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ENANTIOSELECTIVE SYNTHESIS OF DUAL 5-HT$_4$/5-HT$_3$ SEROTONERGIC AZANORADAMANTANE SC-52491

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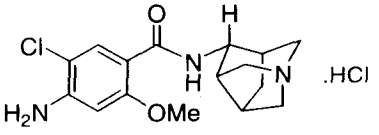
Abstract: A racemic synthesis of azanoradamantane (±)-**3** was accomplished *via* Yamamoto's MAD-catalyzed Diels-Alder protocol. Subsequently, a scalable asymmetric synthesis of azanoradamantane benzamide **SC-52491** was carried out employing Helmchen's asymmetric Diels-Alder methodology to construct all four contiguous asymmetric centers with the correct relative stereochemistry and in 99.3% e.e.

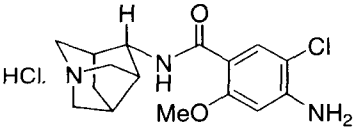
Keywords: asymmetric synthesis; Diels-Alder ; serotonin; 5-hydroxytryptamine; 5-HT; azanoradamantane

Pharmaceutical companies are advancing an increasing number of enantiomerically pure drugs[1] in order to maximize potency and selectivity, and to eliminate the complications which may arise from the presence of a less active or inactive stereoisomer. The asymmetric Diels-Alder[2] reaction is a powerful synthetic method for the construction of non-racemic pharmacologically active agents.

In earlier communications[3] we disclosed a series of azaadamantane and azanoradamantane benzamides, including the potent serotonin 5-HT$_4$ agonist/5-HT$_3$ antagonist **SC-52491**, which has an EC$_{50}$ of 51 nM in the 5-HT$_4$ tunica muscularis mucosae assay[4] and a K$_i$ of 1.2 nM at the 5-HT$_3$ receptor.[5] **SC-52491** was chosen for further study of its gastrointestinal prokinetic activity and its antiemetic activity based on its potent 5-HT$_4$ agonism and its tandem property of potent 5-HT$_3$ antagonism, respectively, combined with its exceptional selectivity *versus* other monoamine receptors.[6] It is orally active and exhibits potent prokinetic activity and antiemetic activity *in vivo*, and compares very favorably with the marketed prokinetic cisapride. **SC-52491** is the more active enantiomer with respect to both 5-HT$_4$ and 5-HT$_3$ activity, as it is 70X as potent as **SC-52490** in the functional 5-HT$_4$ assay, and it is 3X as potent in its binding to the 5-HT$_3$ receptor.



SC-52491



SC-52490

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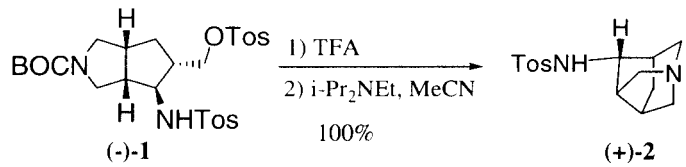
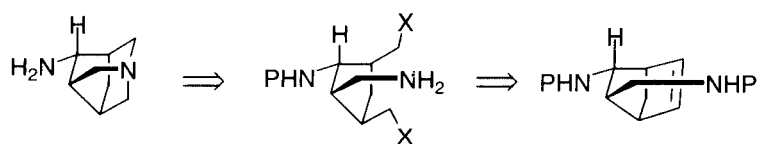
We required a scalable asymmetric synthesis of **SC-52491**, which contains four contiguous asymmetric centers. Our previous[7] synthetic route (**Scheme 1**) employed a reductive Pauson-Khand reaction[8] which was ideal for small-scale synthesis, and a late-stage resolution which provided us with both enantiomers for biological evaluation, but these procedures are not easily scalable. The previous synthesis of **SC-52491** did employ a very efficient closure to the azanoradamantane ring system [(-)-**1** to (+)-**2**], and we hoped that we could utilize a similar cyclization in our new synthetic strategy. We also wanted to eliminate chlorinated solvents from the synthesis and to simplify or eliminate any chromatographic purifications.



(-)-**1** (+)-**2**

Scheme 1

We envisioned a new approach based on the retrosynthetic analysis shown in **Scheme 2**, wherein the azanoradamantane **3** would be formed in one step from a tetrasubstituted cyclopentane **4** *via* a tandem cyclization involving SN_2 displacement of suitable leaving groups (X) by the primary amine. One of the two cyclizations is the same as the efficient cyclization employed in our previous synthetic approach. The tetrasubstituted cyclopentane **4** would then be derived from oxidative cleavage of a rigid norbornene **5**, in which the four contiguous asymmetric centers could be easily defined and prepared *via* an asymmetric Diels-Alder reaction.

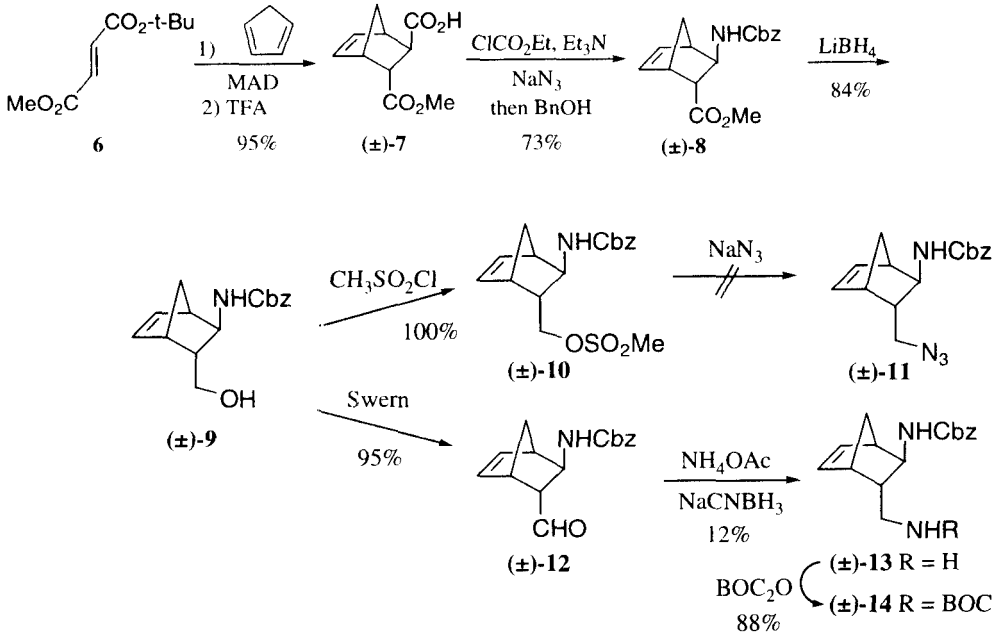


3 **4** **5**

Scheme 2

We first employed Yamamoto's MAD-catalyzed Diels-Alder reaction[9] to prepare norbornene (±)-**7** (**Scheme 3**). This approach assembles the four requisite stereocenters in their proper relative orientation, albeit in racemic fashion. We originally hoped to employ an early-stage resolution or to employ a chiral Lewis acid catalyst in the Diels-Alder reaction to obtain the correct absolute configuration of the four stereocenters. Ultimately the Yamamoto approach allowed us to explore various means of installing functionality to provide the bridgehead nitrogen and the amino substituent of aminoazanoradamantane **3**. As per Yamamoto's protocol, cyclopentadiene is reacted with *tert*-butyl methyl fumarate **6**[10] with MAD catalysis to afford the Diels-Alder

adduct (±)-**7** in high yield and excellent diastereoselectivity (98:2). The esters are easily differentiated by cleaving the *tert*-butyl ester with trifluoroacetic acid to afford carboxylic acid (±)-**7**. We proceeded from Yamamoto's intermediate (±)-**7** with a Curtius rearrangement to install the exo-amino substituent protected as the benzyl carbamate in compound (±)-**8**. Lithium borohydride reduction gave the endo hydroxymethyl derivative (±)-**9**.

