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Chiral aminocyclopentene-based cycloaddition strategies to bicyclic [3.3.0] rings

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ABSTRACT

Two cycloaddition methods were applied to chiral protected aminocyclopentenes **2** and **9** and provided novel bicyclic products **3** and **4** in good yields. The explanation for the observed stereochemistry was based on the sterically encumbered β-face forcing the cycloadditions to occur on the α-face of the cyclopentene ring. The stereochemistry of **4** was confirmed by X-ray of the fumarate salt **10** and showed the *trans*-relationship between the newly formed ring and the chiral –NHBoc group.

1. Introduction

The formation of bicyclic rings from cyclic α,β-unsaturated esters allows for quick entry into fused ring systems. Pseudo-symmetric ring annulations typically employ methods that allow for ring formation with a symmetry element for the newly attached ring. Trost developed a palladium-catalyzed trimethylenemethane method that provided for an all-carbon ring annulation with an *exo*-methylene group at the locus of the three-atom attachment.[1] Padwa et al. pioneered the development of azomethine-ylide cycloaddition methodology that provided three-atom annulations with an *N*-benzyl at the center of the newly formed attachment.[2] Clearly these methodologies allow for entry into bicyclic ring systems in one step that otherwise required multistep synthesis. However, in both cases, the simplicity of the annulations has not been evaluated when the starting acrylates had more diverse substitutions. Cycloadditions of these types have seen little exploration in the literature, although several are reported in patents[3] (see Fig. 1).

We were inspired by the recent publication of an azomethine-ylide cycloaddition reaction applied to chiral 4-substituted-2,3-dihydrothiophene1,1-dioxides, as a means to obtain non-planar, saturated bicycles **1a**.[4] In the case of **1a**, the R-substituent was a directing group for the diastereoselective formation of the product. Chiral acrylate **2** has been featured as an intermediate in the syntheses of many nucleosides that were found to be inhibitors of Reverse Transcriptase.[5] We were unaware of its use as a cycloaddition partner for entry into bicyclic ring systems. Our work described herein focuses on the use of **2** in both cycloaddition strategies as a means to construct novel bicyclic ring products **3** and **4**. Elaboration of cycloaddition products **3** and **4** has been featured as CC-Chemokine receptor-2 (CCR-2) antagonists, generally depicted as **1b**, when decorated with a key functionality that imparted biological activity.[6]

2. Results and discussion

While the preparation of acrylate **2** has been generally described by several groups,[5] our procedure provided some additional optimization of an otherwise acceptable procedure (Scheme 1). Opening of the strained [2.2.1] lactam **5** was a facile reaction, accomplished by the action of HCl in an alcoholic solvent that would ultimately result in the corresponding carboxylic ester. Our initial procedure, which used AcCl/MeOH, was a suitable method for the generation of stoichiometric amounts of HCl, but we chose the conventional procedure ($SOCl_2$/MeOH), which allowed for the isolation of hydrochloride salt **6** by direct precipitation upon dilution of the reaction with IPAc. The Boc protection of the amino group was carried out by using typical conditions (Boc_2O/TEA/DCM), but we found that work-up using non-aqueous removal of $Et_3N{\cdot}HCl$ provided **7**, a low-melting solid in high chemical purity and mass yield. As a benefit, **7** readily crystallized upon standing, making for easy weighing in the next reaction. Conjugation of the double bond in **7** was affected using DBU/DCM at rt and, after aqueous work-up, provided acrylate **2**. We discovered that crude **2** could be recrystallized from heptane and provided pure product in 95% yield. As an aside, an attempt was made to convert **6** into **2** in a one-pot operation using DBU as a base for both reactions; this resulted in the isolation of product **2** which was contaminated with an impurity (identified by LCMS) that appeared to result from the direct reaction of DBU with Boc_2O.[7] The overall procedure for the conversion of **5** into **2** was 76% overall yield, and was performed on multi-hundred gram scale.

