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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · OCTOBER 2012

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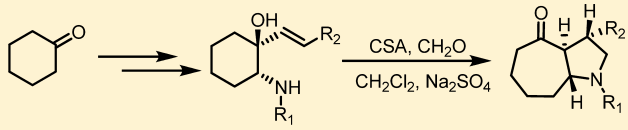
Highly Stereoselective and Scalable Synthesis of *trans*-Fused Octahydrocyclohepta[*b*]pyrrol-4(1*H*)-ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms

Dmitry S. Belov, Evgeny R. Lukyanenko, Alexander V. Kurkin,* and Marina A. Yurovskaya

Department of Chemistry, Lomonosov Moscow State University, 1/3 Leninsky Gory, Moscow, 119991, Russia

Supporting Information

ABSTRACT: We have developed an efficient and stereoselective route to *trans*-fused octahydrocyclohepta[*b*]pyrrol-4(1*H*)-ones. The key features of our synthesis include the regioselective epoxide ring-opening of alkynyl oxiranes and a stereoselective aza-Cope–Mannich reaction. The target compounds were prepared in 3–6 steps from commercially available starting materials (61–75% overall yield) with minimal chromatographic purification. We have devised an stereoselective route to target compounds using Shi epoxidation or (*R*)-1-phenylethylamine as a source of chirality.



INTRODUCTION

Recently, most players in the pharmaceutical industry working on small molecule drug discovery have focused their efforts on enriching the newly designed drug prototype with sp^3-hybridized carbon atoms, as their goal was to bring the chemotypes closer to natural products and to boost chemotypes' three-dimensional properties.[1]

However, the reaction portfolio currently available to the pharmaceutical industry lacks solid synthetic methodologies to produce compound libraries of natural product-like molecules for screening purposes.[2] Furthermore, the synthetic approaches commonly used for small molecule compound libraries often miss a stereocontrolled bond formation. Conversely, most natural products do have well stereodefined structural features.

Hence, the implementation of a robust and stereocontrolled methodology to build a saturated heterocyclic fused system such as the cycloalkano[*b*]fused pyrrolidines may serve to improve the reaction tools available to a chemist, as these scaffolds are well represented among drugs and natural products (Figure 1).[3]

Since Overman's first report in 1979, the aza-Cope–Mannich rearrangement has become a powerful tool for the construction of various substituted pyrrolidines including complex natural products.[3,4] If the starting amino alcohol is cyclic, this transformation provides ring-enlarged pyrrolidine annulated products (Figure 2).[5−7] Because of the restricted conformational freedom in the transition state, this variant of the aza-Cope–Mannich reaction occurs without loss of enantiomeric purity of the starting amino alcohol and typically exhibits excellent stereoselectivity.[7e]

Although the preparation of octahydrocyclohepta[*b*]pyrrol-4(1*H*)-ones with *cis*-fused seven-membered and pyrrolidine rings has been studied in great detail,[7] few analogues with *trans*-stereochemistry at the ring junction have been reported. Overman described the preparation of *trans*-octahydrocyclohepta[*b*]pyrrol-4(1*H*)-ones as mixtures with the *cis*-

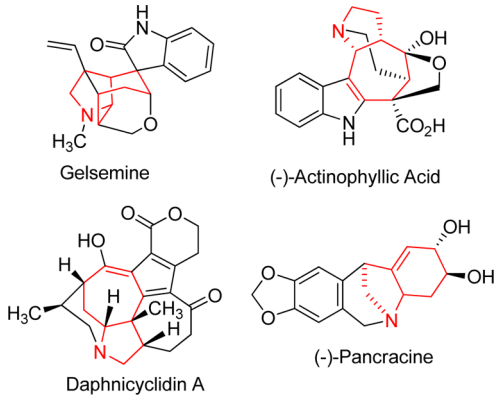


Figure 1. Representative examples of cycloalkano[*b*]pyrrolidine-containing natural products.

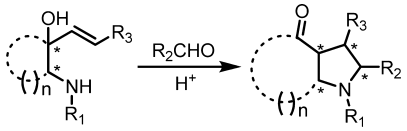


Figure 2. General scheme for cycloalkano[*b*]fused pyrrolidine formation via the aza-Cope–Mannich reaction (* chiral center).

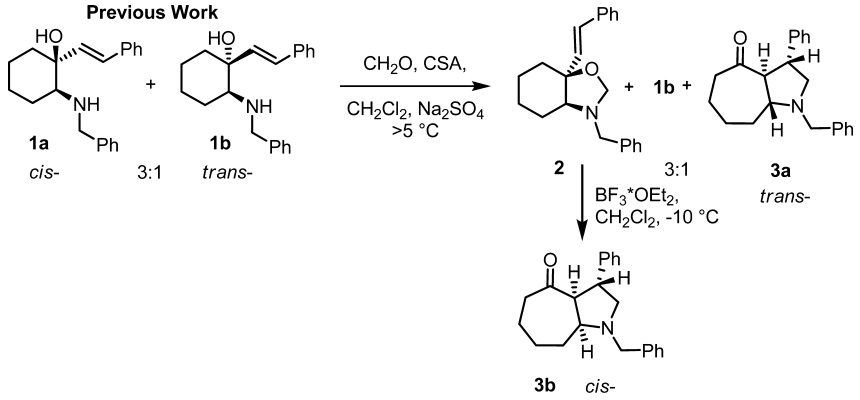
isomers.[6b,e,7a,c] This stereochemistry can also be accessed via the selective epimerization of the C-3a stereocenter (Figure 3).[7e] The major drawbacks of these methods are the need for the laborious chromatographic separation of diastereomeric mixtures and the low overall efficiency.

