}N_2O\cdot C_4H_4O_4$) C, H, N.

***trans*-2-(2-Benzylcyclohexyl)amino-2-oxazoline (4).** A mixture of *trans*-2-benzylcyclohexylamine (0.19 g, 1.0 mmol) and 2-chloroethyl isocyanate (1.1 mL, 10 mmol) in THF (15 mL) was stirred at room temperature overnight. After removal of the solvent, the residue was purified via flash chromatography over silica gel (4:1 ethyl acetate−hexane) to give the desired intermediate (0.278 g, 94% yield). It was treated with KF (0.55 g, 40% on alumina) in acetonitrile (10 mL) and heated at reflux overnight. After removal of the solvent, the residue was purified via flash chromatography over silica gel (5:1 ethyl acetate−2M methanolic ammonia) to give the title compound (0.108 g, 45% yield) as a white solid. It was treated in ethanol with 1 equiv of fumaric acid to give a fumarate salt as white crystals: mp 152−153 °C; ^{1}H NMR (CD_3OD) δ 1.00−1.40 (4H, m), 1.59−1.74 (4H, m), 1.92 (1H, m), 2.30 (1H, dd, J = 13.5, 8.9 Hz), 2.88 (1H, dd, J = 13.4, 2.7 Hz), 3.10 (1H, m), 3.83 (2H, m), 4.73 (2H, m), 6.64 (2H, s), 7.08−7.25 (5H, m). Anal. ($C_{16}H_{22}N_2O\cdot C_4H_4O_4\cdot{}^1/_4C_2H_6O$) C, H, N.

Similarly prepared were the following compounds:

***trans*-2-(2-(2-Phenylethyl)cyclohexyl)amino-2-oxazoline (5).** Fumarate salt (white crystals): mp 160−162 °C; ^{1}H NMR (CD_3OD) δ 1.03−1.40 (6H, m), 1.67−2.05 (6H, m), 2.48 (1H, m), 2.68 (1H, m), 3.08 (1H, m), 3.78 (2H, t, J = 9.0 Hz), 4.63 (2H, t, J = 8.2 Hz), 6.62 (1H, s), 7.07−7.22 (5H, m). Anal. ($C_{17}H_{24}N_2O\cdot{}^1/_2C_4H_4O_4$) C, H, N.

***trans*-2-(2-(3-Phenylprop-1-yl)cyclohexyl)amino-2-oxazoline (6).** Fumarate salt (white crystals): mp 98−99 °C; ^{1}H NMR (CD_3OD) δ 1.24−1.48 (7H, m), 1.65 (2H, m), 1.88 (3H, m), 1.91 (2H, m), 2.53 (2H, m), 3.81 (2H, t, J = 4.4 Hz), 4.69 (2H, t, J = 4.9 Hz), 6.64 (2H, s), 7.11−7.23 (5H, m). Anal. ($C_{18}H_{26}N_2O\cdot C_4H_4O_4\cdot{}^1/_4H_2O$) C, H, N.

2-(3-*exo*-Propyl-2-*exo*-norbornyl)amino-2-oxazoline (7). Amine **23a** (200 mg, 1.30 mmol) was dissolved in dry THF (5 mL), cooled by an ice water bath, and treated with 2-chloro-

ethyl isocyanate (170 μL, 1.99 mmol). The solution was stirred at room temperature for 3 days before it was concentrated to give a white solid. It was treated with 40% KF on alumina (755 mg, 5.20 mmol) in acetonitrile (5 mL) and heated at reflux overnight. Filtration of the reaction mixture through Celite followed by concentration of the filtrate gave a white solid which was dissolved in chloroform and purified via flash chromatography over silica gel (17 g) eluting with EtOAc/hexane (1:1) and EtOAc/hexane/triethylamine (15:15:1) to afford a white solid (135 mg, 47% yield). An analytical sample was obtained by recrystallization from EtOAc: mp 123−125 °C; ^{1}H NMR δ 0.86 (3H, t, J = 7.1 Hz), 0.90−1.55 (10H, m), 1.65 (1H, m), 2.00 (1H, m), 2.13 (1H, m), 3.58 (1H, d, J = 7.7 Hz), 3.76 (2H, t, J = 8.3 Hz), 4.28 (2H, t, J = 8.3 Hz); CIMS m/e = 223 (MH^+). Anal. ($C_{13}H_{22}N_2O$) C, H, N.

