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Synthesis of (3*RS*,3a*SR*,8a*SR*)-3-phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one via the aza-Cope–Mannich rearrangement

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ABSTRACT

A convenient and scalable method for the preparation of (3*RS*,3a*SR*,8a*SR*)-phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one based on the aza-Cope–Mannich rearrangement is described. This approach allows us to synthesize the target compound in nine steps in a high overall yield (42%) with complete stereocontrol and up to 100 g scale.

1. Introduction

Since the *cis*-cyclohepta[*b*]pyrrolidine scaffold was found in many alkaloids with a broad spectrum of biological activities, it started attracting considerable interest from medicinal chemists. Such compounds as ajmaline, stemofoline, gelsemine, actinophyllic acid, and daphnicyclidins were synthesized during the past years[1] (Fig. 1). However, the total synthesis of such complex compounds is a difficult task. At the same time natural-like scaffolds with reduced molecular complexity are of great interest nowadays. As a result, compound **1** (Fig. 1) and analogous structures containing two easily modified functional groups may be useful in the design of natural-like compound libraries.

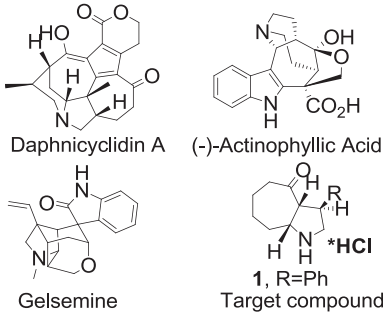

Fig. 1. Representative examples of cyclohepta[*b*]pyrrolidine-containing natural compounds and the target molecule (R=Ar, Het, Alk, H).

2. Results and discussion

In our research aimed at obtaining new biologically active compounds we have encountered a severe problem of developing a convenient method for synthesizing multigram amounts of the (3a*RS*,8a*RS*)-octahydrocyclohepta[*b*]pyrrol-4(1*H*)-one with various aryl, hetaryl, and alkyl fragments at position 3. Analyzing the literature data we took notice of the method developed by Overman et al[2–4] for the preparation of compound **2**—an intermediate for the synthesis of (±)-pancracine (Scheme 1) in a high total yield (35%). Almost all the steps of the synthesis are easy to put into practice. The key step of this method is the aza-Cope–Mannich reaction of amino alcohol **3** with formalin proceeding under mild conditions with complete stereochemical control of the formation of three stereogenic centers of pyrrolidinocyclohexanone **2**.

Using the scheme suggested by Overman for the synthesis of **1** (Scheme 2) we encountered a number of problems: (1) The introduction of a protecting cyanomethyl group at the nitrogen atom suggested in the original approach turned out to be extremely ineffective for producing multigram amounts of the target product, because the addition of the phenylcerium reagent to amino ketone **4** gives a 2.5:1 mixture of cis and trans isomers of amino alcohol **5** difficult to separate by column chromatography. (2) Treating the mixture of the cis and trans isomers of amino alcohol **5** with $AgNO_3$

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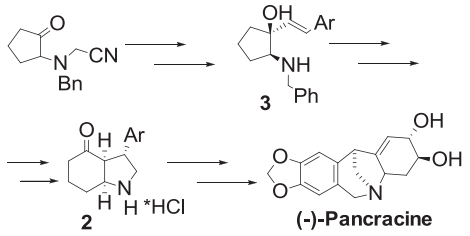
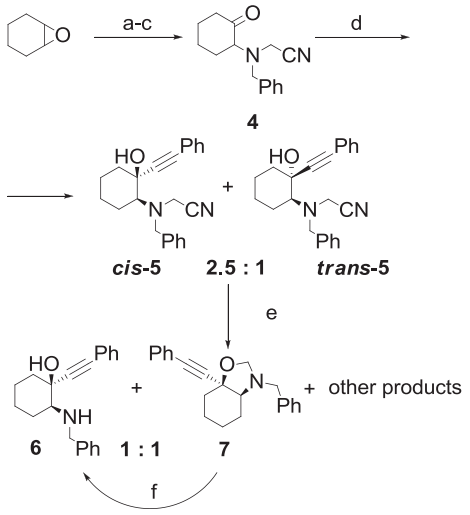


