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Tandem Michael Addition and Azanorbornane Substance-P Antagonists†

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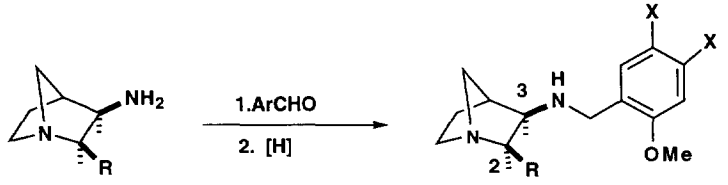
Abstract: Tandem Michael addition product **5** provides a template for azanorbornane derivatives that display potent substance P receptor affinity. The advantages of this synthesis include: the straightforward preparation of both syn and anti azanorbornane diastereomers, access to two, and perhaps more, substituents at C-2 (**a** and **b** series), and the straightforward functionalization of the amine at C-3. Mechanistic studies suggest that the second 1,4-addition proceeds kinetically via syn-addition of the nitronate and ester. Conflicting results in the literature stem from a previously unobserved thermodynamic equilibrium which is described herein.

Substance P (SP) has been implicated in the transmission of pain and in the immune system response in mammalian tissue[1]. This undecapeptide is a member of the tachykinin family of neurotransmitters that selectively bind to three known receptor subtypes (NK_1, NK_2, NK_3). Binding of SP is most favorable at the NK_1 receptor (K_i = < 1 nM), and presumably its biological activity is linked to stimulation of this receptor subtype[2]. Recently, non-peptide antagonists that are potent and selective for the NK_1 receptor have been uncovered and have afforded valuable information regarding the biological actions of SP[3].

Structure activity relationships (SAR) for SP antagonists were established initially in the quinuclidine class and subsequently in other templates[4]. We have developed a concise synthetic route to the corresponding azanorbornane class of antagonist typified by **2**. To cover a broad range of SAR, synthetic access to several types of aromatic residues at C-2 (i.e. series **a** and **b**) was desirable as well as access to a variety of benzylic amine substituents at C-3. The chemistry we describe here accomplishes these goals and permits an investigation of the stereochemical relationship between C-2 and C-3 and its effect on activity.



1a. R = Ph
1b. R = -CHPh$_2$

2a. R = Ph X = H
2b. R= -CHPh$_2$ X = H
2b-1. R= -CHPh$_2$ X =Me

† This paper is dedicated to Professor Samuel Danishefsky in celebration of and in gratitude for his scientific leadership and encouragement spanning four decades.

Synthesis of the azanorbornane system was divided into two operations[5] (see Scheme **1**). Initially, a pyrrolidine template, containing substituents important for the pharmacophor, was assembled from two subunits. The template contained the desired C-2 and C-3 substituents as well as functionality for subsequent formation of the bicyclic ring. This latter functionality, used also in creation of the pyrrolidine system, was then transformed into the correct oxidation state for the intramolecular ring closure. The pivotal amine surrogate at C-3, envisioned as a nitro group, was also used to direct the creation of the template and to adjust the stereochemical relationships of the substituents in a predictable way. Chemistry reported by Barco et. al.[6,7] attracted our interest in this regard because it rapidly afforded pyrrolidines of defined stereochemistry with the correct functionality for further elaboration into the azabicyclic ring (Figure **1**).

Mechanistic Studies:

The assembly of the bicyclic ring was initiated by sequential Michael addition of benzylic amine **3**[6] (Scheme **1**) and the nitro-olefin **4a** or **4b** (MeOH, rt. 16 hrs). This extended the protocol developed by Barco[7] to include nitrostyrene and other substituted nitro-olefins. A single product **5** was produced from each series with the creation of three asymmetric centers. The stereochemical arrangement at C-2 / C-3 and C-3 / C-4 was determined to be *anti-syn* at this stage through nuclear Overhauser enhancement (nOe) analysis and later confirmed through X-ray crystallography of the final product **2b-1** (*vide infra*). Amine **3** initiated the ring closure sequence beginning with Michael addition to the nitro-olefin, and the presumed formation of a nitronate anion. A second stereoselective conjugate addition seamlessly afforded the cyclized product[8]. The stereochemical arrangement of **5** is believed to be kinetically controlled in each series and was influenced by the substituent at C-2.

Although we were gratified with this result, the formation of this diastereomer had not been predicted based upon results reported by Barco et. al.[7] (Figure **1**). In their reaction, unsubstituted nitroethylene and **3** afforded a pyrrolidine of the *anti* configuration at C-3 / C-4 (Figure **1**) as the major product. Minor amounts of the syn isomer (1:20 ratio) were observed, unlike our result with **5.** Their observations led to the conclusion that the anti-isomer was derived exclusively from anti-periplanar intramolecular approach of the nitronate and acceptor chain in the transition state. *However, closer examination of Barco's result by deuterium exchange NMR uncovered an intermediate, determined to be the C-3/C-4-syn-isomer, which subsequently equilibrated to the more stable anti-isomer (Figure 1).* The syn-intermediate was trapped as the bicyclic[3.3.0]lactam through

Figure 1

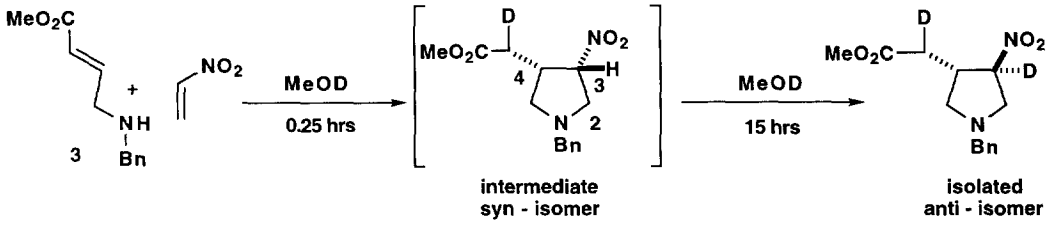
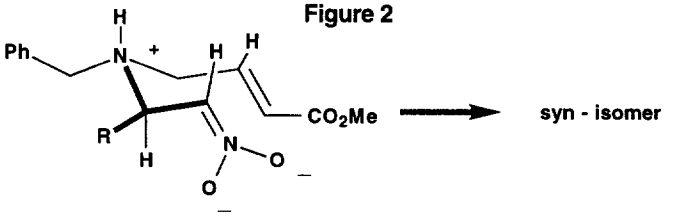
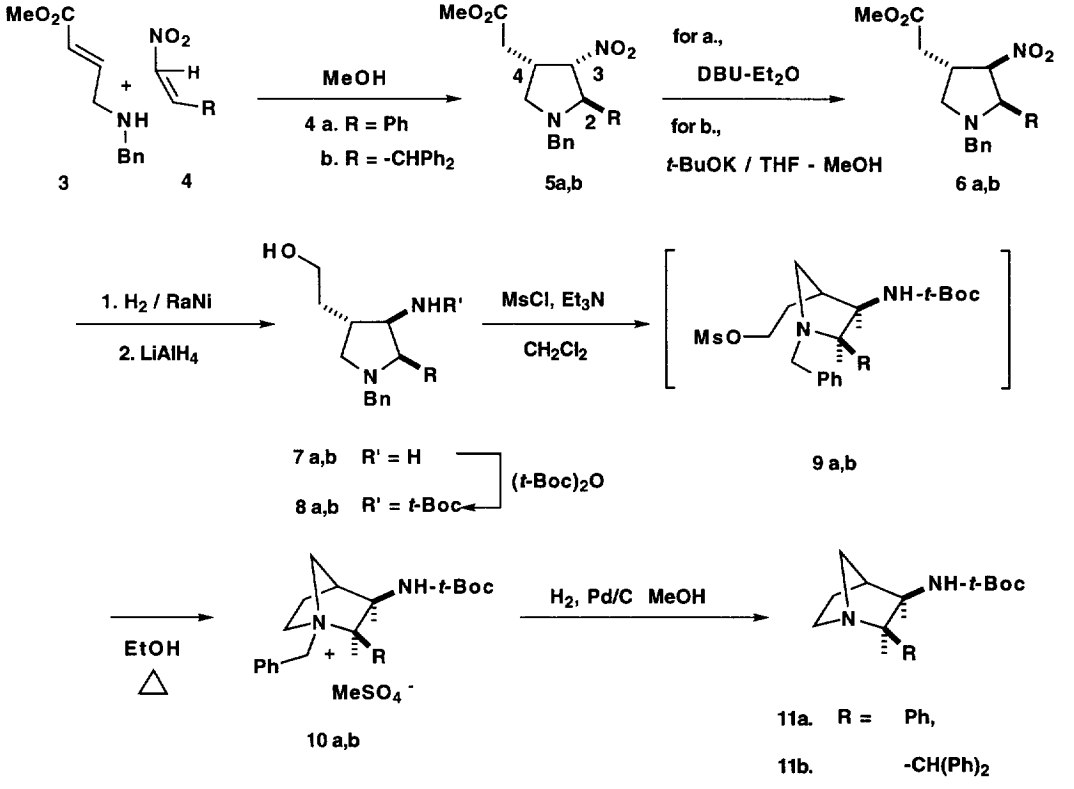


Figure 2



nitro-reduction / ring closure of this reaction intermediate[9]. The base catalyzed equilibration is presumably mediated by the ring nitrogen and occurs well within the 15 hour time frame the authors report for this reaction (Figure 1). Thus, compound **5** did not derive from a mechanistic reversal of the Barco process due to occupation of C-2 but instead became an extension of the process. The substituent at C-2 sterically shields the C-3 proton from deprotonation under the mild conditions of the tandem Michael reaction and thus inhibits epimerization [10a,d]. This may also be the result of allylic strain developing between the nitronate oxygen and the substituent at C-2 which disfavors the anion and allows the isolation of the kinetic product **5** [10 b,c]. In all cases studied thus far, the stereochemical relationship of the initial product at C-2, C-3, C-4 is identical, favoring syn alignment of the unsaturated ester and nitronate in the transition state. The origin of this

Scheme 1



selectivity remains unknown, however, it is possible that secondary orbital interactions favor the observed endo approach (Figure **2**), and exclude a seemingly reasonable anti-periplanar alignment.