Similarly prepared were the following compounds:

2-(3-*exo*-Benzyl-2-*exo*-norbornyl)amino-2-oxazoline (8). Fumarate salt (white crystals): mp 127−130 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (3H, m), 1.38 (2H, m), 1.82 (2H, m), 2.06 (2H, m), 2.44 (2H, m), 3.52 (3H, m), 4.21 (1H, m), 4.39 (1H, m), 6.46 (2H, s), 7.09 (3H, m), 7.21 (2H, m); CIMS m/e = 271 (MH^+). Anal. ($C_{17}H_{22}N_2O{\cdot}C_4H_4O_4$) C, H, N.

2-(3-*exo*-(3-Phenylprop-1-yl)-2-*exo*-norbornyl)amino-2-oxazoline (9). Fumarate salt (white crystals): mp 134−136 °C; ^{1}H NMR (DMSO-d_6) δ 0.90−1.20 (5H, m), 1.40 (3H, m), 1.57 (3H, m), 1.94 (1H, m), 2.00 (1H, m), 2.46 (3H, m), 3.50 (1H, d, J = 8.0 Hz), 3.63 (2H, t, J = 8.3 Hz), 4.45 (2H, m), 6.44 (2H, s), 7.09 (3H, m), 7.20 (2H, m); CIMS m/e = 299 (MH^+). Anal. ($C_{19}H_{26}N_2O{\cdot}C_4H_4O_4$) C, H, N.

***trans*-2-(3-*exo*-(3-Phenyl-2-propen-1-yl)-2-*exo*-norbornyl)amino-2-oxazoline (10).** Fumarate salt (white crystals): mp 150−155 °C; ^{1}H NMR (DMSO-d_6) δ 1.00 (1H, m), 1.10 (2H, m), 1.40 (2H, m), 1.70 (1H, m), 1.82 (1H, m), 2.03 (4H, m), 3.43 (1H, m), 3.55 (2H, m), 4.30 (1H, m), 4.40 (1H, m), 6.17 (1H, m), 6.28 (1H, d, J = 16.0 Hz), 6.46 (2H, s), 7.10−7.33 (5H, m); CIMS m/e = 297 (MH^+). Anal. ($C_{19}H_{24}N_2O{\cdot}C_4H_4O_4$) C, H, N.

***trans*-2-Phenylcyclohexylamine (12).**[16] To a mixture of 2-phenylcyclohexanone (0.87 g, 5 mmol) and ammonium acetate (3.85 g, 50 mmol) dissolved in methanol (20 mL) under argon was added sodium cyanoborohydrate (0.22 g, 3.5 mmol). The solution was stirred at room temperature overnight and acidified to pH 1 with concentrated HCl. After removal of most of the solvent, water (30 mL) was added and the solution was basified to pH 9 with 6 N NaOH solution. The mixture was extracted with chloroform, and the dried (sodium sulfate) extract was concentrated in vacuo. The residue was purified via flash chromatography over silica gel (4:1 ethyl acetate−hexane) to give the desired product (0.235 g, 27% yield) as a white solid: ^{1}H NMR δ 0.96 (2H, s), 1.23−1.45 (4H, m), 1.69−1.78 (3H, m), 1.89−1.94 (1H, m), 2.16 (1H, dt, J = 11.1, 3.4 Hz), 2.76 (1H, dt, J = 12.3, 3.8 Hz), 7.11−7.26 (5H, m).