Scheme 1. Overman's route to pancracine.

results in a mixture of equal amounts of *cis* amino alcohol **6**, *cis* amino acetal **7** and other products (from *trans*-**5**) difficult to separate by column chromatography. (3) The individual *cis* amino acetal **7** cannot be transformed into **6** with a good yield. Even its heating in an ultrasound bath for several hours under the conditions of considerable dilution (c ~0.1 M) stops after ~50% conversion giving a mixture of approximately equal amounts of compounds *cis* **6** and *cis* **7**. All the above difficulties make it impossible to obtain multigram amounts of compound **1** and considerably lower the overall reaction yield.



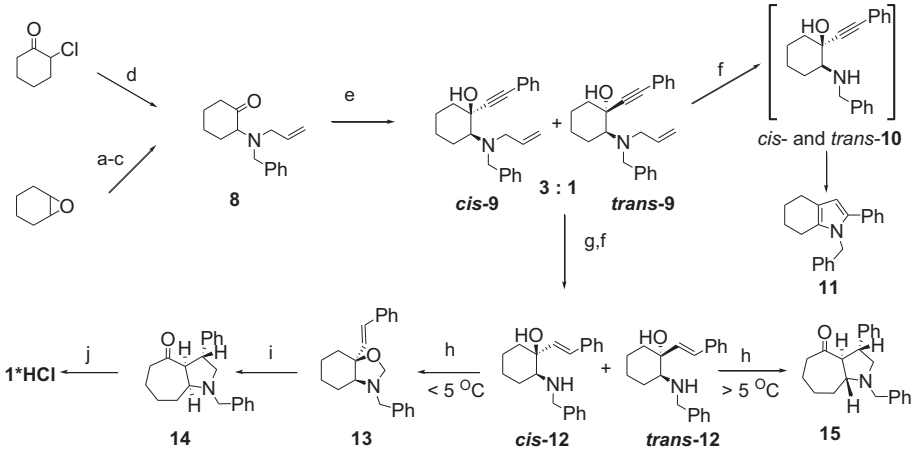
Scheme 2. Reagents and conditions: (a) $PhCH_2NH_2$, 150 °C, 99%; (b) KCN, CH_2O, HCl, 93%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 90%; (d) PhCCH, BuLi, $CeCl_3$, THF, −78 °C, 95%; (e) $AgNO_3$, H_2O, EtOH, sonication; (f) H_2O, EtOH, sonication, 50%.

These facts led us to suggest that we needed another protecting group to make the preparation of the aminoethanol moiety more straightforward. Considering other protecting groups for our synthetic approach we chose the allyl protection of the nitrogen atom.[5] Our choice was due to the fact that, first, this group is readily introduced by direct alkylation of the substrate with an excess of allyl bromide, and second, this protecting group is easily removed by the action of 1,3-dimethylbarbituric acid (DMBA) in the presence of a catalytic amount of $Pd(Ph_3P)_4$.

The initial amino ketone **8** was obtained in three steps from cyclohexene oxide in a high overall yield (~90%, Scheme 3). It is noteworthy that all the steps require no chromatographic purification. Besides, we tried to accomplish an alternative one-step synthesis of this compound from commercially available α-chlorocyclohexanone and allylbenzylamine. Unfortunately, this was unacceptable for our purposes, because the yield of compound **8** was only 40% after chromatographic purification.