Formation of the cis Azanorbornane Series 2a, 2b (Scheme 1):

We demonstrated that the phenyl and benzhydryl substituents were equally well tolerated in the chemistry used to prepare the pyrrolidine template. Furthermore, the stereochemical relationship between C-2 and C-3 was readily altered in both series through base mediated epimerization (Scheme **1**) of the nitro substituent[10]. Treatment of phenyl substituted **5a** with DBU (1 equiv., rt., 4 hrs) in ether led to the direct crystallization of epimeric **6a** from the reaction mixture (68% yield). Somewhat modified conditions were required to induce nitronate formation from benzhydryl substituted **5b**. This was expected as a consequence of increased steric interactions or allylic strain between the developing nitronate oxygen and the benzhydryl group. Heating with potassium *t*-butoxide (1 equiv.) in THF- methanol (3:1, 0.5 hr) completed the formation of the nitronate. The presence of methanol in the reaction medium prevented self-annihilation of the anion by inhibiting an incompletely characterized process which resulted in ester hydrolysis. Quenching of the anion with pivalic acid produced the *syn* epimer **6b** in 75 - 78 % yield. An nOe analysis corroborated the 2,3-*syn* assignment of both aryl substituted pyrrolidines **6**. The C-2 / C-3 syn isomers **6** do not undergo further equilibration upon resubjection to base. Although examination of models does not explain why more stable **6** is not produced directly from the tandem Michael addition, this product is readily obtainable in good yield.

Anionic stabilization by the nitro functionality was critical to the formation of the pyrrolidine ring and in adjustment of stereochemical relationships. *Additionally, the nitro group served as an amine surrogate.* Hydrogenation of **6** over Raney nickel (pH 7, MeOH, 45 psi H_2, 4 hrs, rt) afforded an intermediate amino ester which was further reduced to the amino alcohol **7** ($LiAlH_4$, THF, 0° C, 0.33 hrs, **a**: 72%, **b**:67% for 2 steps). The observation that the intermediate amino-ester from Raney-nickel reduction was stable towards spontaneous lactam formation was consistent with the assignment of stereochemistry at C-3 / C-4 as anti (vide supra). Protection of the amine group was accomplished with *t*-Boc anhydride [$(t\text{-Boc})_2O$, 1:1 $CHCl_3$-aq $NaHCO_3$] to afford **8** (**a**: 78%, **b**: 89%). The multi-step, but isolation free, azanorbornane ring closure was initiated from **8**. Treatment of **8** with methanesulfonyl chloride (Et_3N, CH_2Cl_2, 0° C, 0.1 hrs) afforded an intermediate **9** which was cyclized directly by heating in ethanol (reflux, 16 hrs) to **10** (crystalline **10b**, 84%). The quaternary salts **10** were selectively debenzylated under standard conditions (H_2, 10% Pd / C, EtOH) to afford phenyl substituted **11a** (49% from **8**) or benzhydryl substituted **11b** (52%) respectively[11].

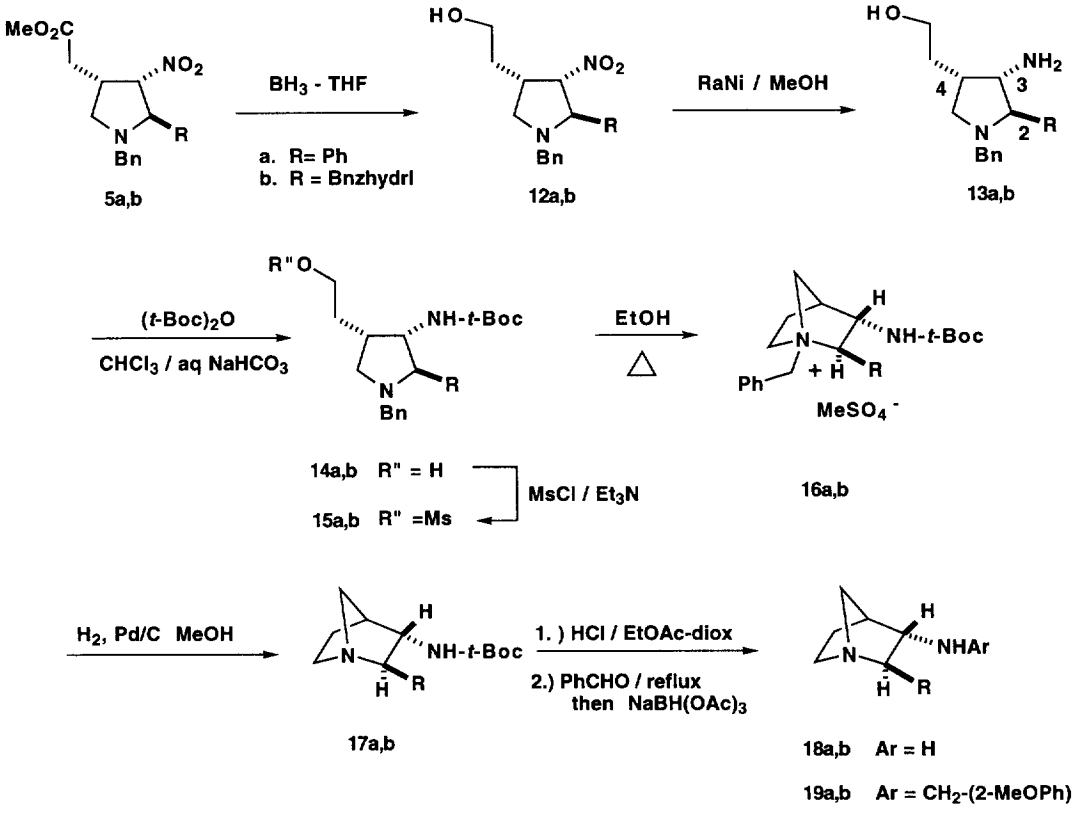
The primary amine residue in **11**, once deprotected, was functionalized through standard reductive amination conditions. Removal of the *t*-Boc protecting group from **11a,b** (HCl, EtOAc-dioxane reflux) afforded a hydrochloride of the amine in each case (**1a**: 60 %, **1b**: 100%). Condensation of the free base **1b** with aldehydes was conducted in toluene under Dean-Stark water separation (2-methoxybenzaldehyde, tol, 5 hrs) with formation of an imine. The intermediate was reduced with sodium triacetoxyborohydride (DCE, 16 hrs) to afford **2b** in 50 % yield[12]. In a similar manner, **1b** was condensed with 2-methoxy,4,5-dimethylbenzaldehyde to afford **2b-1** in 52 % yield. A single crystal of this compound was grown from ether-methanol and an X-ray structure determination confirmed the depiction of **2b-1** as drawn[13]. Compound **2a**

was prepared by a similar sequence in 95 % yield. High field NMR data (nOe and COSY) was consistent with the structures **2**.

Formation of the trans Azanorbornane Series 19a, 19b (Scheme 2):

Formation of the *trans*-azanorbornane isomers required a key modification of the previous approach due to the C-3 / C-4 syn orientation of required intermediate **13** (Scheme **2**). The ester **5a,b** was reduced with borane-THF (reflux) to afford the alcohol **12** (**a**. 87%, **b**. 85%) and thus avoided the certain formation of a bicyclic lactam (the result of direct reduction of nitro-**5** by Raney nickel). With the carboxylate functionality safely disposed of, reduction of the nitro group of **12** was now (as before) accomplished by hydrogenation over Raney nickel (MeOH, 16 hrs) to afford **13** (**a**. 64 %,**b**. 91%) with the required 2,3-anti, 3,4-syn orientation. *Trans*-substituted azanorbornane **17** was formed under identical conditions to those described above for the 2,3-syn azanorbornane **2** (**17a**. 59 %, **17b**. 44 % overall yields) without interference from the *t*-Boc amine. Reductive amination under standard conditions provided **19** in good to moderate yields (**a**. 80 %, **b**. 35 %). High field NMR data (COSY) was consistent with the structures **19**.

Scheme 2



NK_1 Receptor Binding:

Data from *in vitro* receptor binding studies [4g] indicate that derivatives of racemic-**1b** potently displace [^{3}H]-substance P from the human NK_1 receptor. In an analogous fashion to the quinuclidine series [4c], compound **2b** binds at NK_1 receptors in human lymphoblast cells (IM-9) with a $K_i = 0.30 \pm 0.11$ nM and the related **2b-1** with a $K_i = 0.16 \pm 0.06$ nM. In the phenyl series, binding potency experiences a slight negative shift, as compounds **2a** and trans **19a** display reduced potency at the NK_1 receptor (**2a**; $K_i = 79 \pm 24$ nM **19a**; $K_i = 529 \pm 114$ nM respectively). Surprisingly, the trans substituted **19b** displays good binding activity (**19b**; $K_i = 14 \pm 3.5$ nM). The SAR surrounding the potent binding activity of **19b** is not well understood but could reside in the enhanced conformational flexibility of the benzhydryl moiety and the propensity of the appendages of **19b** to occupy the same receptor site as **2b**. Further studies in this area will be published in due course.