***trans*-2-Benzylcyclohexanol (15a).**[20] To a solution of cyclohexene oxide (5 g, 50.9 mmol) in THF (20 mL) being cooled at −78 °C was added benzylmagnesium chloride in THF (2.0 M, 38 mL) under an argon atmosphere. After being stirred for about 4 h, the mixture was slowly warmed to room temperature and allowed to stir overnight. After removal of half of the solvent, water (40 mL) was added. The solution was adjusted to pH 7 with 3 N HCl solution and extracted with ethyl acetate. The dried (sodium sulfate) extract was evaporated in vacuo to give the crude product as a white solid (10.86 g): mp 74−75 °C (lit.[20a] mp 77 °C); ^{1}H NMR δ 0.85−0.90 (1H, m), 1.19 (1H, m), 1.23 (2H, m), 1.26−1.71 (5H, m), 1.95 (1H, m), 2.32 (1H, dd, J = 13.3, 9.2 Hz), 3.14 (1H, dd, J = 13.3, 4.0 Hz), 3.26 (1H, dt, J = 9.6, 4.5 Hz), 7.14−7.35 (5H, m).

Similarly prepared were the following compounds:

***trans*-2-(2-Phenylethyl)cyclohexanol (15b).** Yellow liquid (55% yield): ^{1}H NMR δ 0.96−1.43 (6H, m), 1.65−1.76 (2H, m), 1.92−1.97 (2H, m), 2.05−2.14 (2H, m), 2.54−2.60 (1H, m), 2.75 (1H, dt, J = 11.0, 2.5 Hz), 3.20 (1H, dt, J = 9.5, 4.2 Hz), 7.16−7.32 (5H, m).

***trans*-2-(3-Phenylprop-1-yl)cyclohexanol (15c).** Colorless liquid (59% yield): ^{1}H NMR δ 0.80−0.95 (1H, m), 1.09−1.26 (5H, m), 1.41 (1H, d, J = 4.4 Hz), 1.53−1.93 (7H, m), 2.54−2.63 (2H, m), 3.18 (1H, m), 7.14−7.29 (5H, m).

***cis*-2-Benzyl-1-tosyloxy-cyclohexane (16a).** A portion of **15a** (1.9 g, 10 mmol) was treated with triphenylphosphine (13.1 g, 50 mmol) and zinc tosylate (2.4 g, 6 mmol) in benzene (40 mL). To the mixture was added dropwise diethyl azodicarboxylate (3 mL, 50 mmol). The resulting clear solution was stirred at room temperature overnight. After removal of some solid by filtration, the benzene was evaporated in vacuo. The residue was purified via flash chromatography over silica gel (4:1 hexanes−ethyl acetate) to give the desired product (1.02 g, 30% yield): ^{1}H NMR δ 1.23−1.71 (8H, m), 1.95 (1H, m), 2.36 (1H, m), 2.41 (3H, s), 2.53 (1H, dd, J = 13.7, 5.5 Hz), 4.76 (1H, m), 7.04 (1H, d, J = 8.3 Hz), 7.14−7.32 (3H, m), 7.80 (1H, d, J = 8.3 Hz).

Similarly prepared were the following compounds:

***cis*-2-(2-Phenylethyl)-1-tosyloxy-cyclohexane (16b).** White solid (21% yield): ^{1}H NMR δ 1.24−1.65 (9H, m), 1.9−2.0 (2H, m), 2.37 (3H, s), 2.48 (2H, t, J = 7.6 Hz), 4.78 (1H, m), 7.04−7.26 (4H, m), 7.79 (1H, d, J = 8.3 Hz).

***cis*-2-(3-Phenylprop-1-yl)-1-tosyloxy-cyclohexane (16c).** White solid (29% yield): ^{1}H NMR δ 1.15−1.65 (14H, m), 1.95 (1H, m), 2.41 (3H, s), 2.44 (1H, m), 4.75 (1H, m), 7.06−7.35 (4H, m), 7.75 (1H, d, J = 8.3 Hz).

