1-6-1997

Synthetic Strategies for the Construction of Enantiomeric Azanoradamantanes

Daniel Becker
_Loyola University Chicago_, dbecke3@luc.edu

Roger Nosal

Daniel L. Zabrowski

Daniel Flynn

Author Manuscript
This is a pre-publication author manuscript of the final, published article.

Recommended Citation

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License.

© 1997 Elsevier
Synthetic Strategies for the Construction of Enantiomeric Azanoradamantanes

Daniel P. Becker,* Roger Nosal, Daniel L. Zabrowski, and Daniel L. Flynn*

Department of Medicinal Chemistry, Searle Research & Development, Skokie, Illinois 60077

Abstract: The amino azanoradamantane hexahydro-2,5b-methano-1H-3aS,3aa,6aa-cyclopenta-[c]pyrrole-4a-amine 1 and the corresponding enantiomer ent-1 have been prepared along with benzamide derivatives SC-52491 and SC-52490, respectively, which are of pharmaceutical interest. The key meso-azabicyclo[3.3.0] intermediate 3 was prepared via three separate routes: a [3+2] cycloaddition route, a radical cyclization/ionic cyclization route, and a reductive Pauson-Khand route.

INTRODUCTION

The construction of rigid heterocyclic systems is a topic which continues to attract considerable attention in synthetic organic chemistry. Heterocycles find applications in many areas of research, including a prominent role in medicinal chemistry for the preparation of rigid pharmacophores tailored to complement targeted receptor sites. Amine-containing heterocycles (azacycles) have found widespread application in the discovery of specific agonists and antagonists to many monoamine receptors and also in the discovery of specific antagonists of important bioactive peptides. The preparation of individual enantiomers is of critical importance in cases where asymmetry exists.

We have been interested in the construction of rigid azacyclic systems and their employment for the preparation of agonists and/or antagonists to the serotonin 5-HT3 and 5-HT4 receptor subtypes. Our initial efforts led us to utilize the azaadamantane I, for which we reported the synthesis of the syn- and anti-isomers of the 4-amino substituted derivatives (I, R = NH2). Our continued research led us to consider the utilization of the novel azanoradamantane II3a which is formally derived from I by the removal of the C-10 bridging methylene. The ring system of azanoradamantane II had never been previously described prior to our initial communication.

The isomeric azanoradamantane III, which has been prepared by Speckcamp and is present as a substructural unit of the natural product alkaloid aristofruticosane, is derived formally from I by the removal of the C-10 methylene group.
of the C-8 bridging methylene. The azanoradamantanes II and III occupy somewhat smaller volumes than the parent azaadamantane I. The bridgehead nitrogens of I-III are all more basic\(^7\) than comparable acyclic tertiary amines, and the azanoradamantanes II and III are somewhat more basic than I because of additional ring strain. Thus the tricyclic amines I-III comprise a family of conformationally restricted, basic amines. When substituted derivatives of these azacycles are incorporated into molecules containing other pharmacophoric groups, they provide analogs with a range of vector orientations of the bridgehead nitrogen lone pair, and also offer scaffolds with discreet spatial differences in the carbon framework.

We have previously communicated the utilization of the azanoradamantane II (R = NH\(_2\), anti substitution with respect to the bridgehead nitrogen) in the preparation of the benzamide derivative SC-52491.\(^3a\) SC-52491 exhibits potent 5-HT\(_4\) agonism\(^8\) and 5-HT\(_3\) antagonism without interaction at other monoamine receptors. In contrast, the distomer SC-52490 is 70-fold less potent as an agonist at 5-HT\(_4\) receptors and is 3-fold less potent at the 5-HT\(_3\) receptor, underlining the need for synthesis and biological evaluation of individual enantiomers. Herein we wish to describe the details of our successful synthetic approaches to both enantiomers of azanoradamantane II (R = NH\(_2\), anti) and their subsequent utilization to provide the benzamide SC-52491 and its distomer SC-52490.

**RESULTS AND DISCUSSION**

For the synthesis of molecules incorporating the 4-aminoazanoradamantane II, such as SC-52491, we required the aminoazanoradamantane I. Our retrosynthetic analysis led us to consider the closure of the methanobridge as the penultimate step in the synthesis of I. This suggested the highly functionalized 3-azabicyclo[3.3.0]octane 2 as a key intermediate. Importantly, 2 contains the four contiguous asymmetric centers with the correct relative configurations necessary to produce I. Molecular models suggested that the endo-oriented methylene appendage (CH\(_2\)-LG) was spatially positioned in an optimal manner for displacement of the leaving group (LG) by the ring nitrogen. We then envisioned the meso-azabicyclo[3.3.0]octane olefin 3 as a desirable intermediate for allowing introduction of both the 4-\(exo\) amine functionality and the 5-\(endo\) hydroxymethyl function (LG = OH) present in 2. The immediate task at hand was to efficiently produce the olefin 3. In the course of our research we devised three fundamentally different routes for the synthesis of azabicyclo[3.3.0]octane olefin 3.
Our first approach to the synthesis of azabicyclo[3.3.0]octane 3 employed Trost's palladium-catalyzed [3+2] annulation utilizing 2-trimethylsilylmethyl-2-propen-1-yl acetate. Several attempts to access a bicyclic system via direct annulation of an existing olefin-containing ring were not successful. For example, reaction of 2-trimethylsilylmethyl-2-propen-1-yl acetate with maleimide, N-benzylmaleimide, maleic anhydride, and pyrrolinone did not yield any of the desired methylenecyclopentane-annulated products. Employment of dimethyl maleate proceeded reliably as reported by Trost in good yield (89%) to give the diester as a mixture of cis and predominantly trans isomers. Saponification of 5, either as a mixture of cis and trans isomers, or as the chromatographically purified trans isomer, gave a crystalline trans-diacid (mp 178-179 °C). Isomerization from trans- to cis-substitution and incorporation of the nitrogen was accomplished as follows. Treatment of the diacid with acetic anhydride at 100 °C gave a mixture of trans-substituted (oligomeric) anhydrides which was pyrolyzed under Kugelrohr conditions to afford analytically pure cis-fused cyclic anhydride (bp 112-114 °C at 1 mm Hg) in low yield (28%). It was much more efficient to heat the diacid to 200 °C in acetic anhydride to directly form the crude cyclic anhydride (rather than the oligomeric mixed anhydrides) and then distill it in a Kugelrohr apparatus. The anhydride prepared in this fashion was not as pure, but a superior mass-balance was obtained which led to higher through-put. Reaction of the crude distilled anhydride with ammonia gave the pure crystalline cis-substituted amide ammonium carboxylate (±)-8 (mp 152-153 °C dec) which was cyclized with acetyl chloride to give the imide 9. This acetyl chloride-mediated cyclization proceeded very smoothly up to a two-gram scale, but on a larger scale (12 g), 20-30% of the exocyclic olefin isomerized to the internal position. This isomerization is presumably acid-catalyzed, although the presence of quinoline in the reaction mixture did not prevent the isomerization. Reduction of imide 9 with lithium aluminum hydride followed directly by protection with di-tert-butyl dicarbonate after Fieser workup gave the BOC-protected azabicyclo[3.3.0]octane 3 as an oil. This route was successful in providing initial quantities of 3 for further work leading to the azanoradamantane ring system II.
Although the [3+2] route was successful in providing the pivotal intermediate 3, the cost of 2-trimethylsilylmethyl-2-propen-1-yl acetate and the high cost palladium catalyst for the [3+2] cyclization in the initial step prompted us to examine other routes. We validated another successful approach to azabicyclo[3.3.0]octane 3 utilizing our tandem atom-transfer radical annulation/ionic cyclization protocol. Allylation of methyl phenylsulfonyl acetate 10 gave (±)-11, and the anion of (±)-11 was iodinated with N-iodosuccinimide to give the iodide (±)-12. Reaction of (±)-12 with BOC-allylamine under photolysis conditions in the presence of hexabutylditin gave an intermediate iodide species (±)-12A via an atom-transfer radical annulation which was converted in the same pot to the azabicycle 13 in an overall 51% yield by treatment with triethylamine. The methyl ester 13, which was a mixture of endo and exo isomers, was reduced with lithium borohydride to give the corresponding alcohol 14. Acetylation of 14 with acetyl chloride followed by a Julia elimination with sodium amalgam gave the desired azabicyclo[3.3.0]octane 3 in 96% yield.