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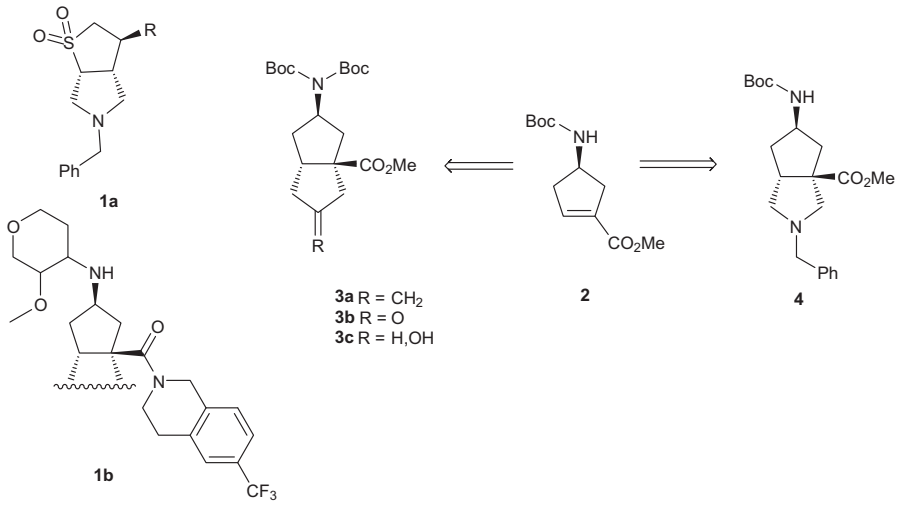
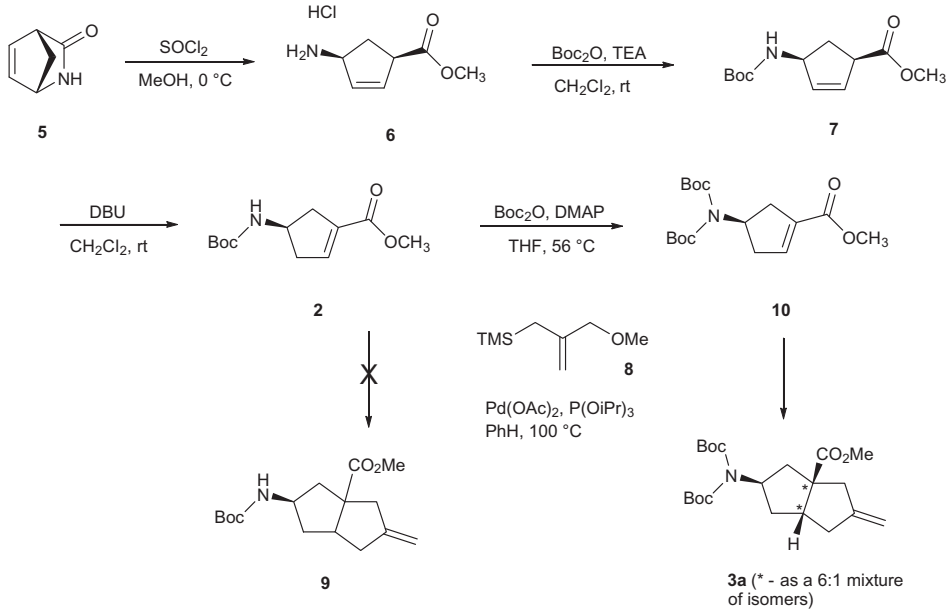


Figure 1. Retrosynthesis of bicycles using a chiral aminocyclopentene.



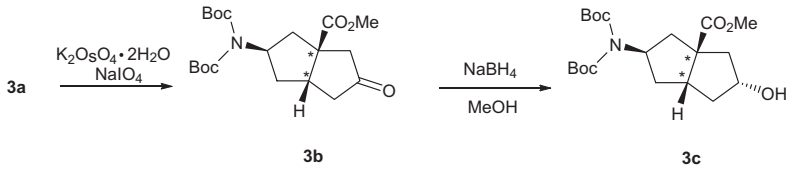
Scheme 1.