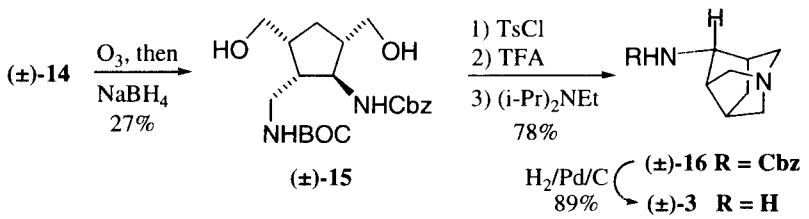


Scheme 3

The alcohol (±)-**9** was converted to the mesylate (±)-**10** in quantitative yield, but the mesylate was unexpectedly resistant toward displacement by azide. Treatment with sodium azide in a variety of solvents, with or without added sodium iodide present in the reaction mixture gave no desired product. Only starting material was observed until the temperature was raised sufficiently for consumption of starting material, at which point the norbornene bicyclic system was also destroyed, presumably *via* a retro-Diels-Alder reaction. To overcome this problem, alcohol (±)-**9** was oxidized to the aldehyde (±)-**12** in 95% yield with no evidence of epimerization. Reductive amination of the aldehyde with ammonium acetate gave the desired primary amine (±)-**13**, but in consistently low yields, along with significant quantities of secondary amine by-product. Attempts to optimize the reductive amination of aldehyde (±)-**12** were unsuccessful. The amine (±)-**13** was protected as the BOC derivative (±)-**14**. Despite the inefficient reductive amination, sufficient quantities of the

BOC-protected amine (±)-**14** were obtained to continue validation of the Diels-Alder approach to aminoazanoradamantanes.

Ozonolysis of the norbornene (±)-**14** followed by workup with sodium borohydride gave the diol (±)-**15** in 27 % yield (**Scheme 4**). Diol (±)-**15** was converted to the azanoradamantane (±)-**16** by a sequence involving bis-tosylation, trifluoroacetic acid removal of the BOC protecting group, and subsequent treatment with diisopropylethylamine, as in the conversion of (-)-**1** to (+)-**2**. We were confident at this point that we had obtained the desired azanoradamantane based on spectroscopic analysis, but final confirmation was provided by reductive removal of the benzyl carbamate protecting group to afford the free aminoazanoradamantane (±)-**3**, which was identical by proton NMR to the chiral material we had obtained by our previous method.[7]

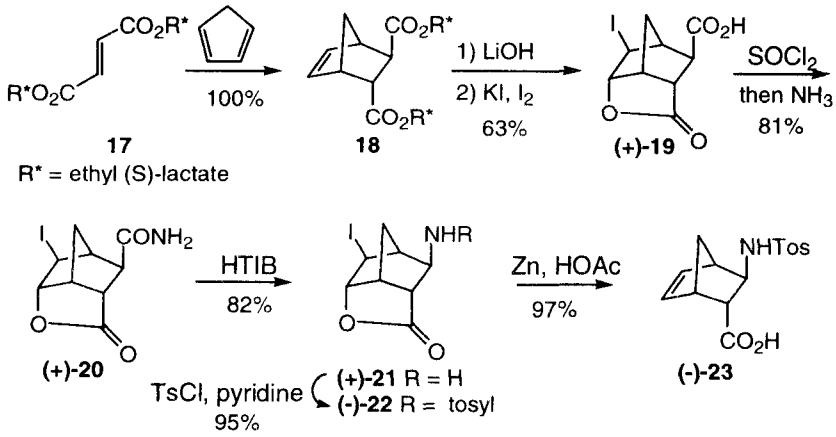


Scheme 4

The utilization of Yamamoto's racemic acid ester (±)-**7** verified the norbornene approach to aminoazanoradamantanes, but we were also still faced with the task of producing non-racemic material. In addition, several steps in the sequence were low yielding and therefore unsuitable for large scale work. Our preliminary attempts at resolution of 5-norbornene-2,3-dicarboxylic acid utilizing chiral bases were not encouraging. Zwanenburg's esterase approach[11] employing dimethyl 5-norbornene-2,3-dicarboxylate is attractive but affords the wrong enantiomer for the production of **SC-52491**. We were ultimately attracted to the highly efficient asymmetric Diels-Alder reaction reported by Helmchen[2c,12] to prepare the requisite norbornene to serve as an intermediate for the preparation of chiral aminoazanoradamantanes. The synthetic approach to **SC-52491** starting with Helmchen's Diels-Alder methodology was realized as outlined in **Schemes 5** and **6**.

The chiral norbornene diethyl-(S)-lactate ester **18** was prepared *via* an uncatalyzed Diels-Alder reaction of the corresponding fumarate diethyl-(S)-lactate ester **17** and cyclopentadiene according to Helmchen[2c,12] (**Scheme 5**). The original procedure reported the use of carbon tetrachloride/hexane (1:3) for this Diels-Alder reaction. Since we did not want to use halogenated solvents on a large scale, particularly not carbon tetrachloride, we examined a number of other solvent systems. All other solvent systems examined gave inferior results (82-90% d.e.), but we found unexpectedly that utilization of triethylamine as a solvent gave the desired diastereomer **18** in 91-95% d.e. The Diels-Alder reaction proceeds smoothly on warming the reaction from -25°C to room temperature. Saponification of **18** and iodolactonization gave the crystalline iodolactone

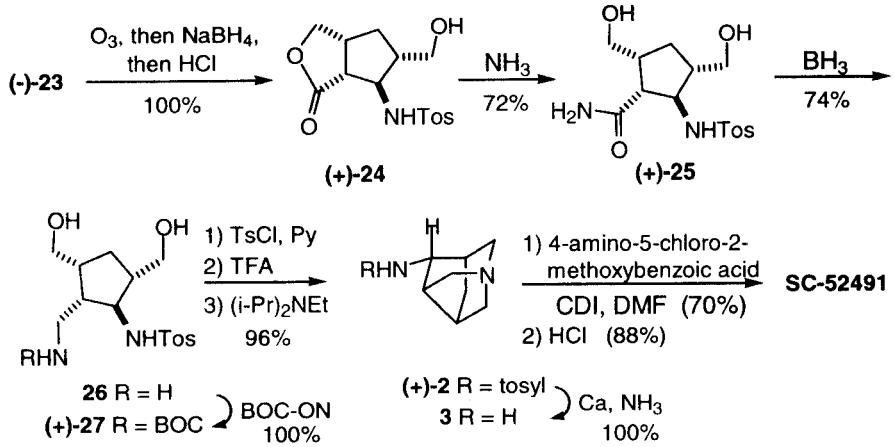
(+)-19 in 63% yield from fumaric ester **17** and in 99.3% e.e. by chiral HPLC. The crystallization of **(+)-19** is responsible for the very high e.e. beyond what may be expected from the diastereomeric ratio of **18**. The carboxylic acid moiety of **(+)-19** was then converted to the primary amide **(+)-20** *via* the acid chloride in 81-96% yield. A Hofmann-type rearrangement was performed utilizing HTIB (hydroxytosyloxy iodobenzene; Koser's reagent[13]) to give the primary amine **(+)-21**. The reaction was driven to completion with the addition of iodobenzene diacetate, which presumably gives rise to the formation of HTIB *in situ*. Subsequent tosylation gave the tosylamide **(-)-22** in high yield. The iodolactone was reductively cleaved with zinc in acetic acid in almost quantitative yield to give the norbornene carboxylic acid **(-)-23**.