Our need to prepare even larger (100-gram lots) of 3 prompted us to pursue yet another approach, particularly since we wanted to avoid the need to use sodium amalgam on a large scale as required for the Julia elimination in the previous route. The third route to azabicyclo[3.3.0]octane 3 employed our reductive
Pauson-Khand protocol\textsuperscript{15}  In this approach, which we have previously published,\textsuperscript{15b} the N-BOC-allylpropargylamine hexacarbonyldicobalt complex \textbf{16} was cyclized directly to the azabicyclo[3.3.0]octanone \textbf{17} in 78\% yield by adsorbing the complex onto silica gel (Smit-Caple dry-state adsorption conditions - DSAC\textsuperscript{16}) and heating under nitrogen at 70 °C for 3 hours. The ketone \textbf{17} tends to decompose on prolonged storage of several months, even in the freezer, so it is best to utilize this compound within several days of preparation. Wittig methylenation utilizing potassium tert-butoxide\textsuperscript{17} with methyltriphenylphosphonium bromide then afforded the azabicyclo[3.3.0]octane \textbf{3} in 82\% yield, as previously described.\textsuperscript{15b} This route afforded the advantage over the two other described routes as being very reproducible on a large scale. We have now performed this \textit{reductive} Pauson-Khand reaction reproducibly on a 1-mole scale (>200 grams).

\[
\begin{align*}
\text{BOCN} & \quad \text{Co}_2(\text{CO})_6 \quad \text{70°C, SiO}_2, \text{N}_2 \quad \text{BOCN} \\
\textbf{16} & \quad \text{78\%, Ref 15b} \quad \textbf{17} \\
\text{H} & \quad \text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^- \quad \text{t-BuOK} \\
& \quad \text{82\%, Ref 15b} \quad \textbf{3}
\end{align*}
\]

With efficient and complementary methods for the production of the azabicyclo[3.3.0]octane \textbf{3} in hand, we turned our attention to introduction of the ring functionality necessary to produce a synthetic equivalent to general structure \textbf{2}, and cyclization of \textbf{2} to afford the desired target azanoradamantane \textbf{1}. The allylic amination described by Sharpless\textsuperscript{18} and also by Kresze\textsuperscript{19} utilizing bis(p-toluenesulfonyl)sulfur diimide \textbf{18}\textsuperscript{20} is a powerful method of introducing allylic amine functionality via a tandem ene/2,3-sigmatropic rearrangement sequence. Sulfur diimide reagent \textbf{18}, which is more reactive than the more commonly encountered N,N'-bis(methoxycarbonyl)sulfur diimide,\textsuperscript{21} has previously been prepared in two steps from p-toluenesulfonamide by N-sulfinylation and isolation of the intermediate N-sulfinyl-p-toluenesulfonamide via distillation. This distillation is quite tedious, as the N-sulfinyl compound rapidly and vigorously decomposes if the temperature is too high.\textsuperscript{22} The second preparative step is a disproportionation and loss of SO\textsubscript{2} to afford the sulfur diimide. We now wish to report that the two steps from p-toluenesulfonamide proceed conveniently in one pot from p-toluenesulfonamide and thionyl chloride if a purge is maintained to remove liberated HCl and SO\textsubscript{2}, and if the appropriate temperature is maintained for distillative removal of the excess thionyl chloride. In this manner the disproportionation takes place directly to afford the diimide \textbf{18}, which may be isolated in excellent purity by direct crystallization (mp 121-127 °C). This protocol proceeds in 48\% yield on a large scale (230 g of \textbf{18} isolated) which compares very favorably with the two-step method, both in terms of yield and convenience. Treatment of \textbf{3} with sulfur diimide \textbf{18} and workup with potassium carbonate afforded the \textit{exo}-tosylamide (±)-\textbf{19}, as previously described.\textsuperscript{15b} It is essential that exocyclic olefin \textbf{3} is reasonably pure to avoid precipitous drops in the yield of this step. The stereochemistry of the tosylamide functionality was critical to the preparation of \textbf{1}, so the structure of (±)-\textbf{19} was determined by X-ray crystallography to verify the \textit{exo} stereochemistry.\textsuperscript{23, 24}
Hydroboration/oxidation of the exocyclic olefin of (±)-19 with thexyl borane gave the requisite endo-alcohol (±)-20 in 41% yield along with 44% of the isomeric exo-alcohol (±)-21.\textsuperscript{15b} We were hoping that production of the endo-alcohol would be preferred due to approach of the borane reagent from the exo-face, however the exo-face is partly blocked by the bulky tosylamide group. The net effect appears to be approximately equal access to both faces. We were able to salvage the exo-alcohol by an epimerization utilizing an oxidation/reduction protocol. Swern oxidation of exo-alcohol (±)-21 afforded the corresponding aldehyde which was reduced \textit{without delay} with sodium borohydride to give a 5:1 (endo:exo) mixture of alcohols from which the desired endo-alcohol was isolated in 67% yield. The preponderance of endo-alcohol from the epimerization apparently reflects the thermodynamic preference for endo-orientation of the intermediate aldehyde, due to the bulky tosylamide group occupying the exo face. It should be noted that immediate reduction of this sensitive aldehyde is critical to avoid base-catalyzed elimination of the tosylamide group.
Resolution of the endo-alcohol (±)-20 was performed by separation of the diastereomeric O-methylmandelate ester derivatives 22 and 23, since this particular derivative was found to give easily separable diastereomers by HPLC. The R-(−)-O-methylmandelic acid as purchased from Aldrich was found by chiral HPLC to be only 92.4% ee, so the ephedrine salt was crystallized as described in the literature to raise the enantiopurity to an acceptable level of 99.6% ee. The R-(−)-O-methylmandelate ester diastereomers were then prepared by the general procedure of Trost utilizing oxalyl chloride in DMF to form the acid chloride of the mandelic acid followed by addition of the alcohol (±)-20 in pyridine. A significant portion of the diastereomer 23 (mp 134.5-135.5 °C) could be crystallized directly from the diastereomeric mixture utilizing ethyl acetate as the solvent. Chromatography of the mother liquor then gave the other diastereomer...
22 (mp 48-52 °C, 44%) plus additional quantities of 23, totaling to 29%. Overlap fractions amounted to 10% of the theoretical yield, and some starting material 20 was recovered. The absolute configuration of the crystalline R-(-)-O-methylmandelate diastereomer 23 was determined by X-ray crystallography\textsuperscript{23} and is as shown. Saponification of the separated mandelate esters 22 and 23 afforded the resolved alcohols (-)-20 and (+)-20 in 95% yield and high enantiomeric purity (er = 99.85:0.15 by chiral HPLC; ee = 99.7%).

With the highly enantioenriched azabicyclic alcohols in hand, we were ready to perform the anticipated cyclization to the azanoradamantane ring system. Parallel tosylation of alcohols (-)-20 and (+)-20 afforded the enantiomeric tosylates (-)-24 and (+)-24, respectively. Direct deprotection of the BOC-amine with trifluoroacetic acid followed by exposure to Hunig's base resulted in facile ring closure to the azatricycle systems (+)-25 and (-)-25 in quantitative yield. This gratifying result confirms the predicted facility of this cyclization, as we had hoped. Reductive removal of the tosyl group under Birch conditions afforded the desired 4-aminoazanoradamantanes 1 and (ent)-1 in high yield.