With acrylate **2** in hand, we were ready to test the cycloaddition strategies and evaluate the effect of the chiral Boc-amino group on the diastereoselectivity. The reaction of acrylate **2** under the reaction conditions of Trost for the formation of TMM (**8**/$Pd(OAc)_2$/$P(OiPr)_3$/100 °C) in toluene failed to give any **9**, most likely due to the competing reaction of the electrophilic reagent with the NHBoc group. Blocking this reactive NH group of **2** by addition of a second Boc group was affected by using more forcing conditions (10 mol % DMAP/Boc_2O/refluxing THF) and provided bis-Boc **10** in 90% yield. Despite a melting point similar in range to **2**, bis-Boc **10** did not succumb to crystallization from heptane and instead was isolated in pure form by chromatography. The reaction of **10** under the TMM cycloaddition conditions provided **3a** as an inseparable mixture of isomers, with the ratio being determined by NMR to be ~6:1 (as drawn). The diastereoselectivity of **3a** was consistent with the cycloaddition having occurred opposite to the hindered top face of the cyclopentene ring. The *trans*-relationship of the new carbon skeleton relative to the NHBoc group was also observed to control the alkylation of the anion of **6**, which gave a preference for the diastereoselectivity away from the Boc-amino group that blocked one side of the extended enolate.[8]

Characterization of the *exo*-olefin product **3a** was accomplished by oxidative cleavage using catalytic osmylation in a one-pot method and gave **3b** in 54% yield (Scheme 2). This reaction method was more convenient than the typical two-step procedure, whereby the dihydroxylation product was isolated and the periodate cleavage would be performed as a separate operation.

Furthering the chemistry around the [3.3.0] core, **3b** was reduced using $NaBH_4$ in MeOH and provided **3c** in 97% yield. The NMR of **3c** indicated the diastereoselection as drawn, with the expected multiplicities for key signals consistent with earlier work reported for a similar [3.3.0] series lacking the –NHBoc group.[9] More importantly our work revealed the sensitivity of the ester group to the excess of reducing agent, since any amount over 0.5 M equiv of borohydride also reduced the ester to the alcohol.

Having demonstrated that the cycloadditions of the acrylate portion of **2** provided the all-carbon containing core **3a** along with derivatives **3b** and **3c**, we turned our attention to the azomethine-



Scheme 2.

ylide cycloaddition reaction. The reaction of **2** under acid-catalyzed conditions (**11**/cat. TFA/CH_2Cl_2) provided **4** as a thick oil in 80% yield (Scheme 3).

We found that **4** formed a 1:1 fumarate salt **12** and readily crystallized from acetone. The X-ray crystal structure (Fig. 2) confirmed the relative stereochemistry of the newly formed pyrrolidine ring to be in a *trans*-relationship to the encumbering NHBoc group. While searching for an explanation for the exclusive formation of the single diastereomer **4** considering the earlier observed 6:1 ratio seen for **3a**, it is postulated that the azomethine-ylide from **11**, with the associated *N*-benzyl group, is sterically more sensitive to directing groups close to the reacting center. In this case, the NHBoc is sufficient to induce exclusive cyclization with acrylate **2**, leading to the observed product.

3. Conclusion

We have described two cycloaddition reactions of acrylates **2** and **10** which provided novel bicyclic ring products **3a** and **4** in fair to good yields. We have provided a preliminary explanation for the degree of diastereoselection seen in the reactions; in the TMM reaction with **10**, the 6:1 ratio seen suggests that the smaller [3+2] cycloaddition partner gives some amount of control but not exclusive. In the case of the azomethine-ylide reaction with **2**, we observed a high degree of stereoselectivity with this reagent on our substrate. We have also characterized novel products **3b** and **3c**, which were prepared to support the characterization of the cycloaddition product **3a**.