***trans*-1-Azido-2-benzylcyclohexane (17a).** Tosylate **16a** (1.15 g, 3.3 mmol) was treated with sodium azide (0.33 g, 5.1 mmol) in DMF (10 mL) and heated at 100 °C overnight. After removal of the solvent, the residue was purified via flash chromatography over silica gel (10:1 hexanes−ethyl acetate) to give the desired product as a colorless oil (0.488 g, 68% yield): ^{1}H NMR δ 0.88−1.79 (8H, m), 2.07 (1H, dd, J = 12.6, 2.9 Hz), 2.31 (1H, dd, J = 13.3, 9.4 Hz), 2.92 (1H, dt, J = 10.7, 6.5 Hz), 3.10 (1H, dd, J = 13.4, 3.3 Hz), 7.12−7.29 (5H, m).

Similarly prepared were the following compounds:

***trans*-1-Azido-2-(2-phenylethyl)cyclohexane (17b).** Colorless liquid (50% yield): ^{1}H NMR δ 0.95−1.43 (6H, m), 1.60−1.80 (2H, m), 1.92−2.07 (3H, m), 2.54 (1H, m), 2.70 (1H, m), 2.91 (1H, dt, J = 10.3, 3.9 Hz), 7.16−7.28 (5H, m).

***trans*-1-Azido-2-(3-phenylprop-1-yl)cyclohexane (17c).** Colorless liquid (35% yield): ^{1}H NMR δ 0.90−0.94 (1H, m), 1.13−1.39 (4H, m), 1.52−2.07 (8H, m), 2.54−2.64 (2H, m), 2.88 (1H, dt, J = 10.4, 4.0 Hz), 7.14−7.29 (5H, m).

***trans*-2-Benzyl-cyclohexylamine (18a).** Azide **17a** (0.488 g, 2.3 mmol) in methanol (50 mL) was subjected to hydrogenation with a hydrogen balloon in the presence of 10% palladium on carbon. The reaction was carried out at room temperature overnight. The catalyst was then filtered off, and the solvent was removed in vacuo. The product was obtained as a white solid (0.426 g, 99% yield): ^{1}H NMR δ 0.83 (1H, m), 1.00−1.22 (3H, m), 1.38−1.64 (4H, m), 1.89 (1H, m), 2.19 (1H, dd, J = 13.2, 10.0 Hz), 2.46 (1H, dt, J = 10.1, 3.9 Hz), 3.15 (1H, dd, J = 13.2, 3.5 Hz), 3.43 (2H, s), 7.10−7.23 (5H, m).

Similarly prepared were the following compounds:

***trans*-2-(2-Phenylethyl)cyclohexylamine (18b).** White solid (88% yield): ^{1}H NMR δ 0.9−1.4 (6H, m), 1.5−2.1 (6H, m), 2.3−2.8 (4H, m), 7.13−7.25 (5H, m); ESMS m/e = 204 (MH^+).

***trans*-2-(3-Phenylprop-1-yl)cyclohexylamine (18c).** Colorless liquid (95% yield): ^{1}H NMR δ 0.8−1.3 (5H, m), 1.5−2.0 (9H, m), 2.3 (1H, m), 2.5−2.7 (2H, m), 7.1−7.3 (5H, m); ESMS m/e = 218 (MH^+).

3-*exo*-Propyl-2-norbornanone (20a). Norcamphor (5.00 g, 45.4 mmol) was dissolved in dry THF (17 mL) and added dropwise to 1 M lithium bis(trimethylsilyl)amide in THF (50 mL, 50 mmol) being cooled by a dry ice-acetone bath. Then 1-iodopropane (4.5 mL, 46.1 mmol) was added dropwise. The solution was allowed to slowly warm to room temperature and stirred overnight. Ice water (20 mL) was added. Extraction with EtOAc (2 × 25 mL) gave a yellow oil (13.50 g). It was dissolved in chloroform and purified via flash chromatography over silica gel (390 g) eluting with EtOAc/hexane (1:20) to afford a colorless oil (5.18 g, 75% yield): ^{1}H NMR δ 0.88 (t, 3H), 1.10−1.90 (11H, m), 2.40 (1H, m), 2.50 (1H, m).