The reaction of cerium phenylacetylenide with amino ketone **8** gives amino alcohol **9** (a mixture of cis and trans isomers, 3:1) in 90% yield. We found that, as the amount of cerium chloride with respect to lithium phenylacetylenide was decreased from 1 equiv to 0.5 equiv, the yield and stereochemical result of this reaction did not change. Decreasing the amount of cerium chloride used considerably facilitates carrying out the reaction when working with multigram amounts. Further decrease in the amount of cerium chloride to 0.33 equiv results in side reactions, and the isolation of compound **9** requires chromatographic purification. In order to facilitate the procedure of phenylacetylene addition to amino ketone **8** we made an attempt of replacing cerium phenylacetylenide with lithium phenylacetylenide. However, the attempt was unsuccessful: the yield was low, and the reaction gave a mixture of cis and trans isomers **9** (1:1 ratio) difficult to separate by column chromatography because of the small difference in chromatographic mobility (ΔR_f <0.1). For the synthesis of multigram amounts of **1** it is possible to neglect the separation of isomers **9** at this step. It is considerably more convenient to separate the isomers at a later step of the suggested scheme.

Unfortunately, the literature method[5] for removing the protecting allyl group from substrate **9** (the 3:1 cis–trans mixture) under the action of DMBA in the presence of catalytic amounts of $Pd(Ph_3P)_2Cl_2$ did not give the required amino alcohol **10**. Instead, pyrrole **11** was isolated in a high yield. We suppose that it is formed from **10** as a result of intramolecular addition of the amino group to the triple bond under the action of palladium followed by dehydration.[6] So, at the next step we reduced the triple bond in

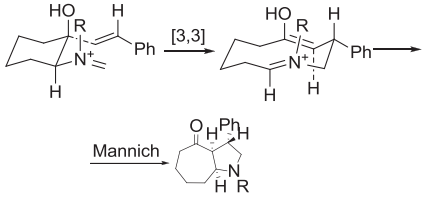


Scheme 3. Reagents and conditions: (a) $PhCH_2NH_2$, 150 °C, 99%; (b) AllBr, K_2CO_3, CH_3CN, 96%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 93%; (d) Bn(All)NH, K_2CO_3, CH_3CN, 40%. (e) PhCCH, BuLi, $CeCl_3$, THF, −78 °C, dr=3:1, 90%; (f) $[Pd(PPh_3)_2]Cl_2$ 1%, *N,N′*-dimethylbarbituric acid, CH_2Cl_2, 94%; (g) 3 equiv $NaAlH_2(OCH_2OCH_3)_2$, THF, 0 °C, 93%; (h) CSA, 2.2 equiv CH_2O, CH_2Cl_2, Na_2SO_4, 100% (i) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C to rt, 95%; (j) H_2, 1 atm, 10% Pd/C, MeOH, HCl, 90%.

substrate **9** into the double bond, and then removed the protecting allyl group. After the allyl deprotection, this sequence of transformations gave compound **12** as a mixture of cis and trans isomers (3:1 ratio) in a high overall yield (87%) for two steps.

Treating the mixture of *cis* and *trans* **12** with 0.9 equiv of formalin in the presence of 0.1 equiv of CSA for 15 min at the temperature below 5 °C gives the mixture of only **13** and *trans*-**12**. The transformation of *cis*-**12** into **13** proceeds quantitatively. Due to the considerable difference in chromatographic mobility **13** and *trans*-**12** were easily separated by column chromatography and isolated in the individual state in 70% and 25% yields, respectively. It is worth noting that increase of the reaction time and higher temperature (>5 °C) leads to the formation of a third component in the reaction mixture: trans-fused bicyclic amino ketone **15** formed by the aza-Cope–Mannich reaction from *trans* amino alcohol **12**. The presence of amino ketone **15** in the reaction mixture considerably complicated the chromatographic purification of **13**, because amino ketone **15** has an intermediate chromatographic mobility between *trans*-**12** and **13**, which complicates the isolation of **13** in the individual state.

The aza-Cope–Mannich reaction of amino acetal **13** at −20 °C proceeds quantitatively and results in the formation of stereochemically pure *cis*-fused amino ketone **14** (Scheme 4). Note that increasing temperature to 0 °C gives by-products, and the reaction yield dramatically falls. After removal of the benzyl group from **14** the target amino ketone **1** was isolated in 90% yield. Thus, we succeeded in accomplishing the suggested synthetical sequence.



Scheme 4. Possible conformation of transition state, R=Bn.

The cis configuration of **14** was confirmed by the NOE-correlation between protons 3a and 8a and the magnitude of their coupling constant (~11 Hz). For the proton pairs 3-3a, 3-8a NOE was not observed.