![Chemical structures](image)

Coupling of the aminoazanoradamantanes 1 and (ent)-1 with benzoic acid derivative 26 proceeded cleanly with carbonyldiimidazole (CDI) to afford the benzamides (+)-27 and (-)-27. Deprotection of the acetamides with potassium hydroxide and treatment with methanolic HCl then afforded the azanoradamantane benzamide derivatives SC-52491 and SC-52490, respectively.

**SUMMARY**

Syntheses of both enantiomers of the amino-azanoradamantane amine 1 have been described. Three separate and complementary approaches to the key azaabicyclo[3.3.0]octane intermediate 3 were validated.
including a palladium-catalyzed [3+2] annulation approach, a tandem atom-transfer radical annulation/ionic cyclization approach, and a very short reductive Pauson-Khand approach. A late-stage resolution provided material of high enantiomeric purity for exceptionally facile ring closure to the enantiomeric azanoradamantanes (+)-25 and (-)-25 in quantitative yield. Both enantiomers of the azanoradamantane amine 1 have been used to generate a number of novel serotonergic agents, as described herein for the 4-amino-5-chloro-2-methoxybenzamide derivative SC-52491, which exhibits very potent affinity for both the serotonin 5-HT_{4} and 5-HT_{3} receptors. Detailed biochemical & pharmacological studies of SC-52491 and related azanoradamantane derivatives will be reported elsewhere.

**EXPERIMENTAL SECTION**

**General.** All reactions were performed under an atmosphere of argon. Chemicals were purchased from Aldrich Chemical Co. and used without further purification unless otherwise noted. Octacarbonyldicobalt was purchased from Alfa Products. Methyl triphenylphosphonium bromide was dried at 61 °C under high vacuum for 16 h immediately prior to use. THF was distilled from sodium benzophenone ketyl immediately prior to use. 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. ¹H NMR spectra were recorded at 300 MHz with TMS as an internal reference. Noise-decoupled and APT ¹³C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer, and for the reporting of IR data s=strong, m=medium, w=weak and sh=shoulder. DSC refers to differential scanning calorimetry. MIR refers to multiple internal reflectance infrared spectroscopy. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument.

**trans-4-Methylene-1,2-cyclopentanedicarboxylic acid (6)**

A suspension of trans-dimethyl ester 5 (1.48 g, 7.48 mmol, prepared by the method of Trost^{26}) and aqueous 2.6 N NaOH (11 mL) was heated under reflux for 1 h. The reaction was cooled and 37% HCl (2.5 mL) was added. After standing for 16 h at 0 °C the suspension was filtered to afford the trans-diacid 5 (1.13 g, 89%) as colorless crystals: mp 178-179 °C; IR (KBr) 3400 (m, sh), 3300-2800 (m, br), 1692 (s), 1430 (m) cm⁻¹; ¹H NMR (300 MHz, CD_{3}OD) δ 4.90 (2 H, s), 3.11 (2 H, m), 2.59 (2 H, dd, J = 16, 7 Hz), 2.37 (2 H, ddd, J = 16, 7, 2 Hz); ¹³C NMR (125 MHz, CD_{3}OD) δ 177.5, 149.2, 107.5, 48.2, 37.3. Anal calcd for C_{8}H_{10}O_{4}: C, 56.47; H, 5.92. Found: C, 56.08; H, 5.87.

**cis-Tetrahydro-5-methylene-1H-cyclopenta[c]furan-1,3(3aH)dione (7)**

A suspension of diacid 6 (689 mg, 4.1 mmol) in freshly distilled acetic anhydride (7 mL) was heated to 100 °C for 4 h. The acetic anhydride was then removed by vacuum distillation (20 Torr) to give an oil. ¹H NMR analysis of this material suggested the presence of a mixture of trans-substituted mixed anhydrides; no
desired product was detected. The oil was then pyrolyzed in a Kugelrohr apparatus at 1 mm Hg (pot temp = 170-175 °C) to give the bicyclic anhydride 7 (175 mg, 28%) as a colorless oil which crystallized: mp 50-51 °C; IR (KBr) 3400 (w), 1860 (m), 1834 (m), 1780 (s) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.02 (2 H, s), 3.52 (2 H, m), 2.9-2.7 (4 H, m). Anal calcd for C\(_8\)H\(_8\)O\(_3\): C, 63.15; H, 5.30. Found: C, 62.91; H, 5.43.

(±)-cis-4-Methylene-2-carboxyamidocyclopentane-1-carboxylic acid, ammonium salt [(±)-8]
A suspension of diacid 6 (20.0 g, 117 mmol) in freshly distilled acetic anhydride (1 L) was heated to 200 °C for 3 h. The acetic anhydride was then removed by vacuum distillation (20 Torr) to give an oil which was distilled twice in a Kugelrohr apparatus (bp 109-114 °C at 1 Torr) to give a pale yellow oil (14.6 g). \(^1\)H NMR of this material indicated the presence of bicyclic anhydride 7 (ca. 75% pure). This crude anhydride was then dissolved in CHCl\(_3\) and dry ammonia gas (distilled from Na) was bubbled into the solution with mechanical stirring for 2 h. The resulting suspension was stirred for an additional 1 h and then filtered to give the desired ammonium salt (±)-8 (11.6 g, 53%) as a colorless powder: mp 152-153 °C (dec); IR 3600-2700 (s), 1690 (m), 1655 (s), 1610 (s), 1545 (s) cm\(^{-1}\); \(^1\)H NMR (300 MHz, d\(_6\)-DMSO) \(\delta\) 7.33 (1 H, s), 6.60 (1 H, s) 5.03 (4 H, br s), 4.78 (2 H, s), 2.89 (2 H, m), 2.7-2.3 (4 H, m); \(^13\)C NMR (125 MHz, d\(_6\)-DMSO) \(\delta\) 175.2, 175.0, 150.5, 105.3, 47.3, 46.3, 36.2, 35.4. Anal calcd for C\(_8\)H\(_{14}\)N\(_2\)O\(_3\): C, 51.60; H, 7.58; N, 15.04. Found: C, 51.45; H, 7.51; N, 14.79.

cis-Tetrahydro-5-methylenecyclopenta[c]pyrrole-1,3(2H,3aH)dione [(±)-9]
A solution of ammonium salt (±)-8 (2.18 g, 11.7 mmol) in freshly distilled acetyl chloride (40 mL) was heated under reflux for 22 h. Concentration gave a dark oil which was redissolved in MeOH (10 mL) and treated with 10 mL of ammonia-saturated MeOH. After 3 h the solution was concentrated to a dark oil which was chromatographed on silica gel eluting with 1/99, then 2/98 EtOH/CH\(_2\)Cl\(_2\) to give the desired imide 9 (1.46 g, 83%) as a colorless solid. Recrystallization from CHCl\(_3\)/hexane gave 1.21 g: mp 135-137 °C; IR (MIR) 3232 (s), 1774 (w), 1751 (m), 1702 (s), 1352 (m), 1194 (m) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.95 (1 H, br s), 4.96 (2 H, s), 3.29 (2 H, m), 2.68 (4 H, m); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 179.8, 145.5, 109.8, 45.6, 36.0. MS calc for C\(_8\)H\(_9\)NO\(_2\) m/z 151, found 151. Anal calcd for C\(_8\)H\(_9\)NO\(_2\) C, 63.57; H, 6.00; N, 9.27. Found C, 63.60; H, 6.03; N, 9.12.