Scheme 5

Ozonolysis of **(-)-23** with a reductive workup employing sodium borohydride followed by acidification of the crude mixture gave the lactone **(+)-24** in quantitative yield (**Scheme 6**). This procedure employing the free carboxylic acid of **(-)-23** to enable direct formation of the lactone was an important factor in obtaining high yields in this ozonolysis, in contrast to the poor yield obtained in the conversion of norbornene **(±)-14** to diol **(±)-15**. In addition, the resulting γ-lactone of **(+)-24** provided a convenient handle for the incorporation of the amine functionality. Ammonolysis of the lactone gave the primary amide **(+)-25.** Reduction with borane gave amine **26**, which was protected as the *tert*-butylcarbamate to afford BOC-amine diol **(+)-27**. Bis-tosylation of the diol was followed directly by removal of the *tert*-butylcarbamate protecting group with trifluoroacetic acid, and subsequent treatment with diisopropylethylamine in acetonitrile gave the tosyl-protected azanoradamantane **(+)-2**[7] in 96% yield without the need for purification. Deprotection of the tosylamide proceeded cleanly with calcium metal in liquid ammonia. Calcium was chosen over lithium, which we employed earlier,[7] because of its safer handling characteristics. Coupling of the derived chiral aminoazanoradamantane **3** with 4-amino-5-chloro-2-methoxybenzoic acid utilizing carbonyldiimidazole (CDI) as the coupling reagent gave the desired benzamide in 70% yield, without the use of the acetamide protecting group that was employed in the earlier synthesis.[7] The

product of the coupling was sufficiently pure to use after trituration with a minimum amount of ethyl acetate. The free base was then converted to the crystalline monohydrochloride salt, **SC-52491**.



Scheme 6

Summary

Utilization of Yamamoto's MAD-catalyzed Diels-Alder methodology provided an initial racemic approach to the key aminoazanoradamantane (±)-**3**. A scalable asymmetric synthesis of the serotonergic azanoradamantane **SC-52491** from inexpensive starting materials *via* tosyl-protected azanoradamantane **(+)-2** and chiral amine **3** was then developed employing Helmchen's asymmetric Diels-Alder reaction. In this approach the asymmetric Diels-Alder step assembles all four requisite asymmetric centers for **SC-52491** with the proper relative and absolute stereochemistry. Halogenated solvents were eliminated and no chromatography was required in this 15-step sequence which afforded **SC-52491** of high enantiomeric purity (>99% e.e.) and 12% overall yield.

Experimental Section

General. All reactions were performed under an atmosphere of argon. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Noise-decoupled and APT ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer. MIR refers to multiple internal reflectance spectroscopy. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument.

(±)-Methyl 3-[[(phenylmethoxy)carbonyl]amino]-2-bicyclo[2.2.1]hept-5-enecar-boxylate [(±)-8]. To a solution of carboxylic acid **7**[9] (1.88 g, 9.58 mmol) and triethylamine (1.65 mL, 1.26 g, 12.5 mmol) in acetone (30 mL) at 0°C was added ethyl chloroformate (0.92 mL, 1.0 g, 9.6 mmol) dropwise over several minutes. After the addition was complete the solution was stirred for 1h at 0°C. A solution of sodium azide (1.87 g, 28.7 mmol) in water (30 mL) was then added and the reaction was stirred for an additional hour at 0°C. The solution was then poured in to ice water and the resulting mixture was extracted with ethyl acetate (4 X 50 mL). The combined organic extracts were washed sequentially with sodium bicarbonate and brine and then dried over sodium sulfate. Concentration gave a residue which was dissolved in dry benzene (50 mL) and heated under reflux for 1.5 h. Benzyl alcohol (2.07 g, 19 mmol) was then added and heating under reflux was continued for and additional 2.5 h. Concentration gave a pale yellow oil which was crystallized from Et_2O/hexane to give the title compound **(±)-8** (2.1 g, 73%) as colorless crystals: mp 73-76°C; IR (MIR) 3362, 1727, 1688, 1538 cm^{-1}; ^1H NMR (300 MHz) δ 7.40-7.28 (5H, m), 6.25-6.18 (1H, m), 6.12-6.06 (1H, m), 5.11 (2 H, s), 4.85 (1H, br s), 3.94-3.84 (1H, m), 3.65 (3H, s), 3.14 (1H, br s), 2.85 (1H, br s), 2.55 (1H, t, J = 4 Hz), 1.65 (1H, d, J = 9.6 Hz), 1.56 (1H, d, J = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 155.7, 136.3, 135.8, 135.4 128.3, 128.0, 127.9, 66.6, 55.2, 52.4, 51.5, 48.8, 46.6, 44.8. MS (EI) calcd for $C_{17}H_{19}NO_4$ 301; found 301. Anal calcd for $C_{17}H_{19}NO_4$ C, 67.76; H, 6.36; N, 4.65. Found C, 67.59; H, 6.46; N, 4.63.

(±)-Phenylmethyl N-[3-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-yl]carbamate [(±)-9]. To a solution of methyl ester **(±)-8** in dry THF (1 mL) and absolute methanol (0.031 mL, 0.76 mmol) was added a solution of lithium borohydride (0.37 mL of a 2M solution in THF, 0.76 mmol) and the solution was stirred for 2 h at rt before quenching with 1N HCl (3 mL). The resulting mixture was extracted with ethyl acetate (3 X 15 mL) and the combined extracts were washed sequentially with sodium bicarbonate, water and brine, and then dried over sodium sulfate. Concentration gave a colorless oil which was purified by chromatography on silica gel eluting with 50/50 ethyl acetate/hexane to give carbinol **(±)-9** (84 mg, 84%) as a colorless oil which crystallized on standing: mp 111-113°C; IR (MIR) 3398, 3250, 1690, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (5 H, m), 6.18-6.08 (2 H, m), 5.37 (1H, br s), 5.11 (1H, d, J = 12 Hz), 5.04 (1 H, d, J = 12 Hz), 4.04 (1H, br s), 3.62-3.52 (1H, m), 3.23 (1H, t, J = 10 Hz), 3.17-3.10 (1H, m), 2.79 (1H, s) 2.73 (1H, s), 2.03-1.95 (1H, m), 1.57 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 136.5, 136.3, 134.9, 128.5, 128.2, 66.8, 65.6, 56.0, 53.1, 48.5, 46.9, 44.1. MH+ (CI) calcd for $C_{16}H_{19}NO_3$ 274, found 274. Anal calcd for $C_{16}H_{19}NO_3.015H_2O$ C, 69.62; H, 7.05; N, 5.07. Found C, 69.81; H, 7.05; N, 5.07.