4. Experimental

4.1. General

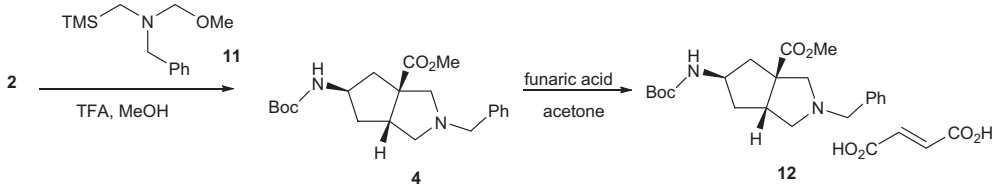
NMR spectra were recorded on a Bruker 400 MHz for ^1H, 100 MHz for ^{13}C. Chemical shifts are given in ppm relative to the internal reference. Coupling constants (J values) are reported in Hertz (Hz), and multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad). The MS spectra were recorded on a Varian LCMS apparatus and molecular ions are reported in nominal mass units. Optical rotation values were measured on a Perkin Elmer 341 and concentrations are given in g/100 mL. Melting points were determined either by Differential Scanning Calorimeter (DSC) versus a blank pan or a Buchi melting point apparatus and are uncorrected. Flash chromatography separations were performed using Merck 60 40–63 μm silica and technical grade solvents. All reagents were used as received and correction factors for purity are used where indicated. Elemental Analyses and Karl Fisher determinations were performed by Intertek.

4.2. (1*R*,4*S*)-Methyl 4-aminocyclopent-2-enecarboxylate hydrochloride 6

A 22-L 4-neck round bottomed flask equipped with an overhead mechanical stirrer, nitrogen inlet, temperature controller, and a 500-mL addition funnel with a nitrogen outlet was charged with MeOH (2.1 L) and **5** (702.1 g, 6.43 mol). The mixture was stirred at 2 °C until the mixture dissolved. Thionyl chloride (282 mL, 3.87 mol) was charged to the addition funnel and added portionwise at a rate not to exceed 12 °C. After 30 min stirring, the reaction was allowed to warm to 8 °C for 1 h. Isopropyl acetate (IPAc, 15.5 L) was added rapidly and the slurry was stirred for 1 h. The solid was filtered and washed with IPAc (1 L) and the resulting white solid was air-dried for a few hours and afforded **6** (1084 g) in 95% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (3H, br s), 6.07 (1H, dt, J = 6, 2 Hz), 5.82–5.96 (1H, m), 4.17 (1H, tt, J = 6 and 2 Hz), 3.66–3.75 (1H, m), 2.44–2.67 (1H, m), 1.83–2.06 (1H, m). ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.61, 134.10, 139.38, 55.10, 51.83, 48.86, 31.15. $[\alpha]_D^{25} = +85.52$ (c 1.0, EtOH). MS (ESI) m/z (%) 142 (M+H, 100). Anal. Calcd for $C_7H_{12}ClNO_2$ C 47.33, H 6.81, Cl 19.96, N 7.89. Found: C 47.34, H 6.72, Cl 20.01, N 7.76. Karl Fisher 0.92.

4.3. (1*R*,4*S*)-Methyl 4-(*tert*-butoxycarbonylamino) cyclopent-2-encarboxylate 7

To a 22-L 4-neck round bottomed flask equipped with a temperature controller, nitrogen inlet, mechanical stirrer, and 500-mL addition funnel with nitrogen outlet was charged **6** (343.3 g, 1.93 mol), dichloromethane (9.6 L), and di-*tert*-butyldicarbonate (426 g, 1.93). The suspension was cooled to 1 °C with an ice bath. Et_3N (270 mL, 1.93 mol) was added via an addition funnel slowly over 50 min not to exceed 2 °C. The resulting clear solution was stirred for 2 h. The volatiles were then evaporated on a rotary evaporator and afforded a crude product, which was contaminated with Et_3NHCl. Et_3NHCl was removed by eluting the crude product through silica gel (500 g) with 50% EtOAc/heptane (500 mL), followed by additional washes (4 × 2 L). The organic filtrates were evaporated to a colorless oil, which slowly crystallized and afforded **7** (650 g) in 96% yield. Mp 48 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (2H, q, J = 6 Hz), 4.79 (2H, br d), 3.72 (3H, s), 3.48 (1H, dd, J = 8 and 4 Hz), 2.51 (1H, dt, J = 14 and 9 Hz), 1.86 (1H, dt, J = 14 and 4 Hz), 1.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.96,



Scheme 3.