Similarly prepared were the following compounds:

3-*exo*-Benzyl-2-norbornanone (20b). Colorless oil (83% yield): ^{1}H NMR δ 1.30 (1H, m), 1.40−1.60 (2H, m), 1.75 (2H, m), 1.89 (1H, m), 2.01 (1H, dt, J = 11.6, 3.7 Hz), 2.38 (2H, m), 2.58 (1H, m), 2.96 (1H, dd, J = 14.0, 4.2 Hz), 7.14−7.30 (5H, m).

3-*exo*-(3-Phenylprop-1-yl)-2-norbornanone (20c). Colorless oil (28% yield): ^{1}H NMR δ 1.20−1.80 (11H, m), 2.38 (1H, m), 2.50 (1H, m), 2.58 (2H, m), 7.15 (3H, m), 7.23 (2H, m).

***trans*-3-*exo*-(3-Phenyl-2-propen-1-yl)-2-norbornanone (20d).** Yellow oil (41% yield): ^{1}H NMR δ 1.40−1.62 (3H, m), 1.78−1.89 (4H, m), 2.01−2.12 (1H, m), 2.46−2.56 (3H, m), 6.16 (1H, ddd, J = 15.8, 8.2, 6.0 Hz), 6.38 (1H, d, J = 15.9 Hz), 7.16−7.34 (5H, m).

3-*exo*-Propyl-2-*endo*-norbornanol (21a). Ketone **20a** (4.91 g, 32.3 mmol) was dissolved in dry THF (45 mL), cooled by an ice water bath, and treated with lithium aluminum hydride (1.10 g, 29.0 mmol). The mixture was stirred at room temperature for 4 h before sodium sulfate decahydrate (4.7 g, 14.6 mmol) was slowly added. Filtration of the mixture followed by concentration of the filtrate gave a colorless oil (2.69 g). The filtered solid was treated with MeOH to give more colorless oil (1.45 g). Each oil was dissolved in carbon tetrachloride and purified via flash chromatography over silica gel eluting with EtOAc/hexane (1:10) to afford a colorless oil (2.94 g, 59% yield): ^{1}H NMR δ 0.88 (3H, t), 0.93 (1H, m), 1.10−1.60 (10H, m), 1.75 (1H, m), 1.87 (1H, m), 2.20 (1H, m), 3.66 (1H, m).

Similarly prepared were the following compounds:

3-*exo*-Benzyl-2-*endo*-norbornanol (21b). White solid (64% yield): mp 71−73 °C; ^{1}H NMR δ 1.20−1.60 (7H, m), 1.78 (1H, m), 1.94 (1H, m), 2.24 (1H, m), 2.57 (2H, d), 3.78 (1H, m), 7.10−7.30 (5H, m).

3-*exo*-(3-Phenylprop-1-yl)-2-*endo*-norbornanol (21c). Colorless oil (84% yield): ^{1}H NMR δ 0.90−1.90 (12H, m), 2.20 (1H, m), 2.59 (2H, t, J = 7.7 Hz), 3.66 (1H, m), 3.72 (1H, m), 7.15 (3H, m), 7.23 (2H, m).

***trans*-3-*exo*-(3-Phenyl-2-propen-1-yl)-2-*endo*-norbornanol (21d).** Colorless oil (57% yield): ^{1}H NMR δ 1.12−1.60 (7H, m), 1.79 (1H, m), 1.97 (1H, m), 2.18 (2H, t, J = 7.4 Hz), 2.23 (1H, m), 3.76 (1H, m), 6.18 (1H, dt, J = 15.8, 7.0 Hz), 6.38 (1H, d, J = 15.7 Hz), 7.14−7.34 (5H, m).