Experimental Procedures[14]:

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino] bicyclo[2.2.1]heptane (2b) and (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-[(2-methoxy-4,5-di methylphenyl) methyl amino]bicyclo[2.2.1]heptane (2b-1):

Preparation of methyl-4-phenylmethylamino-2-butene-1-carboxylate (**3**): A suspension of 100 g 50% KF / Celite in 1400 ml of acetonitrile was treated with 29.93 g (279.5 mmol) benzylamine and 56.4 g (558 mmol) triethylamine and the mixture was cooled to 0 - 5° C. The suspension was treated with 50 g (279.5 mmol) of methyl-4-bromocrotonate over 25 min and the ice bath was then removed. After the reaction mixture was stirred for approximately one hour and was judged complete by thin layer analysis (elution with 94/5/1; CH_2Cl_2-CH_3OH-NH_4OH), the suspension was filtered and the filtrate was evaporated. The residue was partitioned between 1 liter saturated aqueous bicarbonate and washed with 500 ml of ether (3X). The combined organics were washed once with aqueous bicarbonate and then saturated brine. The solution was dried and evaporated *in vacuo* to provide an oil (32.64 g 53.4 %) which was used directly without purification. ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.38 - 7.24 (m, 5H), 7.09 - 6.98 (dt, 1H, J = 15.7 Hz, J = 5.4Hz), 6.08 - 6.01 (dt, 1H, J = 15.7Hz, J = 1.8Hz), 3.82 (2H, s), 3.75 (3H,s), 3.45 - 3.42 (dd, 2H, J = 5.4Hz, J = 1.8Hz), 1.45 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) ∂ 166.8, 147.0, 139.8, 128.5, 128.1, 127.1, 121.2, 53.3, 51.5, 49.5; IR ($CHCl_3$) λ 1720, 1660 cm^{-1}; ms (m/e) 204 p-1.

Preparation of 3,3-diphenyl-1-nitroprop-1-ene (**4b**): 50 g (254.78 mmol) of diphenylacetaldehyde and 18.66 g (305.73 mmol) nitromethane was dissolved in 635 ml of dichloromethane. The stirred solution was treated with 35 g of 3Å molecular sieves followed by 11.64 g (76.43 mmol) 1,8-diazabicyclo[5.4.0]undec-7-ene and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was treated with 700 ml of 2N aqueous HCl. The organic layer was separated and washed with saturated brine solution, dried with sodium sulfate and evaporated *in vacuo*. The residue was treated with 600 ml of hexane and stirred overnight whereupon crystallization occurred. After filtration, a pale yellow solid was obtained 38.22 g (58%) (3,3-diphenyl-2-hydroxy-1-nitropropane) which was used directly in the following step. ^{1}H NMR ($CDCl_3$,

300 MHz) ∂ 7.43 - 7.20 (m, 10H), 5.12 (m, 1H), 4.39 (m, 2H), 3.99 (d, 1H), 2.38 (br.s, 1H) ppm); ^{13}C NMR ($CDCl_3$, 75 MHz) ∂ 140.0, 139.5, 129.3, 129.1, 128.5, 128.0, 127.6, 79.5, 71.2, 55.6 ppm; IR ($CHCl_3$) λ 3582, 1553, 1373 cm^{-1}; ms (m/e) 257.

A solution of 32.81 g (127.5 mmol) of the adduct prepared above in 650 ml of dichloromethane was cooled to 0° C and was treated with 17.53 g (153 mmol) of methanesulfonyl chloride. The resultant solution was treated immediately with a second solution of 25.81gm (255 mmol) of triethylamine in 250 ml methylene chloride over a period of 25 min. The reaction was stirred for 1 hour and then quenched into ether and saturated brine solution. The organic layer was dried and evaporated *in vacuo* to afford 33 g (quant) of a dark oil (**4b**) which was used without purification. ^1H NMR ($CDCl_3$, 250 MHz) ∂ 7.78 - 7.70 (dd, 1H, J = 13.2Hz, J = 7.2Hz), 7.39 - 7.16 (m, 10 H), 6.83 - 6.77 (dd, 1H, J = 13.2Hz, J = 1.5Hz), 5.0 - 4.95 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 143.8, 141.2, 139.8, 129.0, 128.4, 127.6, 50.1 ppm.

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-nitro-4-carbomethoxymethyl-pyrrolidine (**5b**): A solution of the nitroolefin **4b** (5.11 g, 21.36 mmol) and 5.11 g (24.9 mmol) of previously prepared methyl-4-phenylmethylamino-2-butene-1-carboxylate (**3**) in 400 ml methanol was stirred at room temperature for 16 hr. Almost immediate precipitation was evident and by the end of the reaction time a thick slurry was formed. The reaction mixture was filtered directly to afford 4.94 g (52 %) of the desired **5b**. ^1H NMR ($CDCl_3$, 250 MHz) ∂ 7.42 - 7.04 (m, 15 H), 4.89 - 4.86 (d, 1H, J = 6.7Hz), 4.31 - 4.28 (d, 1H, J = 9.1Hz), 4.04 - 4.01 (d, 1H, J = 9.2Hz), 3.61 (s, 3H), 3.47 (br.s, 2H), 3.05 - 2.99 (dd, 1H, J = 8.8Hz, J = 6.3Hz), 2.80 - 2.73 (m, 1H), 2.50 - 2.41 (dd, 1H, J = 11.7Hz, J = 8.9Hz), 2.25 - 2.22 (d, 2H, J = 7.3Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) ∂ 171.3, 141.5, 141.4, 139.1, 129.0, 128.9, 128.7, 128.6, 128.3, 128.1, 127.1, 127.0, 92.7, 72.1, 60.7, 57.2, 56.7, 51.9, 38.2, 31.8 ppm; IR ($CHCl_3$) λ 1735, 1545, 1359 cm^{-1}; ms (FAB) 445 (p+1), 277, 231.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-nitro-4-carbomethoxymethyl pyrrolidine (**6b**): A solution of 264 mg (0.59 mmol) of the pyrrolidine **5b** in 150 ml of THF and 50 ml of methanol was treated with 1.63 ml (1.63 mmol) of 1M potassium t-butoxide in THF. The reaction mixture was heated to reflux for 30 min. The solution was cooled to room temperature and quenched with a 7 ml methanol solution containing 288 mg (2.82 mmol) trimethylacetic acid. The solution was stirred for 5 min and was then diluted with 125 ml of saturated aqueous bicarbonate solution and 400 ml of water to dissolve the precipitate that formed. The aqueous mixture was extracted with methylene chloride (5 X 70 ml) and the combined organic phase was washed with 200 ml of saturated brine solution. The organic solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10 % ethyl acetate in hexane. The fractions containing the more polar material were combined and evaporated to afford 195 mg (75%) of the desired (3RS)nitropyrrolidine **6b**. ^1H NMR ($CDCl_3$, 300 MHz) ∂ 7.48 - 6.98 (m, 15 H), 4.87 - 4.83 (t, 1H, J = 6.9Hz), 4.37 - 4.34 (d, 1H, J = 10.2Hz), 4.23 - 4.16 (dd, 1H, J = 10.1Hz, J = 7.2Hz), 3.61 (s, 3H), 3.48 - 3.44 (d, 1H, J = 12.9Hz), 3.25 - 3.07 (m, 3H), 2.53 - 2.37 (m, 2H), 2.21 - 2.14 (t, 1H, J = 9.8Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) ∂ 171.2, 142.0, 141.3, 139.1, 128.8, 128.6, 128.5, 128.5, 128.2, 127.9, 127.1, 127.0, 126.9, 92.6, 68.9, 58.3, 57.1, 52.2, 51.8, 40.3, 35.7, 31.9 ppm; ms (FAB) 445 (p^{+1}).

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-amino-4-carbomethoxymethyl pyrrolidine: A solution of 164 mg (0.37 mmol) of compound (**6b**) prepared above was dissolved in 4 ml of

THF and 50 ml of methanol and was treated with 650 mg of water washed RaNi (pH 7) stored under ethanol. The mixture was placed in a Parr pressure bottle and placed under 50 psi hydrogen for a period of approximately 4.5 hours. The reaction mixture was purged with nitrogen and then filtered. The filtrate was evaporated *in vacuo* and the residue (150 mg) was used directly in the next step. ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.53 - 7.04 (m, 15 H), 4.24 - 4.21 (d, 1H, J = 9.1Hz), 3.63 - 3.57 (m, obs, 1H), 3.61 (s, 3H), 3.33 - 3.28 (d, 1H, J = 12.6Hz), 3.14 - 3.07 (dt, 2H, J = 6.7Hz), 2.85 - 2.80 (d, 1H, J = 12.7Hz), 2.85 - 2.47 (dd, 1H, J = 15.3Hz, J = 6.0Hz), 2.30 - 2.12 (m, 2H), 1.91 - 1.84 (dd, 1H, J = 9.6Hz, J = 8.8Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz) ∂ 173.0, 143.8, 143.5, 139.5, 128.9, 128.9, 128.6, 128.5, 128.1, 128.0, 127.9, 126.7, 126.5, 126.3, 70.1, 61.0, 59.8, 58.1, 53.4, 51.6, 41.6, 37.2 ppm; IR ($CHCl_3$) λ 3678, 1732, 1185 cm^{-1} ; ms (FAB) 415 (p^{+1}), 247, 167.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-amino-4-(2-hydroxyethyl)pyrrolidine (**7b**): A solution of lithium aluminum hydride was prepared by dilution of 0.72 ml of 1M reagent in THF with 11 ml of anhydrous THF. The solution was cooled to 0° C and was treated with 150 mg (0.36 mmol) of the material from the previous step in 5 ml THF. The reaction mixture was stirred for 20 min at 0° C. The reaction was quenched by the sequential addition of 28 µl water, 28 µl 15% aqueous sodium hydroxide and 86 µl water. The resultant precipitate was granulated for 15 min and the slurry was filtered through Celite. The residue after evaporation was chromatographed on silica gel eluting with CH_2Cl_2, CH_3OH, NH_4OH (97: 2: 1) to afford 93 mg of the desired **7b** (67 %). ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.53 - 6.99 (m, 15 H), 4.13 - 4.10 (d, 1H, J = 9.0Hz), 3.68 - 3.59 (m, 2H), 3.52 - 3.42 (dt, 1H, J = 11.4Hz), 3.28 - 3.21 (t, 1H, J = 9.0Hz), 3.15 - 3.11 (d, 1H, J = 12.4Hz), 2.89 - 2.84 (dd, 1H, J = 9.0Hz, J = 5.9Hz), 2.82 - 2.77 (d, 1H, J = 12.3Hz), 1.93 - 1.86 (dd, 1H, J = 11.0Hz, J = 9.2Hz), 1.82 - 1.39 (m, 3H)ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) ∂ 143.6, 142.9, 139.4, 129.6, 129.0, 128.7, 128.4, 127.9, 126.6, 126.6, 126.5, 70.5, 62.1, 61.7, 60.2, 58.8, 54.3, 46.1, 35.9 ppm; IR ($CHCl_3$) λ 3001, 1601, 1189 cm^{-1}.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-(1,1-dimethylethoxycarbonyl amido)-4-(2-hydroxyethyl)pyrrolidine (**8b**): A solution of 10 gm (25.87 mmol) **7b** in 130 ml chloroform and 130 ml water was treated with 2.17 g (25.87 mmol) sodium bicarbonate and 5.65 g (25.87 mmol) di-*tert*-butyldicarbonate. The reaction mixture was heated under reflux for 90 min and then allowed to cool to room temperature. The organic layer was separated and washed with brine. The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was crystallized from hexanes. There was obtained 11.24 g of **8b** (89.3%). This material was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.58 (d, 2H, J = 7.3Hz), 7.36 - 7.09 (m, 13H), 4.78 (d, 1H, J = 9.6Hz), 4.25 (d, 1H, J = 7.8Hz), 3.92 - 3.83 (m, 1H), 3.70 (t, 1H, J = 7.4Hz), 3.68-3.49 (m, 2H), 3.42 (d, 1H, J = 12.6Hz), 3.07 (br.s, 1H), 2.81 (d, 1H, J = 12.6Hz), 2.55 (br.s, 1H), 1.84 (br.s, 2H), 1.70 - 1.55 (m, 1H), 1.52 - 1.40 (m, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.6, 143.4, 143.2, 139.6, 129.1, 128.6, 128.5, 128.1, 128.0, 126.8, 126.6, 126.2, 79.3, 68.2, 61.2, 61.1, 58.8, 57.8, 53.7, 41.2, 35.6, 28.4 ppm; IR (neat) λ 3400, 2980, 1680, 1530 cm^{-1}; ms (FAB) 487 p+1, 431 (p-*t*-Bu).