cis-1,1-Dimethylethylhexahydro-5-methylenecyclopenta[c]pyrrole-2(1H)-carboxylate (3) via the [3+2] cycloaddition route
To a 1 M solution of LAH in THF (11.8 mL, 11.8 mmol) was added a solution of imide 9 (1.19 g, 7.89 mmol) in dry THF (26 mL) dropwise at rt. After 1.5 h at rt, the reaction was heated under reflux for 2 h. The solution was then cooled to rt and a Fieser work-up\(^27\) was performed as follows. The reaction was quenched with the sequential addition of H\(_2\)O (0.45 mL, diluted with 3 mL THF), 15% NaOH (0.45 mL), and H\(_2\)O (1.4 mL). The resulting suspension was filtered through a fritted funnel and the colorless solid was rinsed with additional THF (11 X 10 mL). To the filtrate at rt was added di-tert-butyl dicarbonate (1.89 g, 8.7 mmol) and
the reaction was stirred at rt for 5 d. Concentration gave a residue which was chromatographed on silica gel eluting with EtOAc/hexane (5/95, then 10/90) to give 3 (1.34 g, 76%) as a colorless oil which solidified: mp 67-70 ºC. Anal. calcd for C_{13}H_{21}NO_{2}·0.1H_2O: C, 69.36; H, 9.49; N, 6.22. Found C, 69.03; H, 9.47; N, 6.20. Spectral data (¹H NMR, ¹³C NMR, IR, HRMS) were identical to that which was previously reported.¹⁵b

**But-3-en-1-carbomethoxy-1-yl-phenylsulfone [(±)-11]**

To a suspension of sodium hydride (20.1 g of a 60% oil dispersion which was washed with hexane, 503 mmol) in THF (1.3L) at 0 ºC was added via cannula a solution of methyl phenylsulfonyl acetate ¹⁰ (100 g, 457 mmol) in THF (250 mL) over 2h and then stirred for an additional 1 hour at 0 ºC. The resulting suspension was warmed to rt and treated rapidly with a solution of allyl bromide (42 mL, 480 mmol) in THF (150 mL). After stirring for 20 h, the mixture was poured into satd aq NH₄Cl (2.5 L) and extracted with Et₂O (3X 450 mL). The combined organic extracts were combined, dried over anhyd MgSO₄, and concentrated to provide the crude product (119 g) which was chromatographed on a Waters Prep 500 system eluting with a gradient of EtOAc/hexane (7:93 to 12:88) at a flow rate of 200 mL/min to afford the allylated acetate (±)-11 (93.5 g, 80.4%) as an oil: IR (MIR) 1736 (s), 1642 (w), 1446 (m), 1324 (m), 1309 (m), 1145 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (2H, d, J = 8.8 Hz), 7.71 (1H, t, J = 8.5 Hz), 7.60 (2H, t, J = 9.0 Hz), 5.67 (1H, m), 5.13 (2H, m), 4.02 (1H, dd, J = 11.0, 4.0 Hz), 3.68 (3H, s), 2.72 (2H, m); HRMS calcd for C_{12}H_{15}NO₄ 255.0691, obs 255.0692; Anal. calcd for C_{12}H_{14}O₄S: C, 56.68; H, 5.56. Found C, 56.37; H, 5.54.

**1-Iodo-but-3-en-1-carbomethoxy-1-yl-phenylsulfone [(±)-12]**

To a suspension of sodium hydride (5.4 g of a 60% dispersion which was washed with hexane, 135 mmol) in THF (400 mL) at rt was added a solution of sulfone (±)-11 (22.8 g, 89.6 mmol) in THF (110 mL) dropwise over 0.5 h. After stirring for an additional 0.5 h, the slurry was treated rapidly in the dark with a solution of N-iodosuccinimide (21.2 g, 89.6 mmol) in THF (250 mL). The resulting suspension was stirred for an additional 5 min, then concentrated and chromatographed directly in the dark on silica gel (550 g) eluting with Et₂O, then EtOAc to provide the labile iodosulfonyl acetate (±)-12 (34.2 g, 100%) as an orange oil which was used directly in the next step without purification.

**2-(1,1-Dimethylethyl) 5-methyl octahydro-5-(phenylsulfonyl)-3α,6α-cyclopenta[c]pyrrole-2,5-dicarboxylate 13**

To a solution of the freshly prepared iodide (±)-12 (33.5 g, 88.1 mmol) and N-BOC-allylamine (27.7 g, 176 mmol) in benzene (250 mL) at rt was added bis(tributyltin) (4.3 mL, 8.8 mmol). The clear homogeneous solution was exposed to light from a sun lamp (General Electric, 275 W, frosted, d = 8 cm) for 0.5 h after which time the light source was removed and triethylamine (120 mL, 810 mmol) was slowly added (exothermic) and the solution was heated under reflux for 14 h. The suspension was then concentrated under reduced pressure to give a brown oil. This material was combined with the crude product from another run starting with iodide (±)-12 (39.0 g, 103 mmol) and chromatographed on silica gel eluting with EtOAc/hexane
(1:2) to afford the azabicyclic amine 13 (39.9 g, 51.0%) as an oil: IR (MIR) 3386 (w, br), 1734 (s), 1689 (s), 1399 (m), 1308 (m), 1147 (m), 1127 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (2H, d, J = 7 Hz), 7.68 (1H, d, J = 7 Hz), 7.54 (2H, m), 3.68 (3H, s), 3.50-3.30 (4H, br m), 2.75-2.50 (4H, br m), 2.35-2.20 (2H, br m), 1.48 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ 167.5, 153.8, 136.0, 133.2, 128.4, 127.9, 79.0, 78.5, 52.1, 49.5, 48.7, 40.7, 40.4, 36.3, 35.1, 27.2; HRMS calcd for C₂₀H₂₈NO₆S 410.1637, obs 410.1617.

1,1-Dimethylethyl 5-(hydroxymethyl)octahydro-5-(phenylsulfonyl)-3α,6ααα-cyclopenta[c]-pyrrole-2-carboxylate 14
To a solution of sulfone methyl ester 13 (22.8 g, 55.7 mmol) in THF (400 mL) at rt was added LiCl (4.77 g, 111 mmol) followed by NaBH₄ (4.3 g, 111 mmol). The resulting slurry was added EtOH (300 mL) and the mixture was stirred for 16 h at rt. The mixture was then cooled to 0°C and the pH was adjusted to pH = 4 by the gradual addition of 10% aqueous citric acid. Concentration gave a slurry which was diluted with H₂O (800 mL) and extracted with CHCl₃ (3X). The combined extracts were dried over Na₂SO₄ and concentrated to give the desired alcohol 14 (21.3 g, 100%) as an oil which solidified. Recrystallization from Et₂O gave an analytical sample: mp 126-127 °C; IR (MIR) 3415 (m, br), 1669 (s), 1407 (s), 1297 (m), 1286 (m), 1133 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.91 (2H, m), 7.72 (1H, m), 7.60 (2H, m), 3.64 (2H, s), 3.48 (2H, dd, J = 12, 8.5 Hz), 3.25 (2H, dd, J = 12, 5 Hz), 2.72 (2H, m), 2.13 (2H, dd, J = 14, 6 Hz), 2.02 (2H, m), 1.48 (9H, s); ¹³C NMR (75 MHz, CDCl₃, doubling due to rotamers) δ 154.1, 136.0, 133.5, 129.2, 128.5, 78.8, 74.4, 63.5, 49.8 and 49.3, 42.0 and 40.7, 33.8 and 33.1, 27.9. HRMS calcd for C₁₉H₂₈NO₅S: C, 59.55; H, 7.15; N, 3.31. Found: C, 59.58; H, 7.14; N, 3.58.