Mesylate (±)-10 To a solution of alcohol **(±)-9** (611 mg, 2.23 mmol), triethylamine (339 mg, 3.35 mmol), and DMAP (14 mg, 0.11 mmol) in dry methylene chloride at -78°C was added methanesulfonyl chloride (384 mg, 3.35 mmol) *via* syringe. After 3 d at -30°C the suspension was diluted with additional methylene chloride (40

mL) and the resulting solution was washed successively with 1 N HCl, water, and brine. After drying over sodium sulfate the solution was concentrated to the desired mesylate (±)-**10** as an oil which solidified to a colorless powder: mp 77-80°C; IR (MIR) 3370, 1691, 1528, 1323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.29 (5H, m), 6.22 (1H, dd, J = 5.7, 2.8 Hz), 6.18 (1H, dd, J = 5.7, 2.7 Hz), 5.10 (2H, s), 4.94-4.82 (1H, m), 4.35 (1H, dd, J = 8.6, 6.1 Hz), 3.91 (1H, t, J = 10 Hz), 3.17-3.08 (1 H, m), 2.98 (4H, br s), 2.78 (1H, s), 2.12 (1H, ddt, J = 9.6, 6.4, 3.5 Hz), 1.72 (1H, dd, J = 9, 1.2 Hz), 1.55 (1H, d, J = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 136.4, 136.2, 135.5, 128.5, 128.1, 128.0, 72.1, 66.8, 54.7, 48.8, 48.6, 46.6, 43.2, 37.2. MS MH+ (CI) calcd for $C_{17}H_{21}NO_5S$ 352, found 352. Anal. calcd for $C_{17}H_{21}NO_5S.1/4H_2O$ C, 57.37; H, 6.09; N, 3.94. Found 57.58; H, 6.14; N, 3.84.

(±)-Phenylmethyl N-[3-formylbicyclo[2.2.1]hept-5-en-2-yl]carbamate [(±)-12]. To a solution of alcohol (±)-**9** (404 mg, 1.48 mmol) and triethylamine (450 mg, 4.44 mmol) in dry DMSO (5 mL) was added sulfur trioxide-pyridine complex (706 mg, 4.44 mmol). The pale yellow solution was stirred at rt for 15 minutes, then poured into ice water (50 mL). The mixture was extracted with ethyl acetate (3 X 50 mL) and the combined organic extracts were washed successively with water (4 X 30 mL) and brine and then dried over sodium sulfate. Concentration gave the title aldehyde (±)-**12** (380 mg, 95%) as a colorless solid: mp 75-79°C. IR (MIR) 3347, 1705, 1686, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 9.59 (1H, s), 7.43-7.29 (5H, m), 6.12 (2H, m), 5.11 (2H, s), 4.92 (1H, br s), 3.89-3.80 (1H, m), 3.21-3.17 (1H, m), 2.93-2.85 (1H, m), 2.57 (1H, q, J = 3 Hz), 1.69 (1H, dd, J = 8.9, 0.95 Hz), 1.61 (1H, d, J = 8.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 155.9, 136.2, 135.8, 135.6, 66.9, 61.4, 53.4, 48.6, 46.7, 43.9. MS (CI) MH+ calcd for $C_{16}H_{17}NO_3$ 272, found 272. Anal calcd for $C_{16}H_{17}NO_3.0.2H_2O$ C, 69.90; H, 6.38; N. 5.10. Found C, 70.05; H, 6.68; N, 5.08.

(±)-Phenylmethyl N-[3-(aminomethyl)bicyclo[2.2.1]hept-5-en-2-yl]carbamate [(±)-13]. To a solution of the aldehyde (±)-**12** (243 mg, 0.89 mmol) in methanol (9 mL) at rt was added ammonium acetate (690 mg, 8.9 mmol) followed by borane-pyridine (83 mg, 0.89 mmol). After stirring for 2.5 h at rt the solution was concentrated *in vacuo* to give a residue which was treated with 20% aqueous potassium carbonate (15 mL) and extracted with chloroform (3 X 15 mL). The combined extracts were washed with water and brine and then dried over sodium sulfate. Concentration gave a residue which was chromatographed on silica gel eluting with 4/96 EtOH(NH_3)/ethyl acetate to give the amine (±)-**13** (30 mg, 12%) as a colorless glass. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (5 H, m), 6.20-6.03 (1 H, m), 6.10 (1 H, dd, J = 5.6, 2.7 Hz), 5.09 (2 H, s), 5.05 (1 H, d, J = 3.3 Hz), 3.12 (1 H, d, J = 5.0 Hz), 2.82 (1 H, br s), 2.74 (1 H, br s), 2.65 (1 H, dd, J = 12, 7.4 Hz), 2.52 (1 H, dd, J = 12, 7.6 Hz), 1.67 (1 H, m), 1.63 (1 H, dd, J = 8.8, 1.1 Hz), 1.50 (1 H, d, J = 8.9 Hz), 1.39 (2 H, s).

(±)-1,1-Dimethylethyl N-[3-[[(phenylmethoxy)carbonyl]amino]bicyclo[2.2.1]hept-5-en-2-yl]methylcarbamate [(±)-14]. To a solution of the amine **(±)-13** (300 mg, 1.10 mmol) in dry THF (30 mL) was added di-*tert*-butyldicarbonate (280 mg, 1.28 mmol). After stirring for 24 h at rt the solution was concentrated *in vacuo* to give a residue which was chromatographed on silica gel eluting with 30/70 ethyl acetate/hexane to afford the title BOC-protected amine **(±)-14** (359 mg, 88%) as a colorless solid: mp 116-117°C; IR (MIR) 3340, 1685, 1522, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (5 H, m), 6.15 (2 H, m), 5.50 (1 H, br s), 5.10 (2 H, s), 4.89 (1 H, d, J = 5 Hz), 3.24-3.07 (2 H, m), 2.79 (2 H, br s), 2.74 (1 H, s), 1.86 (1 H, br s), 1.63 (1 H, d, J = 9 Hz), 1.51 (1 H, d, J = 9 Hz), 1.44 (9 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 156.1, 136.3, 136.0, 135.3, 128.5, 128.1, 66.8, 56.0, 50.1, 49.9, 48.8, 46.8, 44.2, 44.0, 28.3. HRMS M+1 calc for $C_{21}H_{28}N_2O_4$ 373.2127, found 373.2138. Anal calcd for $C_{21}H_{28}N_2O_4$ C, 67.72; H, 7.58; N. 7.52. Found C, 67.59; H, 7.67; N, 7.41.

(±)-1,1-Dimethylethyl N-[1,4-bis(hydroxymethyl)-3-[[(phenylmethoxy)carbonyl]-amino]cyclopentan-2-yl]-carbamate [(±)-15]. Ozone was bubbled through a solution of BOC-amine **(±)-14** (36 mg, 0.097 mmol) in 5:1 CH_2Cl_2/MeOH at -78°C until a blue color persisted (3 min). Argon was then bubbled through the solution until the blue color disappeared. Sodium borohydride (18 mg, 0.48 mmol) was added to the solution at minus 78°C and the reaction was allowed to warm up to rt over 1 h. After stirring for an additional 16 h at rt, brine (10 mL) was added and the reaction was extracted with methylene chloride (4 X 10 mL). The combined organic extracts were washed successively with water and brine and then dried over sodium sulfate. Concentration gave a colorless oil which was purified by preparative thin-layer chromatography on silica gel eluting (2 X) with 4/96 EtOH/ethyl acetate to give the diol **(±)-15** (11 mg, 27%) as colorless crystals: mp 142-144°C; IR (MIR) 3288, 1691, 1667, 1541 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39-7.27 (5 H, m), 5.57 (1 H, br s), 5.28 (1 H, br s), 5.13 (1H, d, J = 13 Hz), 5.07 (1 H, d, J = 13 Hz), 3.64 (2 H, m), 3.58-3.48 (2 H, m), 3.48-3.25 (2 H, m), 3.18-3.07 (1 H, m), 2.59 (1 H, br s), 2.40-2.26 (1 H, m), 2.17-1.76 (4 H, m), 1.43 (9 H, s), 1.28-1.13 (1 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.3, 156.4, 141.4, 136.4, 128.5, 128.2, 128.1, 105.0, 79.3, 67.1, 63.8, 63.0, 56.3, 50.5, 48.1, 47.7, 39.5, 39.4, 28.9, 28.5. MS M+1 calcd for $C_{21}H_{32}N_2O_6$, 409.2339; found 409.2364. Anal. Calcd for $C_{21}H_{32}N_2O_6.1/4H_2O$ C, 61.07; H, 7.93; N, 6.78. Found C, 61.02; H, 7.67; N, 6.73.