2-*exo*-Azido-3-*exo*-propylnorbornane (22a). Alcohol **21a** (2.00 g, 13.0 mmol) was dissolved in dry THF (27 mL), cooled by an ice water bath, and treated with triphenylphosphine (3.77 g, 14.4 mmol), diethyl azodicarboxylate (2.2 mL, 14.0 mmol), and diphenylphosphoryl azide (3.1 mL, 14.4 mmol). The solution was stirred at room temperature overnight and then concentrated to give an orange oil. It was dissolved in dichloromethane and purified via flash chromatography over silica gel (160 g) eluting with EtOAc/hexane (1:50) to afford a colorless oil (2.22 g, 95% yield): ^{1}H NMR δ 0.88 (3H, t, J = 7.1 Hz), 1.00−1.60 (11H, m), 1.97 (1H, m), 2.29 (1H, m), 3.50 (1H, d, J = 7.5 Hz).

Similarly prepared were the following compounds:

2-*exo*-Azido-3-*exo*-benzylnorbornane (22b). Colorless oil (101% yield): ^{1}H NMR δ 1.00−1.20 (3H, m), 1.30−1.70 (3H, m), 1.96−2.01 (2H, m), 2.37 (2H, dd, J = 14.2, 10.3 Hz), 2.78 (1H, dd, J = 14.2, 5.6 Hz), 3.61 (1H, d, J = 7.2 Hz), 7.10−7.28 (5H, m); ESMS m/e = 200 ($MH^+ - N_2$).

2-*exo*-Azido-3-*exo*-(3-phenylprop-1-yl)norbornane (22c). Colorless oil (91% yield): ^{1}H NMR δ 1.00−1.25 (4H, m), 1.40−1.70 (7H, m), 1.97 (1H, m), 2.30 (1H, m), 2.59 (2H, m), 3.50 (1H, d, J = 7.3 Hz), 7.16 (3H, m), 7.25 (2H, m).

***trans*-2-*exo*-Azido-3-*exo*-(3-phenyl-2-propen-1-yl)-2-norbornane (22d).** Colorless oil (65% yield): ^{1}H NMR δ 1.16 (3H, m), 1.60 (3H, m), 1.80 (1H, m), 2.10 (2H, m), 2.40 (2H, m), 3.63 (1H, d, J = 7.6 Hz), 6.22 (1H, ddd, J = 15.8, 7.8, 6.0 Hz), 6.42 (1H, d, J = 15.8 Hz), 7.19−7.39 (5H, m).

2-*exo*-Amino-3-*exo*-propylnorbornane (23a). Azide **22a** (1.00 g, 5.58 mmol) was dissolved in EtOAc (10 mL), cooled by an ice water bath, and treated with 1 M trimethylphosphine in THF (10 mL, 10 mmol) and water (0.4 mL, 22.22 mmol). The solution was stirred at room temperature overnight and then concentrated. The residue was dissolved in chloroform and purified via flash chromatography over silica gel (70 g) eluting with EtOAc/MeOH/triethylamine (20:1:1) to afford a colorless oil (723 mg, 85% yield): ^{1}H NMR δ 0.88 (3H, t, J = 7.0 Hz), 0.90−1.55 (11H, m), 1.66 (2H, br), 1.94 (2H, m), 2.87 (1H, d, J = 7.8 Hz).

Similarly prepared were the following compounds:

2-*exo*-Amino-3-*exo*-benzylnorbornane (23b). White solid (96% yield): ^{1}H NMR (CD_3OD) δ 0.95−1.25 (3H, m), 1.39 (1H, m), 1.54 (1H, m), 1.74 (1H, m), 1.92 (1H, m), 2.00 (1H, m), 2.13 (1H, m), 2.30 (1H, m), 2.76 (1H, dd, J = 13.4, 4.5 Hz), 3.08 (1H, d, J = 7.8 Hz), 7.10−7.26 (5H, m).

2-*exo*-Amino-3-*exo*-(3-phenylprop-1-yl)norbornane (23c). Colorless oil (101% yield): ^{1}H NMR δ 0.95−2.00 (15H, m), 2.59 (2H, m), 2.89 (1H, d, J = 7.6 Hz), 7.15 (3H, m), 7.23 (2H, m).

2-*exo*-Amino-3-*exo*-(3-phenyl-2-propen-1-yl)norbornane (23d). Used without purification for the preparation of **10**.

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

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