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-(1,1-dimethylethoxycarbonylamido) bicyclo[2.2.1]-heptane (**11b**): A solution of 12.3 gm (25.3 mmol) of **8b** in 150 ml of methylene chloride was treated with 24.87 gm (246.2 mmol) triethylamine and the reaction was cooled to 0° C. The solution was treated with 17.78 gm (155.2 mmol) methanesulfonyl chloride dropwise over 10 min. After the addition was

complete, a precipitate was formed. Thin layer analysis (94:5:1; CH_2Cl_2:MeOH:NH_4OH) indicated the reaction was complete 10 min after the addition was complete. The crude mesylate (**9b**) was processed by dilution of the reaction mixture with 300 ml of saturated aqueous bicarbonate. The organic phase was washed with aqueous brine and then was dried and evaporated. The residue was taken up in 250 ml of ethanol and the resulting solution was heated under reflux for 16 hrs.

The reaction mixture was allowed to cool to room temperature and then transferred to a 500 ml Parr bottle. The solution was treated with 6 g of 10 % palladium on carbon and placed under 47 psi hydrogen pressure for a period of 1 hr. At this point the reaction mixture was filtered and fresh catalysis (7.4 gm) was placed together with the reaction mixture into a Parr bottle and further hydrogenated for 2 hrs. The reaction mixture was filtered and the filtrate was treated with 7 gm of fresh catalyst and hydrogenated overnight under 45 psi hydrogen gas. The reaction mixture was filtered through celite and the filtrate was evaporated *in vacuo*. The residue was partioned between saturated aqueous bicarbonate solution and methylene chloride. The organic phase was treated with saturated brine, dried and evaporated *in vacuo*. The residue was slurried in hexane to afford a white solid which amounted to 2.0 gm after filtration. Catalyst from the hydrogenations were slurried in methanol and water (5:3) for a period of 1 hr. The mixture was filtered through celite and the methanol was removed *in vacuo*. The aqueous phase was washed with methylene chloride, dried with sodium sulfate and evaporated. The residue was taken up in methanol (600 ml) and treated with 7.5 gm of 10 % palladium on carbon. The mixture was hydrogenated under 45 psi hydrogen for 2 hrs and was filtered through celite and then evaporated *in vacuo*. The residue was partioned between 500 ml of saturated aqueous bicarbonate solution and methylene chloride (3 X 125 ml). The organic phase was washed with 300 ml of saturated aqueous brine solution, dried and evaporated. The residue was slurried in 200 ml of hexane to afford a white solid amounting to 3.05 gm. The total yield of the desired **11b** was 5.05 gm (52 %). ^{1}H NMR ($CDCl_3$, 250.1 MHz) δ 7.35 - 7.03 (m, 10 H), 4.55 (br.d, 1H), 3.85 (obsc. m, 1H), 3.72 (m, 2H), 2.75 (m, 1H), 2.51 (br.d, 2H), 2.42 (d, 1H), 2.23 (d, 1H), 1.65 (m,1H), 1.25 (s, 9H) ppm; IR ($CHCl_3$) λ 3449, 2951, 1710, 1483, 1367, 1155 cm^{-1}; ms (FAB) 379 (p+1) 323 (p-t-Bu).

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-aminobicyclo[2.2.1]heptanedihydro chloride (**1b**): A solution of **11b** (2.79 gm, 7.37 mmol) in 125 ml of dioxane was treated with 250 ml of ethyl acetate saturated with HCl gas. The reaction mixture was heated to 50° C whereupon a precipitate began to form. The mixture was heated for 2 hrs and then allowed to cool to room temperature. The mixture was filtered and the solids were washed with ether. There was obtained 2.6 gm (100%) of the desired **1b** as the dihydrochloride salt. This material was converted to the free base for analysis. ^{1}H NMR ($CDCl_3$, 250.1 MHz) δ 7.40 - 7.09 (m, 10H), 4.15 (d, 1H, J = 12.1Hz), 3.49 (dd, 1H, J = 12.1Hz, J = 6.2Hz), 3.12 (d, 1H, J = 6.2Hz), 3.05 (d, 1H, J = 9.8Hz), 2.73 (dt, 1H, J = 11.4Hz, J = 6.0Hz), 2.54 - 2.44 (m, 1H), 2.25 (d, 1H, J = 4.8Hz), 2.19 (d, 1H, J = 9.8Hz), 1.69 - 1.56 (m, 1H), 1.22 - 1.09 (m, 1H), 1.2 - 0.8 (br.s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 145.6, 144.3, 128.9, 128.5, 127.7, 127.4, 126.3, 125.9, 73.0, 57.7, 55.8, 54.6, 51.1, 46.1, 27.3 ppm; IR ($CHCl_3$) λ 3360, 2941, 1595, 1449 cm^{-1}; ms (m/e) 278 p+.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl) methylamino]bicyclo[2.2.1]heptane (**2b-1**): The dihydrochloride **1b** (388 mg, 1.1 mmol) from the previous step was partioned between 12 % aqueous sodium hydroxide and methylene chloride. The organic phase was washed with brine solution, dried over sodium sulfate and evaporated *in vacuo* to afford 304 mg (1.09 mmol)

of the corresponding free base. This material was dissolved in toluene (170 ml) and was treated with 197 mg (1.2 mmol) of 2-methoxy-4,5-dimethylbenzaldehyde. The reaction mixture was heated under reflux over a Dean-Stark trap for 24 hrs. Analysis of the NMR spectrum from a small reaction aliquot indicated product formation was complete. The solution was evaporated *in vacuo* to provide the imine as a crude oil which was used directly in the next step without purification.

The crude imine from above was taken into 100 ml of dichloroethane and treated with 347 mg (1.6 mmol) of sodium triacetoxyborohydride. The mixture was stirred overnight (16 hrs). Thin layer analysis (CH_2Cl_2: MeOH: NH_4OH; 94:5:1) indicated the reaction was complete. Reaction quenching with 100 ml of saturated aqueous bicarbonte solution was followed by dilution with methylene chloride, extraction and drying. The organic phase was evaporated *in vacuo* to afford 310 mg of an oil. The dihydrochloride salt was formed after dissolution of the free base in ether and treatment with saturated HCl gas also in ether. The crude salt was obtained by direct evaporation of this reaction mixture. The residue was taken up in methanol (3 ml), filtered and treated with ether until the cloud point. The mixture was stirred overnight whereupon crystallization occurred. The resulting solid (**2b-1**) was isolated in 52 % overall yield (284 mg).^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.34 - 7.06 (m, 10H), 6.53 (s, 1H), 6.43 (s, 1H), 4.22 - 4.18 (d, 1H, J = 12.1Hz), 3.65 - 3.36 (dd, 2H, J = 13.4 Hz), 3.54 (s, 3H), 3.53 - 3.45 (dd, 1H, J = 12.3 Hz, J = 6.9 Hz), 3.09 - 3.06 (d, 1H, J = 9.7 Hz), 2.79 - 2.66 (m, 3H), 2.48 - 2.39 (m, 1H), 2.23 (s, 3H), 2.18 (s, 1H), 2.14 (s, 3H), 1.69 - 1.57 (m, 1H), 1.13 - 1.03 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.5, 145.9, 143.9, 135.7, 130.6, 128.9, 128.4, 127.7, 127.6, 127.4, 126.2, 125.8, 125.0, 111.6, 72.1, 63.7, 56.1, 55.3, 54.8, 50.8, 46.8, 41.4, 26.9, 19.9, 18.6 ppm; HRMS cal'c for $C_{29}H_{34}N_2O$ 426.2663 found 426.26491.

Anal Calc'd for $C_{29}H_{34}N_2O \cdot 2HCl \cdot H_2O$ C; 67.30, H; 7.40, N; 5.41 found C; 66.96, H;7.16, N; 5.18.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-diphenylmethyl-3-(2-methoxyphenylmethyl)aminobicyclo [2.2.1]hep-tane (**2b**):. The azanorbornane dihydrochloride **1b** (381 mg, 1.09 mmol) was partioned between 12 % aqueous sodium hydroxide and methylene chloride. The organic phase was washed with brine solution, dried over sodium sulfate and evaporated *in vacuo* to afford 303 mg (1.09 mmol) of the corresponding free base. This material was dissolved in toluene (50 ml) and was treated with 162 mg (1.19 mmol) of 2-methoxybenzaldehyde. The reaction mixture was heated under reflux over a Dean-Stark trap for 24 hrs. Analysis of the NMR spectrum from a small reaction aliquot indicated product formation was complete. The solution was evaporated *in vacuo* to provide the imine as a crude oil which was used directly in the next step without purification.