(±)-Phenylmethyl N-(hexahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)carbamate [(±)-16]. To a solution of diol **(±)-15** (18 mg, 0.044 mmol) in pyridine (0.6 mL) at 0°C was added solid *p*-toluenesulfonyl chloride (45 mg, 0.24 mmol) with stirring. After dissolution was complete the solution was allowed to stand at 0°C for 23 h. The solution was then poured onto ice (15 g) and extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed successively with water (3 X 30 mL) and brine (30 mL) and then dried over sodium sulfate. Concentration gave the di-tosylate (23 mg) as a colorless oil which was treated directly with freshly-distilled trifluoroacetic acid (0.5 mL) at rt. After stirring for 15 min the

solution was concentrated *in vacuo* to give a residue which was redissolved in acetonitrile (1 mL) and treated with diisopropylethylamine (31 mg, 0.24 mmol). After 21 h at rt the solution was concentrated *in vacuo* to give a residue which was treated with aqueous 15% potassium carbonate (1 mL) and then extracted with chloroform (3 X 15 mL). The combined organic extracts were washed successively with water and brine and then dried over sodium sulfate. Concentration then gave the title azanoradamantane **(±)-16** (9.2 mg, 78%) as colorless crystals. IR (MIR) 3171, 1703, 1454, 1259, 1247 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39-7.27 (5 H, m), 5.08 (2 H, s), 4.71 (1 H, br s), 3.97 (1 H, d, J = 6 Hz), 3.12 (1 H, d, J = 11 Hz), 2.99 (1 H, dd, J = 11, 3 Hz), 2.95-2.68 (4 H, m), 2.55-2.40 (2 H, m), 2.08 (1 H, s), 1.98-1.85 (1 H, m), 1.80 (1 H, d, J = 12 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 128.6, 128.1, 105.0, 66.7, 65.2, 63.8, 57.6, 45.8, 45.6, 42.6, 38.8, 37.7. MS calcd for $C_{16}H_{20}N_2O_2$: 272.1525; found 272.1524.

(±)-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-4α-amine [(±)-3] from Cbz-derivative (±)-16. To a suspension of 10% palladium on carbon (2 mg) in ethanol was added a solution of benzyl carbamate **(±)-16** (9.2 mg, 0.034 mmol) in methanol (0.4 mL) at rt. The suspension was then stirred under an atmosphere of hydrogen (1 atm) for 1 h. Removal of the catalyst by filtration and concentration of the filtrate gave the free amine **(±)-3** (4.2 mg, 89%) as a waxy semisolid which was identical by ^1H NMR to material prepared previously.[7]

***bis*-Lactate fumarate diester (17).** Fumaryl chloride (100 g, 0.653 mol) and ethyl (S)-lactate (147 mL, 1.3 mol) were dissolved in 1.6 liters of toluene with 400 mg of hydroquinone. The reaction mixture was heated between 80°C and 85°C for 18 h, sweeping the HCl from the mixture with a gentle stream of nitrogen. The reaction mixture was then cooled to -25°C. A second portion of ethyl (S)-lactate was added. Triethylamine (191 mL; 1.37 mol) was added to the reaction mixture, keeping the temperature below -10°C. The reaction mixture was stirred for one hour, allowing the reaction mixture to warm to room temperature. The reaction mixture was washed successively with 2 X 200 mL 2N HCl, 200 mL water, 4 X 200 mL 2N NaOH, then 3 X 250 mL brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was diluted to 1 liter with 15% EtOAc/hexane and then filtered through 600 g of silica, eluting with 8 X 500 mL fractions of 15% EtOAc/hexane to yield 186 g (90.3%) of the desired diester **17** as an oil, which was used without further purification. ^1H NMR ($CDCl_3$) δ 7.0 (2H, s), 5.19 (2H, q, J=11 Hz), 4.22 (4H, q, J=12 Hz), 1.57 (6H, d, J=11 Hz), 1.3 (6H, t, J=12 Hz).

Diels-Alder adduct (18). In a modification of Helmchen's[2c] procedure, di-(ethyl (S)-lactate) fumarate **17** (352 g, 1.11 mol) was dissolved in 5.5 liters of Et_3N and cooled to 0°C. Cyclopentadiene (140 mL; 1.71 mol) was added within ten minutes, and the reaction was mildly exothermic. The temperature reached 8°C before dropping again to 0°C. The reaction mixture was allowed to warm to room temperature and stir for 18 h.

Concentration afforded norbornene **18** (450.7 g, 100%) as an oil and used without further purification. The ratio of the two diastereomers was determined by HPLC [Supelco LC-18 DB; 65/35 MeCN/H_2O] to be 92.8:7.2 for (2R,3R)/(2S,3S).

(+)-Hexahydro-6β-iodo-2-oxo-3αR,5α-methano-2H-3aβ,6aβ cyclopenta[b]furan-7S-carboxylic acid [(+)-19]. The saponification of diester **18** (471.5 g, 1.17 mol) to give the corresponding diacid was carried out as described by Helmchen,[2c] and conversion of the diacid to the iodolactone (+)-**19**[2c] was followed with a modified workup using THF/EtOAc (1:1) for the extractions to afford 227.5 g (63% from fumarate **17**) of the iodolactone (+)-**19**. Anal. Calcd for $C_9H_9IO_4$: C, 35.09; H, 2.94; I, 41.19. Found: C, 35.28; H, 2.92; I, 41.23. $[\alpha]_D$ +54.4° (c = 1.0 in EtOH)

(+)-Hexahydro-6β-iodo-2-oxo-3αR,5α-methano-2H-3aβ,6aβ cyclopenta[b]furan-7S-carboxamide [(+)-20]. Iodolactone (+)-**19** (227.5 g, 0.73 mol) was suspended in $SOCl_2$ (132 mL) and gently warmed to reflux, where complete solution occurred. The reaction mixture was concentrated to remove the excess $SOCl_2$. The residue was dissolved in toluene (350 mL) and slowly added to a mixture of liquid NH_3 (85 mL) and 2 liters of THF cooled to -30°C. The reaction mixture was stirred for 0.5 h before adding 500 mL of H_2O. The layers were separated and the organic layer was washed with brine (500 mL), dried over $MgSO_4$ and concentrated to an oil. The oil slowly crystallized when triturated with EtOAc. The solid was filtered and washed with EtOAc and dried in vacuum to yield 181.5 g (81%) of primary amide (+)-**20** as a white solid: DSC 165.65°C; $[\alpha]_D$ +34.5° (c = 1.0 in EtOH); IR (KBr) 3470, 3423, 3362, 3187, 1769, 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, br s), 5.45 (1 H, br s), 5.14 (1 H, d, J = 5.0 Hz), 3.87 (1 H, d, J = 2.6 Hz), 3.21 (1 H, m), 3.07 (1 H, dd, J = 4.8 Hz, 1.1 Hz), 2.93 (1 H, s), 2.69 (1 H, s), 2.33 (1 H, dd, J = 11.9, 1.3 Hz), 2.24 (1 H, dd, J = 11.9, 2.1 Hz); ^{13}C NMR (400 MHz, d_6-DMSO) δ 177.9, 171.2, 88.8, 51.2, 51.0, 46.1, 41.5, 35.2, 35.1, 28.1. Anal. Calcd for $C_9H_{10}INO_3$: C, 35.20; H, 3.28; I, 41.32; N, 4.56. Found: C, 35.40; H, 3.26; I, 41.20; N, 4.50.