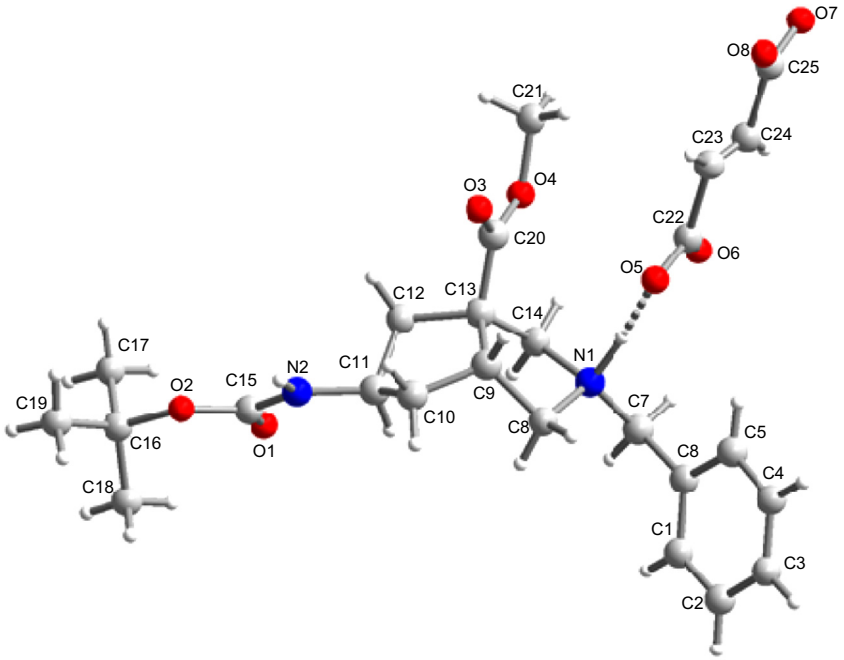


Figure 2. X-ray of fumarate **12**.

155.15/147.00, 134.89, 131.13, 85.18/79.30, 55.81, 52.19, 49.20, 34.58, 28.45/27.44 (rotomers found). $[\alpha]_D^{25} = +59.57$ (*c* 1.05, MeOH). Anal. Calcd for $C_{12}H_{19}NO_4$ C 59.73, H 7.94, N 5.81. Found: C 59.60, H 8.04, N 5.43.

4.4. (*R*)-Methyl 4-(*tert*-butoxycarbonylamino)cyclopent-1-enecarboxylate 2

To a 20-L rotary evaporator flask was charged **7** (368.3 g, 1.53 mol), dichloromethane (2.7 L), and DBU (325 mL, 2.14 mol) at rt and the flask swirled for 66 h. The flask was chilled in an ice-bath, poured into a 22-L separatory funnel containing ice-cold aqueous HCl (0.5 M, 4.2 L) and the contents were gently swirled (to prevent emulsification). The layers were separated and the aqueous layer was back-extracted with dichloromethane (300 mL). The combined organic layers were washed with water (600 mL), dried over Na_2SO_4, filtered, and concentrated under reduced vacuum. The crude product was recrystallized from heptane (900 mL) in a round bottomed flask and heated until all of the solid dissolved. The heat was turned off and the flask swirled as it was allowed to return to rt. The product precipitated as yellow prills, and was collected by filtration and washed with heptane (2 × 150 mL). The collected solid was dried in a vacuum oven (26 °C, 30 in Hg) and provided **2** (341 g) in 93% isolated yield. Mp 88.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69–6.74 (2H, m), 4.74 (1H, br s), 4.36 (1H, br s), 3.73 (3H, s), 2.86–3.01 (1H, m), 2.34–2.48 (1H, m), 1.44 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.11, 155.51, 141.20, 134.43, 79.5, 51.57, 50.2, 41.18, 39.17, 28.42. $[\alpha]_D^{25} = -10.28$ (*c* 1.13, MeOH). Anal. Calcd for $C_{12}H_{19}NO_4$ C 59.73, H 7.94, N 5.81. Found: C 59.97, H 8.04, N 6.03.