3. Conclusion

Thus, this scheme enabled the synthesis of **1** by nine preparatively simple operations in a high overall yield (42%). Absolutely all the steps of this scheme are easily scalable to amounts of 0.6–3 mol per one reaction, and they are carried out in an ordinary 5 L laboratory reactor. Due to the high yields an easy chromatographic purification of the products is used only at three steps: purification of amino alcohol **9** from the excess of phenylacetylene; purification of amino alcohol *cis*-**12** from diallylbarbituric acid formed upon the removal of the protecting allyl group; and purification of amino acetal **13** from amino alcohol *trans*-**12**. At present this scheme is being used for the production of (3a*RS*,8a*RS*)-octahydrocyclohepta[*b*]pyrrol-4(1*H*)-one with other substituents at position 3.

4. Experimental section

4.1. General methods and materials

^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz Bruker Avance spectrometers. Spectra were referenced to residual chloroform (δ 7.28 ppm, ^{1}H; δ 77.00 ppm, ^{13}C) or DMSO (δ 2.50 ppm, ^{1}H; δ 39.51 ppm, ^{13}C). Chemical shifts are reported in parts per million (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in hertz. Infrared (IR) spectra were obtained on FT-IR spectrometer. Flash column chromatography was performed on 60–200 mesh silica gel. Analytical thin-layer chromatography was performed with aluminum backed plates (60 Å, F_{254}). THF was distilled from Na/benzophenone under argon. All materials were purchased from commercial sources and used without purification. Reactions were carried out under an air atmosphere unless otherwise stated. (1*RS*,2*RS*)-2-(benzylamino)cyclohexanol was prepared according to reported procedure.[7]

4.2. Synthesis

4.2.1. (1RS,2RS)-2-[Allyl(benzyl)amino]cyclohexanol. Yield 43.1 g of (1*RS*,2*RS*)-2-(benzylamino)cyclohexanol (0.21 mol) was dissolved in acetonitrile (420 mL). Potassium carbonate (72.4 g, 2.5 equiv, 0.52 mol) and then allyl bromide (32.8 g, 1.3 equiv, 0.27 mol) were added in one portion. The reaction mixture was warmed to 40–50 °C and stirred 6 h at this temperature. The mixture was then allowed to cool to room temperature, quenched with 500 mL of water and then extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over Na_2SO_4 and concentrated. The title compound was obtained as a colorless liquid. Yield 49.5 g (96%); [Found: C, 78.02; H, 9.07; N, 5.67. $C_{16}H_{23}NO$ requires C, 78.32; H, 9.45; N, 5.71%]; ν_{max} (KBr) 3467, 3064, 3028, 2929, 2858, 1643, 1495, 1452, 1404, 1358, 1281, 1151, 1074, 987, 918, 873, 740, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.24 (5H, m, Ph), 5.89–5.73 (1H, m), 5.17 (1H, d, *J* 16.9 Hz), 5.12 (1H, d, *J* 9.5 Hz), 3.89 (1H, d, *J* 13.9 Hz, PhC*H*$_a$H$_b$), 3.90–3.73 (1H, br s, OH), 3.51–3.40 (1H, m), 3.36 (1H, d, *J* 13.9 Hz, PhCH$_a$*H*$_b$), 3.30–3.24 (1H, m), 2.98 (1H, dd, *J* 14.1, 8.4 Hz), 2.51–2.38 (1H, m), 2.17–2.03 (1H, m), 1.95–1.83 (1H, m), 1.83–1.66 (2H, m), 1.29–1.08 (4H, m); δ_C (100.6 MHz, $CDCl_3$) 139.6, 136.8, 128.8 (2C), 128.4 (2C), 127.1, 117.3, 69.2, 65.0, 53.5, 52.8, 33.2, 25.5, 24.2, 22.6; *m*/*z* (I_{rel}) 245 (3MH$^+$), 186 (17), 173 (16), 91 (100), 65 (14), 41 (46), 39 (21%).