(+)-Hexahydro-6β-iodo-2-oxo-3αR,5α-methano-2H-3aβ,6aβ-cyclopenta[b]furan-7S-amine, 4-methylbenzenesulfonate [(+)-21]. Primary amide (+)-**20** (30.0 g, 96.0 mmol) was dissolved in CH_3CN (500 mL). HTIB (hydroxy(tosyloxy)iodobenzene, 42 g, 0.108 mol) was added to the reaction mixture and stirring was continued. The mixture thickened to a solid mass within 5 minutes. The mixture was slowly warmed to reflux where the solid mass became mobile again. The reaction mixture was allowed to cool to 35°C. IBDA (iodobenzene diacetate, 15.4 g, 48 mmol) was added and the mixture thickened again. The mixture was reheated to 65°C where the solid mass became mobile again. The reaction mixture was stirred 18 h, filtered, washed with CH_3CN and suction dried to yield 35.4 g (82%) of primary amine (+)-**21**: $[\alpha]_D$ +32.8 (c= 1.09, EtOH); $[\alpha]_{365}$ +137.5 (c= 1.09, EtOH); IR (KBr) 3470, 3361, 1767, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (1H, d, J=

2 Hz); 3.88 (1H, d, J= 1 Hz); 3.21 (1H,t, J=1 Hz); 3.07 (1H, d, J=1.5 Hz); 2.93 (1H, s); 2.49 (1H, s); 2.33 (1H, d, J=4 Hz); 2.22 (1H, d, J= 4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.8, 171.2, 88.8, 51.2, 51.0, 41.5, 35.1, 28.1. Anal. Calcd for $C_{15}H_{18}INO_5S$: C, 39.92; H, 4.02; N, 3.10; S, 7.11. Found: C, 39.96; H, 4.04; N, 2.90; S, 7.38. For the monotosylate salt: $[a]_D$ +30.0 (c= 1.04, EtOH); $[a]_{365}$ +98.6 (c= 1.04, EtOH); IR(KBr) 3435, 2997, 1792 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.49 (2H, d, J= 4 Hz); 7.12 (2H, d, J= 4 Hz); 5.16 (1H, d, J= 3 Hz); 5.12 (1H, d, J= 2 Hz); 4.11 (1H, d, J= 1 Hz); 3.66 (1H, s); 3.30 (1H, t, J=1 Hz); 2.76 (1H, s); 2.62 (1H, d, J=2Hz); 2.30 (3H, s); 2.29 (1H, d, J= 7 Hz); 2.12 (1H, d, J= 7 Hz). ^{13}C NMR (400 MHz, d_6-DMSO) δ 175.0, 145.6, 137.5, 128.0, 125.4, 87.3, 53.1, 50.8, 45.9, 44.0, 32.9, 24.9, 20.7.

(-)-N-(3aβ,6aβ-hexahydro-6β-iodo-2-oxo-3αR,5α-methano-2H-cyclopenta[b]furan-7S-yl)-4-methylbenzenesulfonamide [(-)-22]. The tosylate salt of **(+)-21** (1.0 g, 2.2 mmol) was dissolved in pyridine (5.0 mL). *p*-Toluenesulfonyl chloride (476 mg, 2.5 mmol) was added and the reaction mixture stirred for 2 h and concentrated. The residue was partitioned between THF and brine. The organic layer was washed subsequently with dilute HCl and dilute K_2CO_3, and dried over $MgSO_4$, and concentrated. The residue was placed on 50 g of silica and eluted with 50 mL of 1:1 EtOAc/heptane. The solution was concentrated to an oil which slowly crystallized to yield 913 mg (95%) of tosylamide **(-)-22**. $[\alpha]_D$ -65.6° (c = 1.0 in EtOH); IR (KBr) 3433, 3238, 1763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, J= 4 Hz); 7.73 (2H, d, J= 4 Hz); 5.16 (1H, d, J= 3 Hz); 5.04 (1H, d, J= 2 Hz); 3.49 (1H, d, J= 1 Hz); 3.12 (1H, t, J=1 Hz, J= 3 Hz); 2.72 (1H, s); 2.43 (3H, s); 2.31 (1H, d, J= 7 Hz); 2.11 (1H, d, J= 7 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.38, 144.4, 136.1, 130.2, 127.3, 87.8, 58.0, 53.4, 47.3, 45.7, 34.6, 24.9, 21.6. Anal. Calcd for $C_{15}H_{16}INO_4S$: C, 41.58; H, 3.72; N, 3.23; S, 7.40. Found: C, 41.49; H, 3.79; N, 3.28; S, 7.77.

(-)-3R-[[(4-Methylphenyl)sulfonyl]amino]-bicyclo[2.2.1]hept-5-ene-2αR carboxylic acid [(-)-23]. Iodolactone **(-)-22** (27.0 g, 0.062 mol) and Zn° (16.2 g, 0.249 mol) were combined in glacial acetic acid (100 mL) and refluxed for 0.5 h. The reaction mixture was cooled and filtered through celite. The filtrate was concentrated and the residue suspended in water, and the resulting crystalline solid was filtered, washed with water and dried to yield 18.4 g (97%) of carboxylic acid **(-)-23** as a white solid. $[\alpha]_D$ -24.9° (c= 1.0, EtOH); $[\alpha]_{365}$ -46.8° (c= 1.0, EtOH); IR(KBr) 3921, 3788, 1707 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.85 (2H, d, J= 4 Hz); 7.69 (2H, d, J= 4 Hz); 6.08-5.94 (2H, m, J= 2 Hz); 3.39 (1H, s); 3.24 - 3.30 (1H, m); 2.76 (1H, s); 2.99 (1H, s); 2.61 (1H, t, J=2 Hz) 2.30 (3H, s); 2.58 (1H, s); 2.48 (3H, s); 1.72 (1H, d, J=2 Hz); 1.40 (1H, d, J=2 Hz). ^{13}C NMR (300 MHz, d_6-DMSO) δ 173.4, 142.4, 138.3, 135.7, 135.4, 129.4, 126.5, 56.1, 50.9, 48.4, 46.5, 44.6, 20.9. Anal. Calcd for $C_{15}H_{17}NSO_4$: C, 56.95; H, 5.73; N, 4.43; S, 10.14. Found: C, 57.08; H, 5.42; N, 4.36; S, 10.33.