4.5. (*R*)-Methyl 4-(bis(*tert*-butoxycarbonyl)amino) cyclopent-1-enecarboxylate 10

To a 3-L 4-neck round bottomed flask equipped with a mechanical stirrer, reflux condenser with nitrogen outlet, and a Claisen head with a temperature controller and nitrogen inlet was charged **2** (90 g, 0.373 mol), THF (900 mL), di-*tert*-butyldicarbonate (130.2 g, 0.596 mol), and DMAP (4.6 g, 0.037 mol). The reaction was heated to 60 °C for 18 h. Additional di-*tert*-butyldicarbonate (17.9 g, 0.082 mol) and THF (100 mL) were added and heating continued for 5 h. The reaction was transferred to a round bottomed flask and the volatiles were removed under reduced pressure. The crude was loaded onto silica gel (800 g) and eluted with a gradient of EtOAc in heptane (1 L heptane, 4 L of 10%, 4 L of 20%). The product fractions were collected and provided **10** (114.1 g) in 90% yield. Mp 86.6 °C. tlc of **10** (20% EtOAc in heptane, $KMnO_4$ stain to visualize): 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 4.87–5.14 (1H, m), 3.73 (3H, s), 2.76–2.94 (4H, m), 1.43–1.54 (18H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.11, 152.81, 141.29, 134.40, 82.57, 54.20, 51.43, 38.43, 36.22, 28.04. $[\alpha]_D^{25} = -6.3$ (*c* 1.19, MeOH). MS (ESI) 364 (M+Na, 15), 705 (2 M+Na, 100). Anal. Calcd for $C_{17}H_{27}NO_6$: C 59.81, H 7.97, N 4.10. Found C 60.12, H 8.03, N 3.95. Karl Fisher 0.2.

4.6. (2*R*,3a*R*,6a*R*)-Methyl 2-(bis(*tert*-butoxycarbonyl) amino)-5-methyleneoctahydropentalene-3a-carboxylate 3a

To a 1-L 4-neck round bottomed flask equipped with a mechanical stirrer, reflux condenser with nitrogen outlet, a temperature controller, and nitrogen inlet was charged **10** (64.1 g, 0.188 mol), toluene (320 mL), 2-(acetoxymethyl)-3-allyltrimethylsilane **8** (70 g, 0.376 mol), and $Pd(OAc)_2$ (2.95 g, 0.013 mol). The deep red solution was degassed with nitrogen through the solution for 15 min. Triisopropylphosphite (26.4 mL, 0.112 mol) was then added via syringe and the greenish yellow solution was heated to 100 °C for 20 h. The reaction was loaded directly onto silica gel (2.5 kg, prewetted with 4 L heptane) and eluted with a gradient of EtOAc in heptane (4 L heptane, 8 L of 5%, 12 L of 10%). The product fractions were collected and provided **3a** (64.4 g) in 87% yield as a clear oil (data below for the major isomer, ratio based on integration of the 4.83 ppm [major] versus 4.87 ppm [minor] of the exo olefin). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79–4.92 (m, 2H), 4.62 (tt, *J* = 7.3, 11 Hz, 1H), 3.65–3.73 (s, 3H), 2.83–2.99 (m, 2H), 2.51–2.74 (m, 2H), 2.21–2.38 (m, 2H), 2.01–2.16 (m, 1H), 1.87–1.99 (m, 1H), 1.57–1.78 (m, 1H), 1.49 (s, 18H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 177.5, 153.0, 150.8, 106.2, 82.3, 82.2, 57.2, 55.6, 52.1, 45.0, 44.5, 40.8, 40.2, 36.3, 28.0. $[\alpha]_D^{25} = -5.4$ (*c* 1.14, MeOH). A satisfactory elemental analysis could not be obtained for this compound.