1,1-Dimethylethyl 5-[(acetyloxy)methyl]octahydro-5-(phenylsulfonyl)-3α,6ααα-cyclo-penta[c]pyrrole-2-carboxylate 15
To a solution of alcohol 14 (19.2 g, 50.2 mmol) and pyridine (12.2 mL, 151 mmol) in THF (300 mL) at rt was added acetyl chloride (5.5 mL, 75 mmol). The suspension was stirred for 18 h after which time it was concentrated under reduced pressure. To the residue was added H₂O (600 mL) and the resulting suspension was extracted with CHCl₃ (5X). The combined organics were washed with brine, dried over MgSO₄ and concentrated to afford the acetate 15 (3.24 g, 89.3%) as an oil: IR (MIR) 1745 (s), 1689 (s), 1401 (m), 1302 (m), 1225 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (2H, d, J = 8 Hz); 7.58 (1H, t, J = 8 Hz), 7.47 (2H, t, J = 8 Hz), 4.16 (2H, s), 1.64 (9H, s); ¹³C NMR (75 MHz, CDCl₃, doubling due to rotamers) δ 170.3, 155.0, 150.4, 138.7, 134.5, 130.3, 129.6, 79.8, 74.6, 64.6, 51.4 and 50.8, 42.9 and 42.2, 35.4 (br), 29.1, 21.0. HRMS calcd for C₂₁H₂₉NO₅S: C, 59.55; H, 6.92; N, 3.31. Found: C, 58.94; H, 7.01; N, 3.09.

cis-1,1-Dimethylhexahydro-5-methylenecyclopenta[c]pyrrole-2(1H)-carboxylate 3 via the radical cyclization/ionic cyclization route
A solution of acetoxy sulfone 15 (21.3 g, 50.3 mmol) in THF (1.2 L) at -22 °C was treated successively with Na₂HPO₄ (71.4 g, 503 mmol) followed by sodium amalgam (830 g, 875 mmol; prepared from 21 g of sodium
and 810 g of mercury) in 50 g portions with mechanical stirring. The mixture was stirred for 1 h and then warmed to -5°C and quenched with satd aq NH₄Cl (300 mL). The mixture was then poured into additional satd aq NH₄Cl (1.5 L) and filtered through celite, rinsing with Et₂O. The layers were then separated and the aqueous layer was extracted with Et₂O (4X 250 mL). The combined extracts were dried over MgSO₄ and concentrated to afford the exocyclic olefin 3 (10.8 g, 96.4%) which was identical (¹H NMR, ¹³C NMR) to the material prepared via the [3+2] cycloaddition route described above.

Key intermediate 3 from hexacarbonyldicobalt complex 16 via 1,1-dimethylethyl 5-oxo-3α, 6α-cyclopenta[c]pyrrole-2-carboxylate 17 utilizing the reductive Pauson-Khand route

Exocyclic olefin 3 was prepared from hexacarbonyldicobalt complex 16 via ketone 17 according to our previously published procedure.¹⁵b

bis-(Toluene-4-sulfonyl)sulfur diimide 18

p-Toluenesulfonamide (444 g, 2.59 mol) was added to thionyl chloride (1100 mL) and the resulting yellow solution was heated under reflux overnight. A nitrogen purge (necessary for reaction progress) led to an aqueous NaOH scrubber to absorb the large volume of liberated HCl. The reflux condenser was then replaced with a distillation head and the excess thionyl chloride (900 mL) was distilled off (bath = 92-96 °C; higher temperatures can lead to pyrolysis with vigorous evolution of SO₂) leaving a dark red-yellow liquid. Further concentration on the rotary evaporator under house vacuum, then under high vacuum (1 mm Hg) gave a residue which was washed in a fritted filter with dry ether under nitrogen in a glove bag, then dissolved through the frit with hot dry benzene. The desired product crystallized from the benzene solution in a mass of yellow needles which were collected by filtration in a glove bag to yield the desired sulfur diimide reagent 18 (230 g, 48%) as a fluffy, canary-yellow crystalline solid after drying under high vacuum at rt: mp 121-127 °C (lit²⁰a 120°C); DSC 107.5°; IR (CHCl₃) 3435 (w), 3340 (w), 3022 (w), 1593 (w), 1349 (s), 1163 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (4H, d, J = 8 Hz), 7.31 (4H, d, J = 8 Hz) δ 2.43 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 146.2, 134.8, 130.0, 128.2 21.7.

1,1-Dimethylethylhexahydro-5-methylene-4β-[[4-methylphenyl)sulfonyl]amino]-3αβ,6αβ-cyclopenta[c]pyrrole-2(1H)-carboxylate [(±)-19]

The exo-tosylamide (±)-19 was prepared in 88% yield as described previously¹⁵b by us. Recrystallization from CCl₄/hexane gave crystals (mp 166.5-168 °C) which were suitable for X-ray crystallography.²³

1,1-Dimethylethylhexahydro-5α-(hydroxymethyl)-4b-[[4-methylphenyl)sulfonyl]amino]-3αβ,6αβ-cyclopenta[c]pyrrole-2(1H)-carboxylate (±)-20

As described previously¹⁵b, hydroboration of olefin (±)-19 (4.59 g, 11.4 mmol) afforded exo alcohol (±)-20 (1.69 g, 35.2%) as a low-melting glass: mp 50-60 °C; IR (MIR) 3460 (m), 3264 (m), 1666 (s), 1407 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (2H, d, J = 8.0 Hz), 7.33 (2H, d, J = 8.0 Hz), 5.20-4.92 (1H, br), 3.78 (1H, br m), 3.52
Epimerization of exo alcohol (±)-21 to endo alcohol (±)-20
To oxalyl chloride (12.9 g, 0.102 mol) in CH$_2$Cl$_2$ (50 mL) at -78 °C was added a solution of DMSO (13.1 g, 0.168 mol) in CH$_2$Cl$_2$ (50 mL). After 20 min a solution of the exo alcohol (±)-21 (34.1 g, 0.083 mol) in CH$_2$Cl$_2$ (140 mL) was added. After 40 min, triethylamine (41.1 g, 0.407 mol) was added and the reaction was allowed to warm to 0 °C over 1 h. Water was added and the mixture was extracted with CH$_2$Cl$_2$ (3 X). The combined CH$_2$Cl$_2$ extractions were washed with water (2X) and brine and dried (MgSO$_4$) and concentrated to give a cloudy yellow oil. The oil was dissolved in ethanol (75 mL), cooled to -10 °C and treated with a solution of NaBH$_4$ (2.03 g, 0.054 mol) in ethanol (225 mL). The reaction was then allowed to warm to rt. and stirred overnight. After the solvent was removed in vacuo, saturated NH$_4$Cl and ether were added and the mixture was stirred rapidly for 1 h. The mixture was extracted with ether (3X) and the combined extracts were washed with water and brine and dried (MgSO$_4$). Concentration gave a viscous oil (29.8 g, 87.3%) of a mixture of endo and exo alcohols (±)-20 and (±)-21 in a ratio of 5:1 as determined by $^1$H NMR and HPLC. Chromatography as described above gave the pure endo alcohol (±)-20 (22.8 g, 67%).

Diastereomeric (R)-(−)-O-methylmandelate esters 22 and 23
The ephedrine salt of the (R)-(−)-a-methoxyphenylacetic acid was crystallized as described in the literature$^{25}$ to raise the ee from 92.4% to an acceptable level of 99.6%. Following the general procedure of Trost,$^{26}$ oxalyl chloride (22.4 mL, 32.5 g, 256 mmol) was added to a solution of DMF (19.8 mL, 28.3 mmol) in acetonitrile (800 mL) at 0 °C followed by the addition of R-(−)-a-methoxyphenyl acetic acid (42.5 g, 256 mmol). After 10 min a solution of alcohol (±)-20 (105 g, 256 mmol) in pyridine (60 mL, 59 g, 740 mmol) was added dropwise. Acetonitrile (200 mL) was used to complete the transfer and facilitate stirring of the thick reaction mixture. After stirring for an additional 20 min, the reaction was diluted with ether (5 L), washed with saturated aqueous CuSO$_4$ (3X) and dried (MgSO$_4$). Removal of the solvent gave a crude mixture of 22 and 23 (140 g, 93%) as a greenish-yellow oil which was dissolved in 600 mL of hot EtOAc and allowed to crystallize at -17 °C giving 38.5 g of the crystalline more polar diastereomer 23. The composition of this material was determined by HPLC to be 97.5% 23 and 1.9% 22. Recrystallization of the 38.5 g from EtOAc gave 33.6 g pure 23 (mp 134.5-135.5 °C; X-ray crystal structure determined$^{23}$). The combined mother liquors were chromatographed on silica gel eluting with isopentanol/heptane to give the less polar diastereomer 22 (61.19 g, 40.5%): mp 48-52 °C; [α]$^D_{25} = -15.0^\circ$ (c = 0.246 in CHCl$_3$); IR (KBr) 3430 (w, br), 3260 (w), 1748 (m), 1692 (s), 1667 (m), 1400 (s), 1157 (s) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.70 (2H, d, J = 8.1 Hz), 7.34-7.48 (5H, m), 7.28 (2H, d, J = 8.1 Hz), 4.92 (1H, br s), 4.74 (1H, s), 4.12-3.75 (2H, br m), 3.41 (3H, s), 3.35-3.17 (2H, m), 3.12-2.93 (2H, m), 2.55 (1H, td, J = 8.2, 1.7 Hz), 2.43 (3H, s), 2.42-2.35 (1H, m), 2.03 (1H, br m), 1.77 (1H, dt, J = 12.8, 7.4 Hz), 1.58 (1H, m), 1.46 (9H, s), 0.88 (1H, td, J = 12.6, 9.9 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.9, 170.2, 154.2, 143.7, 136.1, 129.8, 128.9, 128.8, 127.2, 127.1, 82.5,
79.3, 64.4, 61.9, 57.2, 51.1, 50.0, 47.6 (br), 34.1, 32.4, 28.5, 21.5; MS (NH₃-PCI) MH⁺ calcd for C₂₉H₃₈N₂O₇S 559, found 559. Anal. calcd for C₂₉H₃₈N₂O₇S: C, 62.35; H, 6.86; N, 5.01; S, 5.74. Found C, 62.54; H, 6.95; N, 4.86; S, 5.60.