The crude imine from above was taken into 100 ml of dichloroethane and treated with 347 mg (1.6 mmol) of sodium triacetoxyborohydride. The mixture was stirred overnight (16 hrs). Thin layer analysis (CH_2Cl_2: MeOH: NH_4OH; 97:2:1) indicated the reaction was complete. Reaction quenching with 100 ml of saturated aqueous bicarbonate solution was followed by dilution with methylene chloride, extraction and drying. The organic phase was evaporated *in vacuo* to afford 256 mg of an oil. The residue was chromatographed on silica gel using CH_2Cl_2:CH_3OH:NH_4OH (98:1:1 followed by 97:2:1) to afford 219 mg (50 %) of the desired **2b**. The dihydrochloride salt was formed after dissolution of the free base in ether and treatment with saturated HCl gas also in ether. The crude salt was obtained by direct evaporation of this reaction mixture. The residue was taken up in methanol (3 ml), filtered and treated with ether until the cloud point. The mixture was stirred overnight whereupon crystallization occurred. A white solid (260 mg) was

isolated. ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.31 - 7.05 (m, 12H), 6.83 - 6.70 (m, 2H), 4.21 - 4.17 (d, 1H, J = 12.1Hz), 3.71 - 3.67 (d, 1H, J = 13.7Hz), 3.55 (s, 3H), 3.54 - 3.45 (m, obs, 1H), 3.45 - 3.39 (d, 1H, J = 13.7Hz), 3.09 - 3.05 (d, 1H, J = 9.8Hz), 2.74 - 2.64 (m, 3H), 2.47 - 2.43 (m, 1H), 2.18 - 2.15 (d, 1H, J = 9.9Hz), 1.68 - 1.50 (m, 1H), 1.09 - 1.04 (m, 1H)ppm; ^{13}C NMR ($CDCl_3$, 62.9) ∂ 157.3, 129.3, 128.9, 128.4, 127.8, 127.7, 127.3, 126.2, 125.8, 119.9, 109.8, 72.0, 63.6, 56.1, 55.1, 54.8, 50.8, 47.2, 41.4, 26.9 ppm; IR (KBr) λ 3320, 2950, 1600, 1500,1460 cm^{-1}; ms (m/e) 399 (p^{+1}), 231, 121; HRMS cal'c for $C_{27}H_{30}N_2O$ 398.2351 found 398.23632.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-phenyl-3-(2-methoxyphenylmethyl)amino-bicyclo[2.2.1] heptane (2a):

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-phenyl-3-nitro-4-carbomethoxymethylpyrrolidine (**5a**): A solution of nitrostyrene (3.09 g, 20.7 mmol) and 5.00 g (24.5 mmol) of previously prepared methyl-4-phenylmethylamino-2-butenoate (**3**) in 250 ml methanol was stirred at room temperature for 16 hr. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel with 9/1 hexane ethyl acetate. There was obtained 7.4 g (100 %) of **5a** as a single isomer. ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.5 - 7.23 (m, 10 H), 5.02 - 4.97 (dd, 1H, J = 8.4Hz, J = 4.5Hz), 4.32 - 4.31 (d, 1H, J = 4.5Hz), 3.93 - 3.88 (d, 1H J = 13.1Hz), 3.65 (s, 3H), 3.43 - 3.37 (d, 1H, J = 13.1Hz), 3.29 - 3.23 (t, 1H, J = 6.8Hz), 3.17 - 3.07 (m, 1H), 2.57 - 2.50 (t, 1H, J = 9.5Hz), 2.43 - 2.41 (d, 2H, J = 7.4Hz)ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) ∂ 171.4, 139.8, 128.9, 128.6, 128.4, 128.3, 127.3, 127.2, 95.2, 73.0, 57.4, 56.5, 51.9, 37.6, 32.1ppm; IR ($CHCl_3$) λ 1737, 1546, 1376 cm^{-1}; ms (m/e) 353 (p-1), 308, 234, 91.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-phenyl-3-nitro-4-carbomethoxymethyl-pyrrolidine (**6a**): A solution of 780 mg (2.2 mmol) of the previous product was taken up in 10 ml of ether and treated with 100 mg (0.66 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The reaction mixture was seeded or scratched to induce crystallization and after 2 hrs a white solid was filtered and dried to afford 482 mg of the desired **6a**. The mother liquor was allowed to stir for 16 hours whereupon an additional 46 mg was obtained (total yield 68%). ^{1}H NMR ($CDCl_3$, 250 MHz) ∂ 7.47 - 7.25 (m, 10 H), 5.09 - 5.03 (dd, 1H, J = 8.5Hz, J = 5.2Hz), 4.02 - 3.98 (d, 1H, J = 8.5Hz), 3.93 - 3.88 (d, 1H, J = 13.3Hz), 3.65 (s, 3H), 3.52 - 3.41(m, 2H), 3.09 - 3.03 (d, 1 H, J = 13.3Hz), 2.55 - 2.50 (m, 2H), 2.09 - 2.02 (m, 1H)ppm; IR ($CHCl_3$) λ 1737, 1553, 1377 cm^{-1}; ms (m/e) 354 (p^+), 308 (p-46), 234, 91.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-phenyl-3-amino-4-(2-hydroxyethyl)-pyrrolidine (**7a**): A solution of 464 mg (1.31 mmol) of **6a** was dissolved in 50 ml of methanol and was treated with 1.2 g of water washed RaNi (pH 7; stored under ethanol). The mixture was placed in a Parr pressure bottle and placed under 50 psi hydrogen for a period of approximately 4 hours. The reaction mixture was purged with nitrogen and then filtered. The filtrate was evaporated *in vacuo* and the residue (426 mg) was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) ∂ 7.40 - 7.21 (m, 10 H), 3.92 - 3.87 (d, 1H, J = 13.3Hz), 3.63 (s,3H), 3.61 - 3.59 (d, 1H, J = 7.1Hz), 3.32 - 3.27 (dd, 1H, J = 9.3Hz, J = 7.1Hz), 3.11 - 3.06 (m, obs, 1H), 3.06 - 3.02 (d, 1H, J = 13.3Hz), 2.68 - 2.60 (dd, 1H, J = 15.6Hz, J= 6.0Hz), 2.43 - 2.35 (dd, 1H, J = 15.6Hz, J = 8.6Hz), 2.32 - 2.11 (m, 1H), 1.93 - 1.87 (t, 1H, J = 9.3Hz)ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) ∂ 173.5, 139.4, 139.5, 128.8, 128.6, 128.5, 128.2, 127.4, 126.9, 73.3, 60.7, 58.4, 57.8, 51.6, 43.1, 37.6 ppm; IR ($CHCl_3$) λ 1733 cm^{-1}; ms (m/e) 324 (p^+), 307, 233, 118, 91.

A solution of lithium aluminum hydride was prepared by dilution of 3.57 ml of 1M reagent in THF with 45 ml of anhydrous THF. The solution was cooled to 0° C and was treated with 579 mg (1.78 mmol) of material derived from several runs of previous step in 8 ml THF. The reaction mixture was stirred for 60 min at 0° C. The reaction was quenched by the sequential addition of 135 µl water, 135 µl 15% aqueous sodium hydroxide and 405 µl water. The resultant precipitate was granulated for 15 min and the slurry was filtered through celite. The residue after evaporation was chromatographed on silica gel eluting with CH_2Cl_2:CH_3OH:NH_4OH (97: 2: 1) to afford 380 mg of the desired **7a** (72 %). ^1H NMR ($CDCl_3$, 300 MHz) ∂ 7.43 - 7.24 (m, 10H), 3.89 - 3.84 (d, 1H, J = 13.1Hz), 3.76 - 3.56 (m, 3H), 3.25 - 3.22 (d, 1H, J = 8.3Hz), 3.18 - 3.13 (d, 1H, J = 13.2Hz), 3.08 - 3.02 (dd, 1H, J = 8.8Hz, J = 6.0Hz), 2.28 (s, 1H), 2.06 - 1.98 (dd, 1H, J = 10.7Hz, J = 8.9Hz), 1.83 - 1.56 (m, 3H)ppm; ms (m/e) 296 (p^+), 279, 209, 188, 118, 91.