4.7. (2*R*,3a*S*,6a*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl) amino)-5-oxooctahydropentalene-3a-carboxylate 3b

To a 12-L 4-neck round bottomed flask equipped with a mechanical stirrer, reflux condenser with nitrogen outlet, a temperature controller, and nitrogen inlet was charged **3a** (100.3 g, 0.253 mol) and THF (3.5 L). Water (1.8 L) was then added, followed by $NaIO_4$ (220 g, 1.028 mol) and potassium osmate (VI) hydrate (4.70 g, 0.0127 mol). The reaction exothermed from 24 to 34 °C over the course of 20 min, and the reaction was stirred at rt overnight. The reaction was quenched by the addition of aq sodium thiosulfate (satd, 350 mL) and after stirring was found to be negative with starch–iodide paper. The reaction was diluted with water and EtOAc (2.5 L each), the layers were separated and the aqueous layer extracted with EtOAc (1 L). The combined organics were washed with brine (1 L), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified on silica gel (2.5 kg, prewetted with 4 L heptanes, loaded in DCM) and eluted with a gradient of EtOAc in heptane (4 L of 10%, 16 L of 20%, 8 L of 30%). The product fractions were collected and provided **3b** (87.7 g) in 54% yield as a clear oil. (data reported for major isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.65–4.84 (m, 2H), 3.66–3.77 (m, 3H), 3.12–3.26 (m, 2H), 2.72–2.87 (m, 2H), 2.54–2.71 (m, 1H), 2.47 (ddd, *J* = 8.3, 9.9, 13.6 Hz, 1H), 2.16–2.28 (m, 2H), 2.04–2.16 (m, 2H), 1.66–1.79 (m, 1H), 1.45–1.54 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 176.0, 153.0, 82.7, 55.3, 54.9, 52.5, 46.8, 44.6, 42.4, 38.9, 36.5, 28.0. $[\alpha]_D^{25} = -31.14$ (*c* 1.55, MeOH) MS (ESI) 420 (M+Na, 40), 817 (2 M+Na, 100). Anal. Calcd for $C_{20}H_{31}NO_7$: C 60.44, H 7.86, N 3.52; found C 60.16, H 7.59, N 3.42.

4.8. (2*R*,3a*S*,5*R*,6a*S*)-Methyl 2-(bis(tert-butoxycarbonyl) amino)-5-hydroxyoctahydropentalene-3a-carboxylate 3c

To a 3-L 4-neck round bottomed flask equipped with a mechanical stirrer, nitrogen outlet, a temperature controller, and nitrogen inlet was charged **3b** (72.6 g, 0.182 mol) and MeOH (1.8 L) and the solution was chilled to −70 °C with a CO^2/acetone bath. $NaBH_4$ (3.46 g, 0.091 mol) was added in one portion and the reaction was stirred for 2 h at −70 °C. The bath was removed and the reaction was allowed to warm to −6 °C over the course of 2 h. Water (6.6 mL) was then added and the reaction was transferred to a one-neck flask and the volatiles were removed on a rotary evaporator. The resulting yellow oil was partitioned between water (450 mL) and EtOAc (900 mL). The combined organics were dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give **3c** (71 g) in 97% yield as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (tt, *J* = 6.3, 12.3 Hz, 1H), 4.22 (td, *J* = 4.8, 9.1 Hz, 1H), 3.64–3.70 (m, 3H), 2.69 (q, *J* = 9.0 Hz, 1H), 2.48–2.61 (m, 2H), 2.19–2.32 (m, 2H), 1.87 (dd, *J* = 6.4, 12.2 Hz, 1H), 1.59–1.73 (m, 4H), 1.47–1.52 (m, 18H), 1.34 (dt, *J* = 8.9, 12.7 Hz, 1H). $[\alpha]_D^{25} = -3.29$ (*c* 0.8, MeOH) MS (ESI) 422 (M+Na), 821 (2 M+Na). Anal. Calcd for $C_{20}H_{33}NO_7$: C 60.13, H 8.33, N 3.51; found C 59.78, H 8.53, N 3.42. Karl Fisher 0.4.