*4.2.2. (2RS)-2-[Allyl(benzyl)amino]cyclohexanone (**8**).* A solution of Me_2SO (73.0 mL, 1.03 mol, 2.2 equiv) in CH_2Cl_2 (100 mL) was added dropwise to a solution of oxalyl chloride (47.5 mL, 0.56 mol, 1.2 equiv) in CH_2Cl_2 (850 mL) at −60 to −80 °C. The resulting solution was stirred for 10 min and a solution of (1*RS*,2*RS*)-2-[allyl(benzyl)amino]cyclohexanol (114.25 g, 0.47 mol) in 170 mL CH_2Cl_2, was added dropwise at the same temperature. After 15 min, Et_3N (342 mL, 2.45 mol, 5.3 equiv) was added, and after 5 min the reaction mixture was allowed to warm to ambient temperature. Aqueous workup (CH_2Cl_2, Na_2SO_4) gave a title compound as a slightly yellow oil. Yield 106.4 g (93%). ^{1}H NMR and ^{13}C NMR spectra of **8** correspond to the literature.[8]

*4.2.3. (1RS,2RS)-2-[Allyl(benzyl)amino]-1-(phenylethynyl)cyclohexanol (**9**).* Anhydrous $CeCl_3$ was freshly prepared from 93.2 g of $CeCl_3 \cdot 7H_2O$ (0.25 mol).[9] Freshly distilled THF (510 mL) was added rapidly to the cooled $CeCl_3$ at 0 °C and the resulting slurry was stirred under Ar at room temperature for 24 h. In a separate flask containing 56.2 g (0.55 mol) of phenylacetylene and 550 mL of THF was added 200 mL of n-BuLi (2.5 M in hexane, 0.5 mol) dropwise at −78 °C and the resulting solution was maintained for 30 min at 0 °C. This solution was then cooled to −78 °C and transferred to the precooled $CeCl_3$ slurry in THF at −78 °C via a cannula. The resulting mixture was stirred for 1 h at −78 °C before a solution of **8** (81.1 g, 0.33 mol) in 330 mL of THF was added dropwise at −78 °C. The mixture was stirred for 2 h at this temperature and than was poured into water (400 mL) containing acetic acid (29 mL, 0.5 mol), Et_2O/hexane mixture (1:1, 400 mL). The organic layer was

separated and water layer extracted with Et_2O/hexane mixture (2:1, 2×200). Combined organic layers were dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by means of flash chromatography on silica gel (mainly from excess of phenylacetylene). The title compound was obtained as a mixture of two diastereomers (3:1) in 90% yield (102.6 g). Analytical data shown for main diastereomer. [Found: C, 83.39; H, 7.65; N, 4.25. $C_{24}H_{27}NO$ requires C, 83.44; H, 7.88; N, 4.05%]; ν_{max} (KBr): 3527, 3446, 3061, 3026, 2935, 2858, 2798, 1599, 1491, 1444, 1367, 1140, 1070.3, 1028, 970, 916, 756, 739, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.73–7.39 (4H, m), 7.38–7.16 (6H, m), 6.10–5.82 (1H, m), 5.33–4.99 (2H, m), 4.29 (1H, d, *J* 14.7 Hz), 3.80 (1H, d, *J* 14.7 Hz), 3.55 (1H, dd, *J* 15.2, 5.2 Hz), 3.26 (1H, dd, *J* 15.8, 6.6 Hz), 2.97 (1H, dd, *J* 8.9, 8.9 Hz), 2.45 (1H, br s, OH), 2.20–2.08 (1H, m), 1.94–1.72 (4H, m), 1.63–1.49 (2H, m), 1.41–1.18 (1H, m); δ_C (75.5 MHz, $CDCl_3$) 141.3, 137.4, 131.7 (2C), 128.4 (2C), 128.3 (3C), 128.1 (2C), 126.7, 123.5, 116.6, 94.9, 83.5, 72.2, 64.9, 55.4, 55.3, 40.3, 25.8, 23.2, 20.9; *m*/*z* (I_{rel}) 345 ($2MH^+$), 186 (32), 173 (29), 160 (26), 158 (24), 132 (30), 129 (23), 92 (24), 91 (100), 65 (28), 55 (26), 41 (76), 39 (22%).