Preparation of (2RS,3RS,4SR)-1N-phenylmethyl-2-phenyl-3-(1,1-dimethylethoxycarbonyl amido)-4-(2-hydroxy-ethyl)pyrrolidine (**8a**): A solution of 495 mg (1.67 mmol) **7a** in 10 ml chloroform and 10 ml water was treated with 140 mg (1.67 mmol) sodium bicarbonate and 364 mg (1.67 mmol) di-tert-butyldicarbonate. The reaction mixture was heated under reflux for 90 min and then allowed to cool to room temperature. The organic layer was separated and washed with brine. The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was crystallized from hexanes. There was obtained 515 mg (78%) of **8a**. This material was used directly in the next step. ^1H NMR ($CDCl_3$, 250.1 MHz) δ 7.48 - 7.21 (m, 10H), 4.55 (br.d, 1H), 4.05 (m, 1H), 3.85 (dd, 2H), 3.68 (m, 2H), 3.29 (t, 1H), 3.08 (d, 1H), 2.1 - 1.6 (m, 5H), 1.25 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.5, 138.1, 128.6, 128.5, 128.3, 128.2, 127.3, 126.9, 79.2, 71.1, 61.2, 58.9, 58.4, 58.1, 42.1, 36.1, 28.1, 27.4 ppm; IR (neat) λ 3440, 3300, 1720, 1500, 1460, 1370 cm^{-1} ; ms (FAB) 397 p+1.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-phenyl-3-(1,1-dimethylethoxycarbonylamido)bicyclo [2.2.1]heptane (**11a**): A solution of 200 mg (0.5 mmol) of **8a** in 5 ml of methylene chloride was treated with 485 mg (4.79 mmol) triethylamine and the reaction was cooled to 0° C. The solution was treated with 347 mg (3.03 mmol) methanesulfonyl chloride dropwise over 10 min. After the addition was complete, a precipitate was formed. Thin layer analysis (94:5:1; CH_2Cl_2:MeOH:NH_4OH) indicated the reaction was complete 10 min after the addition was complete. The crude mesylate **9a** was processed by dilution of the reaction mixture with 20 ml of saturated aqueous bicarbonate. The organic phase was washed with aqueous brine and was dried and evaporated. The residue was taken up in 20 ml of ethanol and the resulting solution was heated under reflux for 16 hrs. The reaction mixture was allowed to cool to room temperature and then evaporated *in vacuo*. The residue **10a** was dissolved in 10 ml saturated bicarbonate solution, 6 ml water and 15 ml of methanol and placed in a 250 ml Parr bottle. The solution was treated with 60 mg of 10 % palladium on carbon and placed under 47 psi hydrogen pressure for a period of 1 hr. At this point the reaction mixture was filtered and fresh catalysis (100mg) was placed together with the reaction mixture into a Parr bottle and further hydrogenated for 16 hrs. The reaction mixture was filtered through celite and the filtrate was evaporated *in vacuo*. The residue was partitioned between saturated aqueous bicarbonate solution and methylene chloride. The organic phase was treated with saturated brine, dried and evaporated *in vacuo*. The residue was slurried in hexane to afford a white solid (**11a**) which amounted to 70 mg (49 %) after filtration. ^1H NMR ($CDCl_3$, 250.1 MHz) δ 7.29 (m, 5H), 3.96 (br.d, 3H), 2.87 (m, 1H), 2.59 (m, 3H), 2.41 (d, 1H), 1.73 (m, 1H), 1.31 (s, 9H) ppm; ^{13}C NMR

($CDCl_3$, 75.5 MHz) δ 155.2, 137.6, 128.3, 127.0, 126.6, 79.2, 71.8, 57.5, 56.6, 54.9, 43.9, 28.3, 27.8 ppm; IR (neat) λ 3200, 2960, 1690, 1540, 1480, 1440, 1170 cm^{-1} ; ms (FAB) 289 p+1.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-phenyl-3-aminobicyclo[2.2.1]heptane (**1a**): A solution of the **11a** (64 mg, 0.22 mmol) in 5 ml of dioxane was treated with 5 ml of ethyl acetate saturated with HCl gas. The reaction mixture was heated to 60° C whereupon a precipitate began to form. The mixture was heated for 2 hrs and then allowed to cool to room temperature. The mixture was filtered and the solids were washed with ether. The solids were taken up in 10 ml of 20 % sodium hydroxide and extracted with 3X 10 ml of methylene chloride. The organic layer was washed with saturated brine, dried and evaporated to an oil **1a**; 25 mg (60 %) ^1H NMR ($CDCl_3$, 250.1 MHz) δ 7.28 (m, 5H), 3.85 (d, 1H), 3.15, (d, 1H), 2.88 (m, 2H), 2.60 (m, 1H), 2.41 (d, 2H), 1.75 (m, 1H), 1.30 (br.s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.7, 128.3, 126.9, 126.3, 73.3, 58.7, 56.1, 55.3, 45.5, 27.8 ppm; ms (FAB) 189 p+1.

Preparation of (1RS,2RS,3RS,4SR)-1-aza-2-phenyl-3-(2-methoxyphenylmethyl)aminobicyclo[2.2.1] heptane (**2a**): The azanorbornane **1a** (40 mg, 0.212 mmol) from the previous step was dissolved in toluene (60 ml) and was treated with 29 mg (0.21 mmol) of 2-methoxybenzaldehyde. The reaction mixture was heated under reflux over a Dean-Stark trap for 48 hrs. Analysis of the NMR spectrum from a small reaction aliquot indicated product formation was complete. The solution was evaporated *in vacuo* to provide the imine as a crude oil which was used directly in the next step without purification.

The crude imine from above was taken into 20 ml of dichloroethane and treated with 63 mg (0.297 mmol) of sodium triacetoxyborohydride. The mixture was stirred overnight (16 hrs). Thin layer analysis (CH_2Cl_2:MeOH:NH_4OH; 94:5:1) indicated the reaction was complete. Reaction quenching with 20 ml of saturated aqueous bicarbonte solution was followed by dilution with methylene chloride, extraction and drying. The organic phase was evaporated *in vacuo* to afford 62 mg (95%) of an oil **2a**. ^1H NMR ($CDCl_3$, 250 MHz) ∂ 7.34 - 7.17 (m, 6H), 7.08 - 7.05 (dd, 1H, J = 7.3Hz, J = 1.7Hz), 6.91 - 6.81 (m, 2H), 3.86 - 3.80 (d, 1H, J = 14.0Hz), 3.76 - 3.73 (d, obs, 1H), 3.73 (s, 3H), 3.59 - 3.53 (d, 1H, J = 14.0Hz), 3.10 - 3.06 (d, 1H, J = 9.5Hz), 2.94 - 2.80 (m, obs, 1H), 2.83 - 2.81 (d, 1H, J = 6.4Hz), 2.63 - 2.61 (d, 1H, J = 4.5Hz), 2.62 - 2.55 (m, obs, 1H),2.44 - 2.40 (d, 1H, J = 9.5Hz), 1.78 - 1.67 (m, 1H), 1.2 - 1.11 (m, 1H)ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) ∂ 157.5, 138.7, 129.7, 128.0, 127.0, 126.3, 120.1, 109.9, 71.9, 64.0, 57.0, 55.9, 54.9, 48.5, 41.6, 39.5, 26.9ppm; ms (m/e) 308 (p^+), 252, 187, 121, 91; HRMS calc'd for $C_{20}H_{24}N_2O$ = 308.1883 found = 308.1889.

This material was dissolved in ether and treated with HCl - ether to provide a white solid which was recrystallized in methanol - ether to afford 60 mg of the dihydrochloride salt, mp = 218° C.

Experimental procedure for the preparation of (1RS,2RS,3SR,4SR)-1-aza-2-phenyl-3-(2-methoxy-phenyl)methylaminobicyclo[2.2.1]heptane (19a):

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-phenyl-3-nitro-4-(2-hydroxyethyl)-pyrrolidine (**12a**): To a flame dried flask containing 15.5 gm (44 mmol) of (2RS,3SR,4SR)-1N-phenylmethyl-2-phenyl-3-nitro-4-carbomethoxymethylpyrrolidine (**5a**) in 750 ml of dry THF at 0° C was added 1M borane - THF complex (175 ml, 175 mmol). During the addition, gas evolution was noted and the reaction mixture became cloudy. The resultant mixture was allowed to warm to room temperature where it remained for 3 hrs and was then heated to reflux for 1 hr. Thin layer analysis (30% ethyl acetate in hexane) indicated the reaction had proceeded to a mixture of borane complexes. The reaction mixture was allowed to cool to room temperature

and was then cooled to - 20^{O} C. The mixture was treated with 15 ml of water (gas evolution!) followed by 90 ml of of 6N HCl. Finally the mixture was warmed to room temperature and then reheated to reflux for 2.5 hr. After cooling, the purple reaction mixture was quenched with a solution of 0.6 gm sodium hydroxide in 125 ml water. The THF was evaporated and the mixture was partioned between 100 ml brine and 400 ml of ethyl acetate. The organic phase was washed with brine, dried and evaporated *in vacuo* to afford a crude oil. Chromatography on silica gel (gradient 5% then 10 % followed by 30% ethyl acetate in hexanes) afforded 12.5 gm (87%) of the nitro-alcohol **12a**. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.49 - 7.25 (m, 10H), 4.95 - 4.90 (dd, 1H, J = 8.4Hz, J = 4.3Hz), 4.35 - 4.34 (d, 1H, J = 4.2Hz), 3.93 - 3.88 (d, 1H, J = 13Hz), 3.71 - 3.54 (m, 2H), 3.46 - 3.41(d, 1H, J = 13Hz), 3.26 - 3.20 (dd, 1H, J = 8.7Hz, J = 6.3Hz), 2.95 - 2.77 (m, 1H), 2.59 - 2.51 (dd, 1H, J = 11.0Hz, J = 8.8Hz), 1.8 - 1.50 (m, 2H) ppm; IR ($CHCl_3$) λ 3640, 3580, 2980, 1525, 1420, 1220 cm^{-1}; ms (m/e) 326 (p+), 279, 234; HRMS calc'd for $C_{19}H_{22}N_2O_3$: 326.1631; found: 326.1626.

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-phenyl-3-amino-4-(2-hydroxyethyl)-pyrrolidine (**13a**): A solution of **12a** (13.0 gm, 40 mmol) in 125 ml of methanol was treated with 1.7 g of Raney nickel which had been previously washed with water until the washings were neutral. The mixture was hydrogenated under 48 psi hydrogen pressure for 16 hrs. At this point the reaction mixture was filtered through celite and the filtrate was evaporated *in vacuo* to an oil (13.2 gm). The residue was taken up in ethyl acetate and treated with hexane to effect crystallization (yield: 5.29 gm in two crops). Chromatography of the residue from evaporation of the filtrate (silica gel; elution with CH_2Cl_2:MeOH:NH_4OH; 96:3:1) afforded 2.29 gm for a total of 7.58 gm (64 %) of the desired **13a**. ^{1} H NMR ($CDCl_3$, 250 MHz) δ 7.49 - 7.23 (m, 10 H), 3.82 - 3.74 (m, 2H), 3.62 - 3.52 (m, 1H), 3.31 - 3.20 (m, 2H), 3.03 - 2.96 (m, 2H), 2.61 - 2.47 (m,1H), 2.05 - 2.00 (t, 1H, J = 9.6 Hz), 1.93 - 1.75 (m, 1H), 1.63 - 1.51 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) ∂ 141.2, 138.8, 128.8, 128.7, 128.2, 127.8, 127.7, 126.9, 79.6, 62.0, 61.0, 58.9, 57.8, 39.7, 31.1 ppm; IR ($CHCl_3$) λ 3340, 3200, 2920, 2800, 1620, 1500, 1460, 1060 cm^{-1}; ms (SIMS) 297 (p +1).