4.9. (3a*R*,5*R*,6a*R*)-Methyl 2-benzyl-5-(*tert*-butoxycarbonylamino)-octahydrocyclopenta[c]pyrrole-3a-carboxylate 4

To a 5-L 4-neck round bottomed flask equipped with a mechanical stirrer, nitrogen outlet, temperature controller, and a 25-mL addition funnel with nitrogen inlet was charged **2** (130.65 g, 0.541 mol), dichloromethane (3.4 L) and *N*-(methoxymethyl)-*N*-trimethylsilylmethyl)benzylamine **11** (263 g, 1.11 mol). The solution was cooled in an ice bath to 2 °C, TFA (4.1 mL, 0.0542 mol) was charged to the addition funnel and added to the reaction dropwise over 3–5 min. The reaction was stirred for 2 h. The reaction was quenched at 2 °C by the addition of aqueous saturated sodium bicarbonate (500 mL) and stirred for 30 min. The layers were separated and the aqueous layer back-extracted with dichloromethane (2 × 200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was split into two even portions and purified on silica gel (5 kg, prewetted with 8 L of 20% EtOAc in heptane) and eluted with 72 L of 20% EtOAc in heptane. The product fractions from both runs were collected and provided **4** (167.1 g) in 80% yield as a thick yellow oil.

4.10. (3a*R*,5*R*,6a*R*)-Methyl 2-benzyl-5-(*tert*-butoxycarbonylamino)-octahydrocyclopenta[*c*]pyrrole-3a-carboxylate fumarate 12

To a 3-L 3-neck round bottomed flask equipped with a heating mantle, mechanical stirrer, reflux condenser with nitrogen outlet, and Claisen adapter with a temperature controller and nitrogen inlet was charged fumaric acid (50.3 g, 0.433 mol) and a small amount of acetone. A solution of **4** (162.7 g, 0.433 mol) in acetone (1.62 L) was prepared by swirling until completely dissolved. The solution of **4** was quickly poured into the reaction flask, and washed with a small amount of acetone. The mixture was stirred, and may or may not be clear at this point. A white precipitate started to form at rt, but the mixture was heated to 50 °C for 1 h. The heating was stopped and allowed to cool to rt over 1 h. The mixture was immersed in an ice bath, stirred until reasonably cold, and the solid was filtered and washed with ice-cold acetone (300 mL). The white solid was dried in a vacuum oven (30 in Hg, 29 °C) and provided **12** (159.8 g) in 75% yield as a white solid. Mp 175.3–176.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.01–13.32 (m, 1H), 7.17–7.42 (m, 5H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 2H), 3.98–4.21 (m, 1H), 3.61 (s, 3H), 2.76–2.95 (m, 2H), 2.64 (t, *J* = 8.4 Hz, 1H), 2.44 (d, *J* = 9.3 Hz, 1H), 2.27 (dd, *J* = 4.4, 8.8 Hz, 1H), 1.76–1.96 (m, 2H), 1.56–1.73 (m, 2H), 1.37 (s, 9H). $[\alpha]_D^{25} = +11.3$ (*c* 1.03, MeOH). MS (ESI) 375 (M+H for free-base, 100), 397 (M+Na for free-base, 20%). Anal. Calcd for $C_{25}H_{34}N_2O_8$: C 61.21, H 6.99, N 5.71; found C 61.13, H 6.99, N 5.65. Karl Fisher 0.59.

Full crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 931521. These data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk.

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