4.2.4. (1RS,2RS)-2-[Allyl(benzyl)amino]-1-[(E)-2-phenylvinyl]cyclohexanol. A solution of amino alcohol **9** (30 g, 0.087 mmol) and 217 mL of THF was slowly added dropwise to a solution of RedAl (105 mL, 0.261 mmol, 3 equiv) in 217 mL of THF at 0 °C. After gas evolution subsided, the mixture was then allowed to warm to room temperature and stirred overnight. Excess hydride was quenched by successive dropwise addition 12 mL of water, 18 mL 10% NaOH and 12 mL of water to reaction mixture at −10 °C. The reaction mixture was allowed to warm to room temperature stirred for an hour and then filtered through thin layer of silica. The precipitate was washed with THF. The organic layer was concentrated to give dark oil, which solidified upon standing (28.4 g, 94%). Mp=52 °C; [Found: C, 82.79; H, 8.23; N, 4.26. $C_{24}H_{29}NO$ requires C, 82.95; H, 8.41; N, 4.03%]; ν_{max} (KBr) 3562, 3460, 3061, 3026, 2931, 2856, 2800, 1641, 1601, 1493, 1448, 1367, 1265, 1146, 1070, 966, 910, 743, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45–7.21 (10H, m, 2Ph), 6.62 (1H, d, *J* 16.2 Hz), 6.36 (1H, d, *J* 16.2 Hz), 5.94–5.82 (1H, m), 5.19 (1H, dd, *J* 17.3, 0.9 Hz), 5.11 (1H, d, *J* 10.3 Hz), 4.11 (1H, d, *J* 14.4 Hz), 3.55 (1H, d, *J* 14.4 Hz), 3.55–3.48 (1H, m), 3.06 (1H, dd, *J* 14.6, 7.5 Hz), 2.72–2.64 (1H, m), 1.96–1.53 (8H, m), 1.38–1.25 (1H, m); δ_C (100.6 MHz, $CDCl_3$) 141.2, 139.1, 137.9, 137.6, 128.6 (4C), 128.2 (2C), 127.0, 126.6, 126.3 (2C), 126.2, 116.3, 76.7, 63.9, 55.5, 55.0, 39.4, 26.1, 21.8, 21.4; *m*/*z* (I_{rel}) 347 ($7MH^+$), 186 (10), 160 (28), 131 (17), 103 (15), 92 (15), 91 (100), 77 (16), 65 (21), 55 (14), 41 (52), 39 (18%).

*4.2.5. (1RS,2RS)-2-(Benzylamino)-1-[(E)-2-phenylvinyl]cyclohexanol (**12**).* To solution containing 32.1 g (92.3 mmol) (1*RS*,2*RS*)-2-[allyl(benzyl)amino]-1-[(*E*)-2-phenylvinyl]cyclohexanol and 28.7 g *N*,*N*′-dimethylbarbituric acid (183.8 mmol, 2 equiv) in l80 mL CH_2Cl_2, 0.65 g of $[Pd(PPh_3)_2]Cl_2$ (1 mol %) was added and under argon. The mixture was stirred for 2–4 h under reflux (TLC control). After cooling, the CH_2Cl_2 was extracted twice with 5% aqueous K_2CO_3 to remove the unreacted NDMBA and its mono *C*-allyl derivative. The organic phase was dried over Na_2SO_4 and concentrated. Purification flash column chromatography (1:5 CH_2Cl_2/hexane) gave an oil, which solidified upon standing (26.3 g, 93%). Mp=65 °C; [Found: C, 81.94; H, 8.02; N, 4.37. $C_{21}H_{25}NO$ requires C, 82.04; H, 8.20; N, 4.56%]; ν_{max} (KBr) 3059, 3024, 2912, 2850, 1682, 1601, 1460, 1446, 995, 987, 814, 746, 698, cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43–7.37 (2H, m, Ph), 7.37–7.29 (4H, m, Ph), 7.29–7.23 (4H, m, Ph), 6.81 (1H, d, *J* 15.8 Hz), 6.19 (1H, d, *J* 15.9 Hz), 3.85 (1H, d, *J* 13.3 Hz), 3.77 (1H, d, *J* 13.5 Hz), 3.70–3.20 (1H, br s), 2.65 (1H, dd, *J* 4.3, 10.8 Hz), 1.85–1.24 (9H, m); δ_C (100.6 MHz, $CDCl_3$) 140.5, 137.2 (2C), 128.6 (2C), 128.5 (2C), 128.3, 127.9 (2C), 127.3, 127.0, 126.4 (2C), 73.1, 60.5, 51.5, 36.3, 27.3, 24.3, 20.8; *m*/*z* (I_{rel}) 307 ($8MH^+$), 198 (13), 146 (15), 132 (12), 131 (24), 120 (24), 106 (27), 103 (19), 91 (100), 77 (18), 65 (21), 56 (12%).