Also obtained was the lower (more polar) diastereomer 23 from the crystallization noted above, as well as from crystallization of overlap fractions (43.16 g, 28.6%): mp 134.5-135.5 °C; [α]D²⁵ = -13.0° (c = 0.077 in CHCl₃); IR (MIR) 3425 (w, br), 3235 (m), 1752 (s), 1688 (s), 1678 (s), 1391 (s), 1159 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (2H, d, J = 8.2 Hz), 7.45-7.34 (5H, m), 7.24 (2H, d, J = 8.0 Hz), 4.92 (1H, d, J = 6.6 Hz), 4.77 (1H, s), 3.92 (2H, br m), 3.42 (3H, s), 3.31 (1H, m), 3.29 (1H, m), 3.13 (1H, m), 3.10 (1H, m), 3.00 (1H, dt, J = 9.8, 6.6 Hz), 2.60 (1H, quint of d, J = 8.7, 3.6 Hz), 2.50 (1H, m), 2.42 (3H, s), 2.05 (1H, br m), 1.87 (1H, quint, J = 6.5 Hz), 1.46 (9H, s), 1.06 (1H, ddd, J = 12.6, 11.8, 8.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 154.5, 143.6, 137.6, 136.1, 129.8, 128.9, 128.8, 127.2, 127.0, 82.5, 79.3, 65.1, 62.3, 57.3, 51.1, 50.0, 47.5 (br), 32.6, 28.5, 21.5; MS (NH₃-PCI) MH⁺ calcd for C₂₉H₃₈N₂O₇S 559, found 559. Anal. calcd for C₂₉H₃₈N₂O₇S: C, 62.35; H, 6.86; N, 5.01; S, 5.74. Found C, 62.28; H, 6.83; N, 4.96; S, 5.84.

In addition there was an overlap section of 22/23 (15.1 g, 10%) plus recovered alcohol 20 (8.8 g, 8.4%) for a total mass balance of 87.5%.

Resolved alcohol (-)-20 from mandelate saponification

The mandelate ester 22 (23.8 g, 42.7 mmol) was dissolved in 2.5% NaOH/EtOH (300 mL, containing a trace of H₂O) and stirred at rt for 20 min. The reaction was then concentrated in vacuo and the residue was partitioned between CH₂Cl₂ and H₂O. The aqueous layer was extracted with CH₂Cl₂ (4X) and the combined CH₂Cl₂ extracts were washed with water (2X) and brine and dried (MgSO₄). Concentration gave the alcohol (-)-20 as a pale yellow solid (16.62 g, 94.8%); mp 144-144.5 °C, [α]D²⁵ = -12.4° (c = 1.23 in CHCl₃). The ee of the alcohol was determined by chiral HPLC to be >99.5%.

Resolved alcohol (+)-20 from mandelate saponification

As described for the diastereomer 22 above, mandelate ester 23 (15.98 g, 27.06 mmol) was saponified to afford (+)-20 (11.1 g, 100%) as a colorless foam: mp 143.5-144 °C; [α]D²⁵ = +13.4° (c = 1.51 in CHCl₃).

(-)-1,1-Dimethylethyl 4α-[(4-methylphenyl)sulfonyl]amino]-5β-[(4-methylphenyl)-sulfon-yloxy]-3aS,3aα,6αα-cyclopenta[c]pyrrole-2-carboxylate (-)-24

To the alcohol (-)-20 (248 mg, 0.604 mmol) in at 0 °C was added p-toluenesulfonyl chloride (345 mg, 1.81 mmol). After the p-toluenesulfonyl chloride was completely dissolved, the reaction was allowed to stand for 64 h at 0 °C. Ice (10 g) was then added and the mixture was extracted with ether (5X). The extracts were washed with water (5X) and brine and dried (Na₂SO₄). Concentration gave a residue (632 mg) which was redissolved in a minimal amount CHCl₃. Toluene (50 mL) was added and the solution was concentrated
again at rt. The residue was taken up in ether and washed with H₂O (3X) and brine and dried (Na₂SO₄). Concentration gave the tosylate (-)-24 (354 mg, 100%) as a colorless foam: [α]D²⁵ = -5.9°, [α]₃⁶⁵²⁵ = -47.4° (c = 0.135 in CHCl₃); IR (KBr) 3420 (w, br), 3260 (w), 1691 (m), 1662 (m), 1400 (m), 1361 (m), 1172 (s), 1156 (s) cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 7.78 (2H, d, J = 8.2 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.27 (2H, d, J = 8.0 Hz), 4.97 (1H, br s), 4.08 (1H, br m), 3.99 (1H, br m), 3.49-3.37 (2H, m), 3.18 (1H, dd, J = 11.7, 8.0 Hz), 3.11-2.87 (2H, br m), 2.69 (1H, m), 2.50 (3H, s), 2.43 (3H, s), 2.41 (2H, m), 1.83 (1H, ddd, J = 14.5, 8.5, 6.7 Hz), 1.63 (1H, ddd, J = 12.6, 8.0, 4.4 Hz), 1.41 (9H, s). Anal calcd for C₂₇H₃₆N₂O₇S₂C, 57.43; H, 6.42; N, 4.96; S, 11.35. Found for (±)-24 C, 56.72; H, 6.34; N, 4.94; S, 11.18.