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-phenyl-3-[(1,1-dimethylethoxy)carbonylamino]-4-(2-hydroxyethyl)-pyrrolidine (**14a**): A solution of 6.7 gm (22.6 mmol) of **13a** was taken up in 380 ml of chloroform and a solution of 2.85 gm (34 mmol) sodium bicarbonate in 180 ml water. To the rapidly stirred mixture was added 5.43 gm (24.8 mmol) of di-*tert*-butyldicarbonate and the resulting mixture was heated to reflux for 5 hrs. The reaction was diluted with methylene chloride and water. The organic phase was separated, dried and evaporated to afford a crude oil 9.2 gm (quant) which was used directly in the next step. An analytical sample was prepared by chromatographed on silica gel (elution with CH_2Cl_2:MeOH:NH_4OH; 97:3:1). ^{1} H NMR ($CDCl_3$, 250 MHz) δ 7.51 - 7.21 (m, 10H), 4.67 - 4.63 (br. d, 1H, J = 9.1Hz), 4.14 - 4.05 (dd, 1H, J = 16.0Hz, J = 9.0Hz), 3.87 - 3.82 (d, 1H, J = 13.2Hz), 3.63 - 3.50 (m, 2H), 3.29 - 3.05 (m, 3H), 2.60 - 2.42 (m, 1H), 2.06 - 1.99 (t, 1H, J = 9.8 Hz), 1.8 - 1.6 (1H, m), 1.55 - 1.30 (obsc. m, 1H), 1.40 (s, 9H)ppm; ^{13}C NMR (DMSO, 75.5 MHz) ∂ 155.5, 142.1, 139.0, 128.4, 128.3, 128.2, 127.4, 127.2, 126.8, 77.6, 73.2, 60.6, 59.4, 58.3, 57.3, 35.7, 32.0, 28.3 ppm; IR (KBr) λ 3380, 2940, 2800, 1680, 1520, 1460, 1170 cm^{-1}; ms (FAB) 397 (p +1), 341, 305.

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-phenyl-3-[(1,1-dimethylethoxy)carbonylamino]bicyclo [2.2.1]heptane (**17a**): A solution of **14a** (2.05 g, 5.7 mmol) in 300 ml methylene chloride was treated with 6.8 ml(49 mmol) triethylamine and the solution was cooled to 0^{0} C before the addition of methanesulfonylchloride (2.4 ml, 31 mmol). After addition was complete, the reaction mixture was allowed to warm to room

temperature over 1 hr and was then quenched with 10 ml of saturated aqueous bicarbonate solution. The mixture was treated with 100 ml water and separated. The organic phase was washed with brine solution and then dried and evaporated. The residue **15a** was taken directly into 300 ml of methanol and heated to reflux for 1 hr. At this point, the reaction mixture was allowed to cool to room temperature and evaporated *in vacuo*. The residue was crystallized from methanol - ether to provide 1.51 gm of quarternary ammonium salt **16a**. A portion of this material was used directly in the next phase of this reaction.

The product **16a** (460 mg, 0.97 mmol) was dissolved in 25 ml methanol, 1 ml water and 60 mg sodium bicarbonate, placed in a 250 ml Parr bottle, treated with 60 mg of 10% palladium on carbon and hydrogenated under 48 psi hydrogen gas for 3.5 hr. The catalyst was removed via filtration, 150 mg catalyst was charged and hydrogenation was continued for a period of 4 hrs. (occassionally a third catalyst recharge was necessary) The catalyst was removed via filtration through celite and the filtrate was evaporated *in vacuo*. The residue was partitioned between methylene chloride and saturated aqueous bicarbonate solution. The organic phase was dried and evaporated *in vacuo* to afford an oil. Chromatography on silica gel (elution with CH_2Cl_2: MeOH: NH_4OH; 97:3:1) afforded 160 mg (59%) of the more polar material which was the desired **17a**. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.48 - 7.18 (m, 5H), 5.05 - 4.95 (br.s, 1H), 4.22 - 4.11 (br.s, 1H), 3.18 - 3.17 (br.d, 1H), 3.11 - 2.99 (dt, 1H, J = 12.3Hz, J = 5.7Hz), 2.91 - 2.82 (br.s, 1H), 2.77 - 2.68 (dd, 2H, J = 16.7Hz, J = 7.8Hz), 2.46 - 2.41 (d, 1H, J = 9.9Hz), 1.78 - 1.45 (obsc. m, 2H), 1.47 (s, 9H) ppm; IR (KBr) λ 3300, 2960, 2880, 1660, 1530, 1360, 1170 cm^{-1}; ms (m/e) 288 (p+), 232, 215, 187, 132; HRMS calc'd for $C_{17}H_{24}N_2O_2$: 288.1832; found: 288.18498.

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-phenyl-3-aminobicyclo[2.2.1]heptane (**18a**): Compound **17a** (380 mg, 1.31 mmol) was dissolved in 20 ml of ethyl acetate and was added to a cold (0° C) solution of HCl (g) in 30 ml of ethyl acetate. After 2 hrs, the reaction mixture was evaporated *in vacuo* and the powdery residue was dissolved in 10 ml of water and adjusted to pH 12 with sodium hydroxide solution. The aqueous mixture was extracted with methylene chloride and the organic phase was dried and evaporated. The residue was chromatographed on silica gel (elution with CH_2Cl_2:MeOH:NH_4OH; 95:4:1) to afford 190 mg (76 %) of the desired **18a**. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.5 - 7.1 (m, 5H), 3.39 (m, 1H), 3.05 (m, 2H), 2.70 (m, 2H), 2.50 (m, 1H), 2.41 (m, 1H), 1.90 (m, 1H), 1.50 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 144.0, 128.3, 128.2, 126.2, 125.5, 125.4, 75.4, 62.8, 58.1, 55.4, 44.9, 20.6 ppm; IR (KBr) λ 3360, 3280, 2960, 2880, 1600, 1490, 1440, 1000 cm^{-1}; HRMS calc'd for $C_{12}H_{16}N_2$: 188.1310; found: 188.13039.

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-phenyl-3-[(2-methoxyphenylmethyl)amino]bicyclo[2.2.1] heptane (**19a**): The compound (166 mg, 0.88 mmol) from the previous step was dissolved in 30 ml of dichloroethane along with with 131 mg (0.97 mmol) of 2-methoxybenzaldehyde and 260 mg (1.23 mmol) sodium triacetoxyborohydride. The mixture was stirred for 16 hrs at room temperature and was then partioned between methylene chloride and 2 N HCl. The aqueous phase was adjusted to pH 13 and repeatedly extracted with methylene chloride. The combined organics were dried and evaporated. The residue was chromatographed on silica gel (elution with CH_2Cl_2:MeOH:NH_4OH; 97:2:1) to afford 214 mg (80 %) of the desired **19a**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, 2H), 7.29 - 7.20 (m, 5H), 6.92 (dd, 2H), 3.89 (s, 3H), 3.78 (dd, 2H), 3.22 (m, 1H), 3.15 (m, 1H), 3.02 (m, 1H), 2.78 (m, 1H), 2.70 (m, 2H), 2.45 (br.d, 1H), 2.18 (br.s, 1H), 2.0 (m, 1H), 1.49 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 157.7, 144.3, 129.9, 128.4,

128.3, 126.2, 125.7, 120.5, 110.3, 73.8, 68.5, 57.9, 55.4, 55.2, 49.4, 41.3, 21.0 ppm; IR (KBr) λ 2960, 2880, 1600, 1490, 1460, 1240, 1050, 1030 cm^{-1}; HRMS calc'd for $C_{20}H_{25}N_2O$: 309.1961; found: 309.19953.

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-diphenylmethyl-3-(2-methoxyphenylmethyl)aminobicyclo [2.2.1]heptane (19b):

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-nitro-4-(2-hydroxyethyl)-pyrrolidine (**12b**): To a flame dried flask containing 1.0 gm (2.25 mmol) of (2RS,3SR,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-nitro-4-carbomethoxymethylpyrrolidine (**5b**) in 30 ml of dry THF at 0° C was added 1 M borane - THF complex (9 ml, 9 mmol). During the addition, gas evolution was noted and the reaction mixture became cloudy. The resultant mixture was allowed to warm to room temperature where it remained for 1 hr followed by heating to reflux for 16 hrs. Thin layer analysis (50% ethyl acetate in hexane) indicated starting material had been consummed. The reaction mixture was allowed to cool to room temperature and was then cooled to - 20° C. The mixture was treated with 0.96 ml of water (gas evolution!) followed by 5.8 ml of of 6N HCl. Finally the mixture was warmed to room temperature and then reheated to reflux for 2 hr. After cooling, the reaction mixture was neutralized to pH 7 with aqueous sodium hydroxide solution. The THF was evaporated and the mixture was partioned between 10 ml brine and 26 ml of ethyl acetate. The organic phase was washed with brine, dried and evaporated *in vacuo* to afford a crude oil. Chromatography on silica gel (50% ethyl acetate in hexanes) afforded 798 mg (85%) of the desired nitro-alcohol **12b**. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.43 - 7.03 (m, 15H), 4.8 (d, 1H), 4.29 (d, 1H), 4.00 (d, 1H), 3.62 - 3.40 (m, 3H), 3.02 (m, 1H), 2.51 (m, 2H), 1.56 (m, 2H), 1.32 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.7, 141.6, 139.3, 129.0, 128.9, 128.8, 128.6, 128.2, 128.1, 127.1, 126.9, 126.9, 93.7, 72.4, 60.7, 60.6, 57.4, 57.2, 39.1, 30.3, 14.2 ppm; IR (KBr) λ 3600, 3580, 3480, 3060, 3030, 2920, 2840, 2820, 1540, 1490, 1450 cm^{-1}; ms (m/e) 417 (p+1).