*4.2.6. (3aRS,7aRS)-3-Benzyl-7a-[(E)-2-phenylvinyl]octahydro-1,3-benzoxazole (**13**).* To a mixture containing **6** (182 g, 0.59 mol), anhydrous Na_2SO_4 (286 g, 2 mol, 3.4 equiv), camphorsulfonic acid (29 g, 0.12 mol, 0.21 equiv), and CH_2Cl_2 (590 mL) 98 mL of formalin (37% in water, 1.31 mol, 2.2 equiv) was added dropwise at 0 °C. The reaction mixture was vigorously stirred at 23 °C for 6 h. The mixture was washed with saturated $NaHCO_3$ solution (500 mL) and dried (Na_2SO_4). Concentration gave 188 g an oil, which was purified on silica gel flash chromatography using petroleum/EtOAc (10:1) to furnish 131.9 g of **13** (70%) and unreacted *trans*-**12** (45 g, 25%). [Found: C, 82.32; H, 7.80; N, 4.17. $C_{22}H_{25}NO$ requires C, 82.72; H, 7.89; N, 4.38%]; ν_{max} (KBr) 3026, 2932, 2857, 2802, 1681, 1494, 1448, 1226, 1072, 1029, 968, 745, 694; δ_H (400 MHz, $CDCl_3$) 7.52–7.23 (10H, m), 6.79 (1H, d, *J* 16.1 Hz), 6.43 (1H, d, *J* 15.9 Hz), 4.70 (1H, d, *J* 2.2 Hz), 4.19 (1H, d, *J* 2.2 Hz), 4.07 (1H, d, *J* 13.5 Hz), 3.40 (1H, d, *J* 13.4 Hz), 2.72 (1H, dd, *J* 3.9, 3.9 Hz), 2.09–1.97 (1H, m), 1.97–1.87 (1H, m), 1.87–1.70 (3H, m), 1.70–1.60 (1H, m), 1.52–1.38 (2H, m); δ_C (100.6 MHz, $CDCl_3$) 139.3, 137.2, 131.9, 128.8, 128.6 (2C), 128.4 (2C), 128.2 (2C), 127.5, 127.1, 126.5 (2C), 85.9, 82.4, 65.9, 55.7, 33.4, 25.0, 22.7, 20.2; *m*/*z* (I_{rel}) 319 ($2MH^+$), 131 (26), 117 (12), 115 (11), 106 (9), 105 (10), 104 (8), 103 (22), 92 (10), 91 (100), 77 (13), 65 (8), 41 (8%).