(+)-1,1-Dimethylethyl 4αααααααααα-[((4-methylphenyl)sulfonyl)amino]-5ββββββββββ-[[((4-methylphenyl)sulfonyl)oxy]-3aR,3aαααααααααα,6aαααααααααα-cyclopenta[c]pyrrole-2-carboxylate (+)-24

As for the preparation of (-)-24 above, the alcohol (+)-20 (269 mg, 0.655 mmol) afforded tosylate (+)-24 (370 mg, 100%) as a colorless foam: [α]D²⁵ = +15.1°, [α]₃⁶⁵²⁵ = +47.0° (c = 0.185 in CHCl₃)

(+)-4-Methyl-N-(hexahydro-1H,2,5β-methano-3aαααααααααα,6aαααααααααα-cyclopenta[c]pyrrole-4αααααααααα-yl)benzene-sulfonamide [(+)-25]

To the tosylate (+)-24 (354 mg, 0.604 mmol) at 0 °C was added freshly distilled trifluoroacetic acid (3 mL) and the resulting pink solution was allowed to warm to rt over 0.5 h. Removal of the TFA gave a residue which was dissolved in toluene and concentrated again to give a pink foam. To the foam dissolved in acetonitrile (12 mL) was added diisopropylethylamine (234 mg, 1.81 mmol) and the reaction was stirred for 16 h at rt. Concentration gave a yellow oil which was partitioned between CHCl₃ and 4 N KOH (4 mL presaturated with NaCl). The aqueous layer was extracted with CHCl₃ (5X), and the combined extracts were washed with H₂O and brine and dried (Na₂SO₄). Concentration gave the tosylamide azanoradamantane (+)-25 (218 mg, 100%) as colorless fine needles: mp 204-205 °C; [α]D²⁵ = +3.1 (c = 0.585 in CHCl₃); IR (MIR) 3022 (m), 1597 (w), 1490 (w), 1316 (s), 1159 (s) cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 7.76 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.2 Hz), 4.39 (1H, d, J = 6.2 Hz), 3.56 (1H, d, J = 6.2 Hz), 2.96-2.84 (3H, m), 2.80-2.69 (3H, m), 2.44 (3H, s), 2.44-2.37 (2H, m), 2.03 (1H, m), 1.93 (1H, br s), 1.74 (1H, d, J = 12.0 Hz); 13C NMR (75 MHz, CDCl₃) δ 143.4, 138.0, 129.7, 126.9, 66.3, 65.5, 65.1, 57.3, 45.8, 42.8, 38.5, 37.5, 21.5. Anal calcd for C₁₅H₂₀N₂O₂C, 61.62; H, 6.89; N, 9.58; S, 10.97. Found C, 61.31; H, 6.91; N, 9.30; S, 10.80.

(-)-4-Methyl-N-(hexahydro-1H,2,5β-methano-3aαααααααααα,6aαααααααααα-cyclopenta[c]pyrrole-4αααααααααα-yl)benzene-sulfonamide [(-)-25]

As described for the preparation of (+)-25 above, tosylate (+)-24 (370 mg, 0.655 mmol) was converted to tosylamide azanoradamantane (-)-25 (191 mg, 100%) as a colorless fine needles: mp 204-205 °C; [α]D²⁵ = -2.4° (c = 0.124 in CHCl₃); Anal calcd for C₁₅H₂₀N₂O₂C, 61.62; H, 6.89; N, 9.58; S, 10.97. Found C, 61.28; H, 7.20; N, 9.36; S, 11.12.

Hexahydro-2,5β-methano-1H-3aS,3aαααααααααα,6aαααααααααα-cyclopenta[c]pyrrole-4αααααααααα-amine (1)
To liquid ammonia (350 mL) was added a solution of tosylazanoradamantane (+)-25 (3.50 g, 12.0 mmol) in dry THF (100 mL). It was necessary to warm the THF to effect dissolution of (+)-25. To the solution at -33 °C was then added lithium metal (360 mg, 52 mmol) in several pieces over 5 min. The reaction was stirred for an additional 20 min and then quenched with slow, careful addition of solid NH₄Cl (3.20 g, 49.8 mmol). The NH₃ was allowed to evaporate overnight under a slow stream of nitrogen and the residual THF solvent was removed on the rotary evaporator to give a residue which was treated with 4 N KOH (70 mL, presaturated with NaCl solid) and then extracted with CHCl₃ (5 X 50 mL). The combined extracts were concentrated without washing, since losses of the water-soluble diamine have been suffered even on washing with brine. Careful concentration on the rotary evaporator with water aspirator vacuum followed by < 10 min. under high vacuum gave the aminoazatricycle 1 (1.99 g, 100%) as a waxy, off-white solid:

1H NMR (300 MHz, CDCl₃) δ 3.25 (1H, s), 3.01-2.92 (3H, m), 2.86-2.78 (3H, m), 2.47 (1H, q, J = 5.6 Hz), 2.33 (1H, m), 2.21 (1H, m), 1.83 (1H, s), 1.75 (1H, d, J = 11.7 Hz), 1.31 (2H, br s); the 1H NMR also revealed the presence of an aromatic by-product of the Birch reduction: 7.38 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz); 13C NMR (75 MHz, CDCl₃) δ 66.0, 64.4, 63.7, 57.4, 47.4, 44.0, 37.5, 36.9. This material was used immediately without further purification in the preparation of (+)-27. An analytical sample was prepared of the dihydrochloride salt of 1: mp >200 °C (dec); DSC 65.6 °C and 212.3 °C; IR (MIR) 2781 (s), 1609 (m), 1500 (m), 1400 (m) cm⁻¹; 1H NMR (300 MHz, d₄-MeOD) δ 3.91 (1H, s), 3.74 (1H, dd, J = 11.5, 2.6 Hz), 3.65-3.48 (5H, m), 3.11 (2H, m), 2.74 (1H, br s), 2.18 (2H, m); HRMS calcd for C₈H₁₄N₂ 138.1157, obs 138.1167. Anal calcd for C₈H₁₄N₂.2HCl.1/₄H₂O C, 44.56; H, 7.71; N, 12.99; Cl, 32.88. Found C, 44.81; H, 7.59; N, 12.83; Cl 33.23.

Hexahydro-2,5β-methano-1H-3aR,3α,6α-cyclopenta[c]pyrrole-4α-amine [(ent)-1]
As described above for the preparation of 1, tosylamide (-)-25 (2.30 g, 1.28 mmol) was deprotected under Birch conditions to afford (ent)-1 (1.28 g, 100%) as a waxy off-white solid. This material was used immediately without further purification in the preparation of (-)-27. An analytical sample was prepared of the dihydrochloride salt of (ent)-1: mp >200 °C (dec); DSC 70.1 °C and 211.5 °C. HRMS calcd for C₈H₁₄N₂ 138.1157, obs 138.1162. Anal calcd for C₈H₁₄N₂.2HCl.1/₄H₂O C,44.56; H, 7.71; N, 12.99; Cl, 32.88. Found C, 44.55; H, 7.55; N, 12.84; Cl 33.23.

4-(Acetylamino)-5-chloro-N-(hexahydro-2,5β-methano-1H-3aS,3α,6α-cyclopenta[c]-pyrrol-4α-yl)-2-methoxybenzamide [(+)-27]
To 4-acetamido-5-chloro-2-methoxybenzoic acid 26 (2.90 g, 12 mmol) in DMF (12 mL, freshly distilled under high vacuum) was added carbonyldiimidazole (1.93 g, 12 mmol) which gave rise to a visible effervescence and a pale yellow solution. After 1 h at rt the crude amine 1 (1.65 g, 12.0 mmol) was added as a solution in DMF (12 mL; freshly distilled) and the reaction was stirred for 3 days. Concentration under a stream of nitrogen gave an off-white solid which was partitioned between CHCl₃ and 15% K₂CO₃ (55 mL, presaturated with NaCl) after filtering through celite to break up the emulsion. The aqueous layer was extracted with CHCl₃ (5X) and the combined extracts were washed with H₂O (2X) and brine and dried.
(Na$_2$SO$_4$). Concentration gave a pale yellow foam (4.58 g) which was applied to a bed of silica gel (140 g) and eluted with 7/93 MeOH (presaturated with NH$_3$ gas)/CHCl$_3$ to give the acetamide (+)-27 as a colorless foam (3.94 g, 86% for 0.25HCl.0.5H$_2$O): [α]$_D^{25} = +9.4^\circ$ (c = 0.139 in CHCl$_3$); IR (KBr) 3450 (m, br, sh), 3390 (m), 1694 (s), 1507 (s), 1238 (m) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.32 (1H, s), 8.20 (1H, s), 7.80 (2H, br s), 4.36 (1H, d, J = 6.9 Hz), 3.97 (3H, s) 3.21 (1H, dd, J = 11.6, 2.9 Hz), 3.05 (1H, dd, J = 12.2, 2.9 Hz), 2.96 (2H, br s), 2.92 (1H, m), 2.83 (1H, dd, J = 11.0, 4.6 Hz), 2.63 (1H, td, J = 5.5, 1.6 Hz), 2.55 (1H, q, J = 5.5 Hz), 2.28 (3H, s), 2.15 (1H, s), 2.03 (1H, m), 1.91 (1H, d, J = 11.9 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.6, 162.5, 156.7, 137.9, 132.0, 117.8, 114.2, 104.0, 66.7, 65.2, 62.4, 57.6, 56.6, 45.7, 42.4, 39.3, 37.7, 25.1; HRMS calcd for C$_{18}$H$_{22}$N$_3$O$_3$Cl 363.1350, found 363.1347. Anal calcd for C$_{18}$H$_{22}$N$_3$O$_3$Cl.0.25HCl.0.5H$_2$O C, 58.11; H, 6.08; N, 11.30; Cl, 10.96. Found C, 57.80; H, 6.04; N, 11.06; Cl, 10.71.