(+)-N-(5aS-hydroxymethyl-3-oxo-3aα,6aα-cyclopenta[c]furan-4βR-yl)-4-methylbenzene-sulfonamide [(+)-24].

Ozone was bubbled through a solution of carboxylic acid **(-)-23** (2.0 g, 6.5 mmol) in ethyl acetate/methanol (24 mL; 5:1) at -78°C until a light blue color persisted. *Caution should be exercised when utilizing ozone in flammable solvents to avoid fire.* After stirring for an additional 0.5 h at -78°C, argon was bubbled through the solution for 25 min to remove excess ozone. To the colorless solution was then added sodium borohydride pellets (1.07 g, 32.5 mmol) at -78°C. The reaction mixture allowed to warm to room temperature and stirred for 40 h. To the reaction mixture was added 3 drops of methyl orange/methanol indicator followed by a solution of 2N HCl/methanol to give a light pink color and the reaction was then stirred for 72 h at room temperature. The mixture was concentrated *in vacuo*. To the residue was added brine (35 mL) and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed successively with water and brine, dried over $MgSO_4$, filtered and concentrated to give the desired lactone **(+)-24** as a waxy white solid (2.01 g, 100%): $[\alpha]_D$ = +1.4° (c = 0.70 in CH_3OH); IR (MIR) 3453, 3219, 1753, 1156 cm^{-1}; ^1H NMR (CD_3OD) δ 7.82 (2H, d, J = 8 Hz), 7.34 (2H, d, J = 8 Hz), 4.27 (1H, dd, J = 9, 6 Hz), 4.06 (1H, d, J = 9 Hz); 3.68 (1H, dd, J = 7, 3 Hz), 3.50 (1H, dd, J = 10, 4 Hz), 3.36 (1H, dd, J = 11, 6 Hz), 2.97 (1H, m), 2.78 (1H, dd, J = 9, 3 Hz), 2.40 (3H, s); 2.09 (2H, m), 1.25 (1H, m); ^{13}C (CD_3OD) δ 178.4, 142.8, 138.5, 128.8, 126.6, 70.8, 60.8, 57.8, 46.9, 46.6, 38.9, 32.2, 19.7.

(+)-1a,4a-bis(hydroxymethyl)-3b-[[(4-methylphenyl)sulfonyl]amino] cyclopentane-2a-carboxamide (25). A solution of lactone **24** (2.0 g, 6.5 mmol) in methanol in a Parr Shaker was pressurized with ammonia gas to 50 psi for 4 h at 60°C. The solution was then filtered through celite and concentrated *in vacuo* to give a white solid. The solid was recrystallized from ethanol to give primary amide **25** (1.52 g, 72%): mp = 191.5 - 192.5°C; $[\alpha]_D$ = +46.8° (c = 1.10 in CH_3OH); IR (MIR) 3453, 3219, 1753, 1156 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.70 (2H, d, J = 7.5 Hz) 7.33 (2H, d, 7.5 Hz) 3.66 (3H, m), 3.66 (1H, dd, J = 6.0, 2.0 Hz) 3.42 (1H, dd, J = 7.5, 2.5 Hz), 2.70 (1H, m), 2.42 (3H, s), 2.41 (1H, m), 2.37 (1H, m), 1.99 (1H, m), 1.25 (1H, m); ^{13}C (100.6 MHz, CD_3OD) δ 177.6, 144.6, 139.5, 130.7, 120.2, 64.3, 64.0, 60.0, 54.8, 50.0, 44.5, 33.0, 21.5; Anal. Calcd for $C_{15}H_{22}N_2SO_5 \cdot 0.5\ H_2O$: C, 51.27; H, 6.60; N, 7.97. Found: C, 51.16; H, 6.53; N, 7.96.

Amine 26. To a suspension of primary amide **25** (1.0 g, 2.9 mmol) in THF (100 mL) was added dropwise a 1M solution of borane-THF over 20 min. The reaction mixture stirred for 1 h at rt followed by refluxing for 18 h. The reaction mixture was cooled to 0°C and 15% aqueous HCl (100 mL) was added. The reaction was then allowed to warm up to stir at rt for 14 h The solution was then concentrated *in vacuo* to a white foam which was dissolved in water (10 mL) and then treated with 1N NaOH (10 mL). The solution was stirred for 3 h, saturated with NaCl, and extracted with THF. The combined extracts were dried over $MgSO_4$ and then concentrated *in vacuo* to give oil. The oil was passed through a pad of silica eluting with ethyl acetate followed

by 20% $CH_3OH(NH_3)$/THF to give the free amine **26** (700 mg, 74%): ^1H (300 MHz, CD_3OD) δ 7.76 (2H, d, J = 9.0 Hz), 7.38 (2H, d, J = 9.0 Hz), 3.48 (2H, m), 3.26 (1H, d, J = 4 Hz), 3.05 (2 H, m), 2.72 (2H, d, J = 4 Hz), 2.41 (2H, s), 2.31 (1H, m), 1.12 (1H, m), 1.84 (1H, m), 1.96 (2H, m); ^{13}C (100.6 MHz, CD_3OD) δ 143.7, 139.5, 129.8, 127.0, 62.8, 62.7, 58.3, 49.9, 40.0, 39.2, 29.6, 20.6. This amine was protected directly as the BOC derivative without further purification.

(+)-1,1-dimethylethyl-N-[[1α,4α-bis(hydroxymethyl)-3β-[[(4-methylphenyl)sulfonyl]amino]-cyclopentan-2α-yl]methyl]carbamate (27). Thus, to a solution of the amine **26** (570 mg, 1.73 mmol) and triethyl amine (0.45 mL, 1.9 mmol) in acetone/water (10 mL) was added BOC-ON (2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile; 470 mg, 2.9 mmol) and the reaction stirred for 18 h at rt. The solution was extracted with ethyl acetate (3X). The combined extracts were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. The oil was passed through a pad of silica gel eluting with ethyl acetate to give the BOC-protected amine **27** (740 mg, 100%). $[\alpha]_D$ +22.4 (c = 0.157, $CHCl_3$); IR (MIR) 3384, 3291, 1684 (str), 1516, 1156 cm^{-1}; ^1H NMR (300 Hz, CD_3OD) δ 7.77 (2H, d, J = 8.0 Hz) 7.37 (2H, d, J = 8.0 Hz), 3.49 (2H, m), 3.35 (2H, m), 3.19 (1H, m), 3.12 (1H, t, J= 7.5 Hz), 2.92 (2H, m), 2.24 (1H, m), 2.41 (3H, s), 1.92 (1H, m), 2.04 (1H, m), 1.42 (9H, s); ^{13}C NMR δ (100.6 Hz, CD_3OD) 143.6, 139.5, 129.7, 127.1, 78.5, 63.1, 62.4, 58.6, 48.4, 40.7, 38.5, 29.7, 27.8, 20.5. Anal Calcd for $C_{20}H_{32}N_2SO_6$:1/2 H_2O: C, 54.90; H, 7.60; N, 6.40. Found: C, 54.91; H, 7.47; N, 6.07.