*4.2.7. (3RS,3aRS,8aSR)-1-Benzyl-3-phenyloctahydrocyclohepta[b]pyrrol-4(1H)-one (**14**).* To a solution of **13** (169 g, 0.53 mol) in CH_2Cl_2 (530 mL) $BF_3 \cdot Et_2O$ (160 mL, 1.3 mol, 2.4 equiv) was added dropwise at −20 °C for 30 min and then the reaction solution was allowed to warm to 23 °C. After 15 min, the resulting solution was washed with 1.0 N NaOH solution and water phase was extracted with CH_2Cl_2 (2×100 mL). The organic portions were dried (Na_2SO_4) and concentrated to give 160.8 g (95%) of a white solid compound. The product was homogeneous by TLC analysis. Mp=125–7 °C; [Found: C, 82.36; H, 7.54; N, 4.37. $C_{22}H_{25}NO$ requires C, 82.72; H, 7.89; N, 4.38%]; ν_{max} (KBr) 3424 (w), 2933, 1698, 1454, 1263, 1201, 1169, 1064, 757, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37–7.31 (4H, m), 7.31–7.22 (5H, m), 7.22–7.16 (1H, m), 4.07 (1H, d, *J* 13.2 Hz), 3.85 (1H, ddd, *J* 11.30, 8.80, 6.60 Hz), 3.42 (1H, dd, *J* 10.3, 9.1 Hz), 3.29 (1H, d, *J* 13.0 Hz), 3.26 (1H, dd, *J* 8.8, 6.9 Hz), 3.07 (1H, ddd, *J* 2.40, 10.6, 10.6 Hz), 2.60–2.50 (1H, m), 2.42 (1H, dd, *J* 11.2, 8.90 Hz), 2.48–2.38 (1H, m), 2.05–1.94 (1H, m), 1.94–1.81 (2H, m), 1.81–1.72 (1H, m), 1.72–1.61 (1H, m), 1.56–1.44 (1H, m); δ_C (100.6 MHz, $CDCl_3$) 211.0, 142.2, 138.8, 128.8 (2C), 128.4 (2C), 128.3 (2C), 127.8 (2C), 127.0, 126.4, 64.6, 62.5, 60.5, 57.8, 42.6, 42.4, 29.9, 24.4, 24.2; *m*/*z* (I_{rel}) 319 ($13MH^+$), 277 (24), 262 (11), 235 (18), 234 (16), 209 (22), 144 (13), 115 (17), 91 (100), 65 (14%).

*4.2.8. (3RS,3aRS,8aSR)-3-Phenyloctahydrocyclohepta[b]pyrrol-4(1H)-one hydrochloride (**1**).* A solution of 151 g of **14** in MeOH (470 mL) was acidified with aqueous HCl to pH ~3 (approximately 40 mL needed). Pd/C (l0%, 15 g) was added, and the mixture was degassed and stirred under 1 atm of hydrogen gas at 30 °C for 2 h. The catalyst was then removed by filtration and the filtrate was concentrated under reduced pressure. Recrystallization from ethanol 112.4 g (90%) gave white solid amine **9** in hydrochloride form. Mp=255–260 °C (decomp.); [Found: C, 67.59; H, 7.40; N, 5.21. $C_{15}H_{20}NOCl$ requires C, 67.79; H, 7.58; N, 5.27%]; ν_{max} (KBr) 3437 (w), 2929, 2866, 2740, 1701, 1632, 746, 699; δ_H (400 MHz, DMSO-d_6) 10.10–9.50 (2H, br s), 7.40–7.28 (4H, m), 7.28–7.20 (1H, m), 4.22 (1H, dd, *J* 10.5, 10.5 Hz), 3.94–3.79 (2H, m), 3.56 (1H, dd, *J* 11.2, 6.8 Hz), 3.11 (1H, dd, *J* 11.5. 11.5 Hz), 2.61–2.52 (1H, m), 2.30–2.25 (1H, m), 2.07–1.98 (1H, m), 1.98–1.86 (1H, m), 1.81–1.70 (1H, m), 1.68–1.56 (1H, m), 1.56–1.43 (2H, m); δ_C (100.6 MHz, DMSO-d_6) 208.8, 139.3, 129.0 (2C), 128.4 (2C), 127.6, 58.7, 58.6, 49.8, 43.1, 42.4,

29.1, 24.5, 23.3; m/z (I_{rel}) 229 (11MH^+), 172 (15), 144 (27), 119 (100), 116 (19), 91 (19), 83 (12), 77 (12), 70 (13), 68 (23), 56 (18), 55 (16), 41 (21%).

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