4-(Acetylamino)-5-chloro-N-(hexahydro-2,5ββββ-Methano-1H-3aR,3aαααα,6aαααα-cyclopenta[c]-pyrrol-4αααα-yl)-2-methoxybenzamide [(+)-27]

As described above for the preparation of (+)-27, (ent)-1 (1.086 g, 7.86 mmol) was coupled with 4-acetamido-5-chloro-2-methoxybenzoic acid 26 to afford benzamide (-)-27 (2.86 g, 93%) as a colorless foam: [α]$_D$ = -3.1° (c = 0.128 in CHCl$_3$).

(+)-4-Amino-5-chloro-N-(hexahydro-2,5ββββ-methano-1H-3aS,3aαααα,6aαααα-cyclopenta[c]pyrrol-4αααα-yl)-2-methoxybenzamide, monohydrochloride [SC-52491]

To a solution of the acetamide (+)-27 (3.92 g, 10.8 mmol) in absolute ethanol (540 mL) at rt was added solid KOH pellets (3.63 g, 64.6 mmol). The resulting solution was then heated under reflux for 2 h, then concentrated to give a colorless oil. Water (150 mL) was added and the mixture was extracted with CHCl$_3$ (4 X 100 mL). The combined extracts were washed with water (2X) and brine and dried over Na$_2$SO$_4$ and concentrated to give the free base SC-52491A (3.20 g, 92.3%) as a colorless solid: mp 224 °C (dec); [α]$_D$ = +8.2 (c = 0.679 in CHCl$_3$); IR (KBr) 3440 (m, sh), 3380 (m), 3320 (m, sh), 3190 (w), 1627 (s), 1589 (s), 1530 (s), 1244 (m) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (1H, s), 7.65 (1H, d, J = 6 Hz), 6.28 (1H, s), 4.39 (2H, br s), 4.36 (1H, d, J = 7 Hz), 3.21 (1H, dd, J = 11.6, 2.9 Hz), 3.04 (1H, dd, J = 11.2, 2.9 Hz), 2.95 (2H, br s), 2.89 (1H, dd, J = 11.9, 6.0 Hz), 2.82 (1H, dd, J = 6.8 4.0 Hz), 2.61 (1H, td, J = 5.0, 0.9 Hz), 2.52 (1H, q, J = 5.5 Hz), 2.13 (1H, s), 2.04 (1H, m), 1.88 (1H, d, J = 11.9 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.3, 157.3, 146.5, 133.1, 112.8, 111.8, 97.8, 66.5, 65.0, 62.1, 57.4, 56.2, 45.6, 42.2, 39.2, 37.6; HRMS calcd for C$_{16}$H$_{20}$N$_3$O$_2$Cl 321.1244, found 321.1247. Anal calcd for C$_{16}$H$_{20}$N$_3$O$_2$Cl·1/2H$_2$O C, 58.09; H, 6.40; N, 12.70; Cl, 10.72. Found C, 58.13; H, 6.25; N, 12.52; Cl, 11.23. To a solution of the free base SC-52491A (3.11 g, 9.66 mmol) in methanol (25 mL) was added HCl/MeOH [freshly prepared from the addition of acetyl chloride (681 mg, 9.66 mmol) to 25 mL of methanol]. Concentration gave a colorless crystalline solid which was redissolved in a minimum amount of methanol (ca. 9 mL) and added dropwise over 1 h to ether (2 l) with vigorous stirring. The suspension was cooled in an ice bath for 1 h with continued stirring. The colorless precipitate was then collected by filtration and dried at 70 °C at <1 mm Hg for 60 h to give SC-52491 (3.06 g,
84%) as a colorless powder: mp 241-242 °C; [α]D²⁵ = +6.3° (c = 0.783 in MeOH); IR (KBr) 3440 (m, sh), 3385 (m), 3320 (m, sh), 1640 (s, sh), 1621 (s), 1597 (s), 1537 (s), 1498 (s), 1258 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.09 (<1H (partly exchanged), d, J = 5.5 Hz), 7.75 (1H, s), 6.51 (1H, s), 4.36 (1H, br s), 3.91 (3H, s), 3.73 (1H, dd, J = 11.0, 2.5 Hz), 3.02 (2H, m), 2.62 (1H, br s), 2.18 (1H, d, J = 12.8 Hz); ¹³C NMR (100 MHz, d₄-MeOD) δ 166.7, 159.3, 150.0, 132.8, 111.8, 111.4, 98.7, 64.5, 63.5, 61.8, 56.7, 56.0, 43.6, 41.2, 37.5, 36.8; HRMS calcd for C₁₆H₂₀N₃O₂Cl 321.1244; found 321.1245.

Anal calcd for C₁₆H₂₀N₃O₂Cl·HCl·H₂O C, 51.07; H, 6.16; N, 11.17; Cl, 18.84. Found C, 50.71; H, 5.78; N, 11.02; Cl, 18.96.

(-)-4-Amino-5-chloro-N-(hexahydro-2,5β-methano-1H-3αβ,3αβ,6αβ-cyclopenta[c]pyrrol-4α-yl)-2-methoxybenzamide, monohydrochloride [SC-52490]

As described above for the preparation of SC-52491, the acetamide (-)-27 (2.66 g, 7.32 mmol) was treated with KOH in ethanol to afford the free base SC-52490A (1.87 g, 79%) as a colorless solid: mp 224 °C (dec); [α]D = -5.2° (c = 0.840 in CHCl₃); A solution of the free base SC-52490A (1.87 g, 5.81 mmol) in methanol was treated with HCl/MeOH as described above for SC-52491A to afford SC-52490 (1.89 g, 86%) as a colorless powder: mp 241-242 °C; [α]D²⁵ = -6.3° (c = 0.795 in MeOH); Anal calcd for C₁₆H₂₀N₃O₂Cl·HCl·1/2H₂O C, 53.32; H, 6.04; N, 11.44; Cl, 19.31. Found C, 52.62; H, 5.99; N, 11.37; Cl, 19.27.

REFERENCES AND NOTES


7. 1-Azaadamantane and azanoradamantane II have been reported to have pKb values in water of 2.96 and 2.61, respectively, corresponding to pKa values of 11.0 and 11.4 for the corresponding conjugate acids.


22. This thermal instability during distillation has been noted by others for the corresponding N-sulphinylbenzene sulphonamide: Deleris, G.; Dunogues, J.; Gadrás, A. *Tetrahedron* **1988**, **44**, 4243-4258.
23. X-ray crystallographic data sets for compounds (±)-19 and 23 have been deposited with the Cambridge Crystallographic Data Centre.

24. The exo-stereochemistry of (±)-19 was also confirmed by an x-ray crystal structure of a tricyclic derivative of (±)-21 as described in reference 15b.


Acknowledgement

Professor Peter Beak is gratefully acknowledged for helpful discussions and advice. The authors gratefully acknowledge Kevin Howe, Jim Murphy, and Dorothy Honda for performing the chromatographic separation of diastereomers 22 and 23, Mamta Desai and Brian Callihan for HPLC determinations, and MediChem, Inc. of Darien, IL for contract scaleup work.