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-amino-4-(2-hydroxyethyl)-pyrrolidine (**13b**): A solution of **12b** (550 mg, 1.3 mmol) in 167 ml of methanol was treated with 1.16 g of Raney nickel which had been previously washed with water until the washings were neutral. The mixture was hydrogenated under 50 psi hydrogen pressure for 24 hrs. At this point the reaction mixture was filtered through celite and the filtrate was evaporated *in vacuo* to an oil. Chromatography of the residue (silica gel; elution with CH_2Cl_2:MeOH:NH_4OH; 98.5:0.5:1) afforded 466 mg (91 %) of the desired **13b**. ^1H NMR ($CDCl_3$, 250 MHz) δ 7.5 - 7.0 (m, 15H), 4.02 (d, 1H), 3.7 - 3.43 (m, 4H), 3.3 (d, 1H), 3.2 (br.s, 1H), 3.12 (d, 1H), 2.90 (br.s, 1H), 2.21 (m, 2H), 2.0 (br.s, 3H), 1.62 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) ∂ 143.1, 143.0, 139.6, 129.1, 128.8, 128.6, 128.5, 128.4, 128.0, 126.7, 126.5, 79.0, 61.8, 61.3, 57.7, 57.3, 57.1, 40.0, 29.8 ppm; IR (KBr) λ 3350, 3290, 3060, 3020, 2920, 2800, 1600, 1500, 1450 cm^{-1}; ms (FAB) 387 (p +1).

Preparation of (2RS,3SR,4SR)-1N-phenylmethyl-2-diphenylmethyl-3-(1,1-dimethylethoxycarbonyl amido)-4-(2-hydroxyethyl)pyrrolidine (**14b**): A solution of 410 mg (1.06 mmol) **13b** in 85 ml chloroform and 19 ml water was treated with 130 mg (1.5 mmol) sodium bicarbonate and 250 mg (1.16 mmol) di-*tert*-butyldicarbonate. The reaction mixture was heated under reflux for 5 hrs and then allowed to cool to room temperature. The organic layer was separated and washed with brine. The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was crystallized from hexanes. There was obtained 450 mg of **14b** (87%). This material was used directly in the next step. ^1H NMR ($CDCl_3$, 250.1 MHz) δ 7.45 - 7.0 (m, 15H), 4.5 (br.d, 1H), 4.1 (br.t, 2H), 3.63 - 3.3 (m, 4H), 3.19 (d, 1H), 2.9 (br.dd, 1H), 2.03 (m, 1H), 1.9 (m,

1H), 1.49 (s, 9H), 1.31 (br.s, 3H) ppm; IR (KBr) λ 3260, 2920, 1680, 1600, 1490, 1450, 1380, 1360 cm^{-1}; ms (FAB) 487 (p+1).

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-diphenylmethyl-3-(1,1-dimethylethoxycarbonylamido) bicyclo[2.2.1]heptane (**17b**): A solution of 370 mg (0.76 mmol) of **14b** in 10 ml of methylene chloride was treated with 1.13 ml (8.1 mmol) triethylamine and the reaction was cooled to 0° C. The solution was treated with 0.315 ml (4.1 mmol) methanesulfonyl chloride dropwise over 10 min. After the addition was complete, a precipitate was formed. Thin layer analysis (91:8:1; CH_2Cl_2:MeOH:NH_4OH) indicated the reaction was complete 20 min after the addition. The crude mesylate was processed by dilution of the reaction mixture with 25 ml of saturated aqueous bicarbonate. The organic phase was washed with aqueous brine and then was dried and evaporated. The residue was taken up in 15 ml of ethanol and the resulting solution was heated under reflux for 3 hrs. Upon cooling, the reaction mixture afforded the quaternary salt **16b** (0.26 gm) which was isolated by filtration.

The solid was transferred to a 250 ml Parr bottle and dissolved in 10 ml water 13.8 ml of saturated bicarbonate solution and 40 ml of methanol. The solution was treated with 52 mg of 10 % palladium on carbon and placed under 45 psi hydrogen pressure for a period of 4 hrs. At this point the reaction mixture was filtered and fresh catalysis (50 mg) was placed together with the reaction mixture into a Parr bottle and further hydrogenated for 2 hrs. The reaction mixture was filtered through celite and the methanol was evaporated to leave an aqueous solution. The celite was washed with 50 ml of saturated bicarbonate solution and 100 ml of methylene chloride. The combined washings and aqueous filtrate were separated and the aqueous was washed twice more with methylene chloride (50 ml each). The organic phase was treated with saturated brine, dried and evaporated *in vacuo*. The residue was triturated in ether to afford a white solid **17b** which amounted to 129 mg (45%; in two crops). ^1H NMR ($CDCl_3$, 250.1 MHz) δ 7.35 - 7.03 (m, 10 H), 4.15 (br.s 1H), 3.83 (d, 1H), 3.69 (br.s, 1H), 2.91 (m, 1H), 2.65 (br.s, 4H), 2.32 (d, 1H), 1.5 (m), 1.25 (s, 9H) ppm; IR (KBr) λ 3260, 1700, 1380, 1160 cm^{-1}; ms (FAB) 379 (p+1) 323 (p-*t*-Bu).

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-diphenylmethyl-3-aminobicyclo[2.2.1]heptane (**18b**): A solution of **17b** (99 mg, 0.26 mmol) in 8 ml of dioxane was treated with 8 ml of ethyl acetate saturated with HCl gas. The reaction mixture was heated under reflux for 5hrs whereupon a precipitate formed. The mixture was allowed to cool to room temperature before it was filtered and the solids were washed with ether. The solids were partitioned between 15 ml of 20 % sodium hydroxide solution and 25 ml methylene chloride. The aqueous layer was extracted three times. The organic phase was washed with brine and dried and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with CH_2Cl_2:MeOH:NH_4OH (93:6:1). There was obtained 66 mg (91 %) of **18b**. ^1H NMR ($CDCl_3$, 300.1 MHz) δ 7.3 - 7.02 (m, 10H), 3.68 (d, 1H), 3.02 (t, 1H), 2.85 (m, 1H), 2.7 (m, 3H), 2.35 (t, 1H), 2.25 (d, 1H), 1.82 (m, 1H), 1.35 (m, 1H), 0.7 (br. s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 143.6, 142.4, 128.7, 128.7, 128.5, 128.0, 126.6, 126.2, 75.8, 59.1, 57.0, 56.4, 55.8, 44.1, 20.5 ppm; IR (KBr) λ 3360, 3290,3020, 2950, 1580, 1480, 1440 cm^{-1}; ms (FAB) 279 (p+1).

Preparation of (1RS,2RS,3SR,4SR)-1-aza-2-diphenylmethyl-3-(2-methoxyphenylmethyl)aminobicyclo [2.2.1]-heptane (**19b**): The azanorbornane **18b** (22 mg, 0.079 mmol) from the previous step was dissolved in toluene (30 ml) and was treated with 12 mg (0.087 mmol) of 2-methoxybenzaldehyde. The reaction mixture was heated under reflux over a Dean-Stark trap for 60 hrs. Analysis of the NMR spectrum from a small

reaction aliquot indicated product formation was complete. The solution was evaporated *in vacuo* to provide the imine as a crude oil which was used directly in the next step without purification.

The crude imine from above was taken into 20 ml of dichloroethane and treated with 25 mg (0.12 mmol) of sodium triacetoxyborohydride. The mixture was stirred for 24 hrs. Thin layer analysis (CH_2Cl_2: MeOH:NH_4OH; 93:6:1) indicated the reaction was complete. Reaction quenching with 10 ml of saturated aqueous bicarbonate solution was followed by extraction with methylene chloride and drying. The organic phase was evaporated *in vacuo* to afford an oil. The oil was chromatographed on silica gel using CH_2Cl_2: CH_3OH:NH_4OH (98:1:1 followed by 97:2:1) to afford 11 mg (35 %) of **19b**. The dihydrochloride salt was formed after dissolution of the free base in ether and treatment with saturated HCl gas also in ether. The crude salt was obtained by direct evaporation of this reaction mixture. The residue was taken up in methanol (3 ml), filtered and treated with ether until the cloud point. The mixture was stirred overnight whereupon crystallization occurred. Data for the free base **19b**: ^{1}H NMR ($CDCl_3$, 300.1 MHz) ∂ 7.3 - 7.09 (m, 11H), 6.85 (m, 3H), 3.7 (m, 1H), 3.68 (s, 3H), 3.49 (d, 1H), 3.21 (d, 1H), 2.82 (m, 5H), 2.65 (m, 1H), 2.35 (d, 1H), 1.98 (m, 1H), 1.4 (m, 1H) ppm;^{13}C NMR ($CDCl_3$, 75.5) ∂ 157.3, 143.8, 142.3, 129.4, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8, 126.5, 126.1, 120.2, 110.1, 73.8, 64.8, 56.7, 56.3, 55.7, 55.1, 47.8, 40.9, 20.6 ppm; IR (KBr) λ 2930, 1600, 1500 cm^{-1}; ms m/e 399 (p+1), 231; HRMS cal'c for $C_{27}H_{30}N_2O$ 398.2351 found 398.23410.

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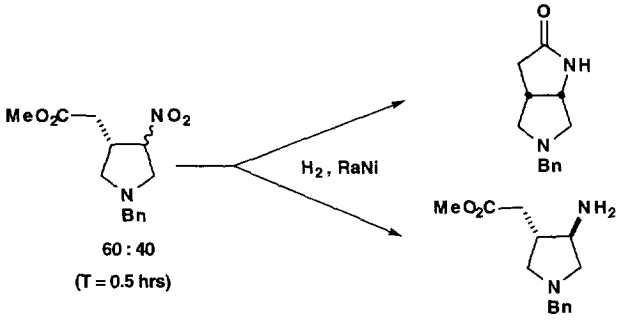

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