(+)-N-(hexahydro-2,5β-methano-1H-3aS,3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-4-methyl-benzenesulfonamide [(+)-2]. To a solution of BOC-amine diol **(+)-27** (207 mg, 0.484 mmol) in dry pyridine (2.4 mL) at 20°C was added *p*-toluenesulfonyl chloride (369 mg, 1.94 mmol) with stirring. After dissolution was complete the solution was allowed to stand at 0°C for 21 h. The reaction was then poured onto ice and extracted with ethyl acetate (3X). The combined extracts were washed successively with water (5X) and brine and then dried over sodium sulfate. Concentration gave a colorless foam (357 mg). The foam was dissolved in trifluoroacetic acid (5 mL) and allowed to stand for 15 min at rt after which time the reaction was concentrated under vacuum. The resulting residue was dissolved in acetonitrile (10 mL) and treated with diisopropylethylamine (433 mg, 3.35 mmol). After 4 days at rt the pale yellow solution was warmed to 46°C for 2h. Concentration gave a residue which was treated with 4N KOH/presaturated with NaCl (5 mL) and extracted with ethyl acetate (5X). The combined extracts were washed with water (2X) and brine and dried over sodium sulfate. Concentration then gave the tosylamide azanoradamantane **(+)-2** (134 mg, 96%) as a pale yellow solid: mp 203-205°C; $[\alpha]_D$ = +3.0° (c = 0.76 in $CHCl_3$). The proton NMR was identical to the material prepared *via* the previously described route.[7]

Hexahydro-2,5β-methano-1H-3aS,3aα,6aα-cyclopehta[c]pyrrol-4α-amine (3). To liquid ammonia (30 mL) at -33°C was added a solution of tosylamide **(+)-2** (539 mg, 1.84 mmol) in THF (7 mL). Calcium metal (319 mg, 7.96 mmol) was added in three portions over 5 min. After 30 min the dark blue reaction was quenched with addition of solid ammonium chloride (985 mg, 18.4 mmol). Concentration gave a residue which was treated with 4N KOH-presaturated with NaCl (9.2 mL). The suspension was filtered through celite and the solid was washed with THF. The filtrate was extracted with THF (7X) and the combined THF rinses and extracts were dried over sodium sulfate. Concentration gave chiral aminoazanoradamantane **3** (0.29 g, 100%) as a colorless waxy solid. The proton NMR was identical to the material prepared *via* the previously described route.[7]

(+)-4-amino-5-chloro-N-(hexahydro-2,5β-methano-1H-3aS,3aα,6aα-cyclopenta[c]-pyrrol-4α-yl)-2-methoxybenzamide, (free base of SC-52491). To a solution of 4-amino-5-chloro-2-methoxybenzoic acid (371 mg, 1.84 mmol) in DMF (1.8 mL) was added carbonyldiimidazole (298 mg, 1.84 mmol). After 1 h at rt a solution of the chiral aminoazanoradamantane **3** derived from **(+)-2** (255 mg, 1.84 mmol) in DMF (1.9 mL) was added and the resulting pale yellow solution was stirred at rt for 24 h. Concentration under vacuum at 36°C gave a yellow solid which was triturated with ethyl acetate (5 mL), filtered, and rinsed with cold (0°C) ethyl acetate (1.5 mL). The solid was then dried *in vacuo* at 52°C to give the free base of **SC-58241** as a pale yellow solid (413 mg, 70%), which was converted directly to the hydrochloride salt.

(+)-4-amino-5-chloro-N-(hexahydro-2,5β-methano-1H-3aS,3aα,6aα-cyclopenta[c]-pyrrol-4α-yl)-2-methoxybenzamide, monohydrochloride (SC-52491). To a solution of free base of **SC-52491** (343 mg, 1.04 mmol) in 95% ethanol (10 mL) was added ethanolic HCl [prepared from acetyl chloride (75 mg, 1.07 mmol) and 95% ethanol (0.5 mL)]. The solution was allowed to stand at 0°C for 24 h. Filtration of the resulting crystalline solid and rinsing with cold (0°C) 95% ethanol (1.5 mL) gave the desired material which was dried at 63°C *in vacuo* for 16 h to afford the hydrochloride **SC-52491** (337 mg, 88%) as an off-white powder. $[\alpha]_D$ = +7.1° (c = 0.23, MeOH). Anal. Calcd for $C_{16}H_{20}N_3O_2Cl.HCl.H_2O$: C, 51.07; H, 6.16; N, 11.17; Cl, 18.84. Found: C, 50.80; H, 6.16; N, 11.00; Cl, 18.54. The proton NMR was identical to the material prepared *via* the previously described route.[7]

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References

1. Shinkai, I., *Pure Appl. Chem.* **1997**, *69*, 453-458.

2. a) Whiting, A., "Asymmetric Diels-Alder Reactions", in *Adv. Asymmetric Synth*; Stephenson, G. Richard, Ed.; Chapman & Hall: London, 1996, pp. 126-145. b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019. c) Helmchen, G.; Karge, R.: Weetman, J. "Asymmetric Diels-Alder Reactions with Chiral Enoates as Dienophiles", in *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer-Verlag Berlin Heidelberg, 1986, Vol. 4, pp. 261-306. For the application of asymmetric Diels-Alder reactions in the efficient preparation of pharmaceutically important molecules, see for example: d) Martinelli, M. J. *J. Org. Chem.* **1990**, *55*, 5065-73. e) Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchison, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775-85.

3. a) Flynn, D. L.; Becker, D. P.; Spangler, D. P.; Nosal, R.; Gullikson, G. W.; Moummi, C.; and Yang, D. -C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1613-8. b) Becker, D. P.; Goldstin, B.; Gullikson, G. W.; Loeffler, R.; Moormann, A.; Moummi, C.; Nosal, R.; Spangler, D.; Villamil, C. I.; Yang, D. -C.; Zabrowski, D. L.; Flynn, D. L. in "Perspectives in Receptor Research", ed. D. Giardina et. al. , *Pharmacochemistry Library, Vol 24*, Elsevier Science B. V.: Amsterdam, **1996**, pp. 99-120.

4. Baxter, G. S.; Craig, D. A.; Clarke, D. E.; *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, *343*, 439.

5. The assay of Kilpatrick was employed using ^{3}H-GR65630 as the radioligand with male rat cortical tissue. Kilpatrick, G. J.; Jones, B. J.; Tyers, M.B.; *Nature*, **1987**, *330*, 746.

6. **SC-52491** exhibits IC_{50} values >10,000 nM for 5-HT_1-like, 5-HT_2, dopamine D_1 and D_2, α_1-, α_2-, and β-adrenergic receptors).

7. Becker, D. P.; Nosal, R.; Zabrowski, D. L.; Flynn, D. L. *Tetrahedron* **1997**, 53, 1-20.

8. Becker, D. P.; Flynn, D. L. *Tet. Lett.* **1993**, *34*, 2087-90; Becker, D. P.; Flynn, *Tetrahedron* **1993**, *49*, 5047-54.

9. Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 1089-90.

10. Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1986**, 695-697.

11. Klunder, A. J. H.; van Gastel, F. J. C.; Zwanenburg, B. *Tet. Lett.* **1988**, *29*, 2697-2700.

12. a) Hartmann, H.; Abdel Hady, A. F.; Sartor, K.; Weetman, J.; Helmchen, G. *Angew. Chem.* **1987**, *99*, 1188-1189; b) Hartmann, H.; Fattah Abdel Hady, A.; Sartor, K.; Weetman, J.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1143-1145. c) Helmchen, G.; Poll, T.; Hartmann, H.; Karge, R. DE 3702084 A1 (**1987**); CAN 108:111830. d) Helmchen, G.; Goeke, A.; Lauer, G.; Urmann, M.; Fries, J.; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1024-5.

13. Lazbin, I. M.; Koser, G. F.; *J. Org. Chem.* **1986**, *51*, 2669-71.