In an earlier study, we found that the treatment of unsaturated amino alcohols **1a** and **1b** with CH_2O at ambient temperature results in a mixture of oxazolidine **2** and *trans*-

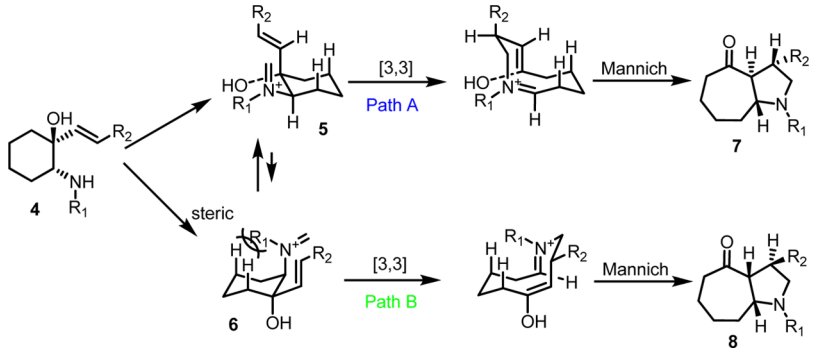
Received: August 17, 2012
Published: October 31, 2012

   dx.doi.org/10.1021/jo301762a | *J. Org. Chem.* 2012, 77, 10125–10134

Scheme 1. Construction of Cyclohepta[*b*]pyrrol Core via the Aza-Cope–Mannich Reaction[8]



Scheme 2. Rationalization of the *trans*-Cyclohepta[*b*]pyrrol Formation



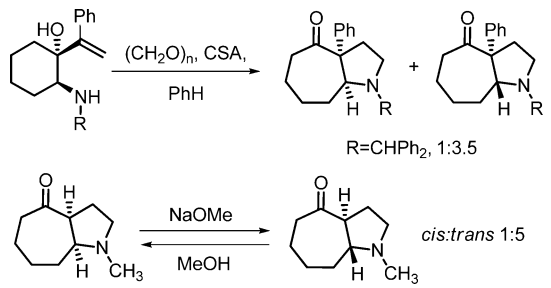


Figure 3. Earlier work on the syntheses of *trans*-octahydrocyclohepta-[*b*]pyrrol-4(1*H*)-ones.

fused *β*-amino ketone **3a** (Scheme 1).[8] Given that the ratio of **2** to **3a** is also that of **1a** to **1b** and pure **1a** only yielded **2** under these conditions, we deduced that that the *β*-amino ketone **3a** arose from the *trans*-amino alcohol **1b**. The observed stereoselectivity was attributed to the preferred transition state **5**, which minimizes unfavorable interactions between the *N*-alkyl substituent and the cyclohexane ring (Scheme 2). This result and the mechanistic considerations suggest that an appropriately substituted *trans*-amino alcohol **4** would lead exclusively to *trans*-amino ketone **7**. Herein, we report the concise and highly stereocontrolled synthesis of *trans*-octahydrocyclohepta[*b*]pyrrol-4(1*H*)-ones.

RESULTS AND DISCUSSION

Preparation of *trans*-3a-Phenyloctahydrocyclohepta-[*b*]pyrrol-4(1*H*)-ones. Our synthetic studies began by preparing the starting amino cyclohexanol with the requisite *trans* relationship between the amino and alcohol groups. Although many methods are available for the construction of such systems, most of these methods are based either on the reactions between *α*-amino ketones and vinyl lithium[6,10] or cerium[3d,e,8] reagents or are based on vinyl epoxide ring-openings.[3a,b,4,6c,9] However, in general, organometallic addition favors *cis*-amino alcohols,[3] and vinyl epoxide ring-openings tend to give allyl amines rather than allyl alcohols.[11,12] To develop a general method for this class of compounds, we proposed that 2-vinyl amino alcohols **9** could arise from the reduction of 1-alkynyl 2-amino alcohols **10**. In turn, **10** could be easily prepared by the Lewis acid-promoted, regioselective epoxide ring-opening of known oxiranes **11** (Figure 4).[12−15]

To test the viability of this method, we synthesized alkynyl oxirane **14** using a previously described three-step procedure.[13] The addition of a lithium phenylacetylenide species to cyclohexanone smoothly delivered the propargyl alcohol **12** (82%), which was then dehydrated through the action of $POCl_3$ in pyridine to afford alkene **13** in 90% yield. The

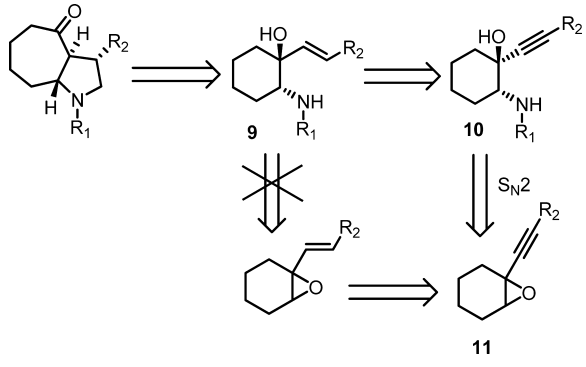


Figure 4. Retrosynthetic analysis.

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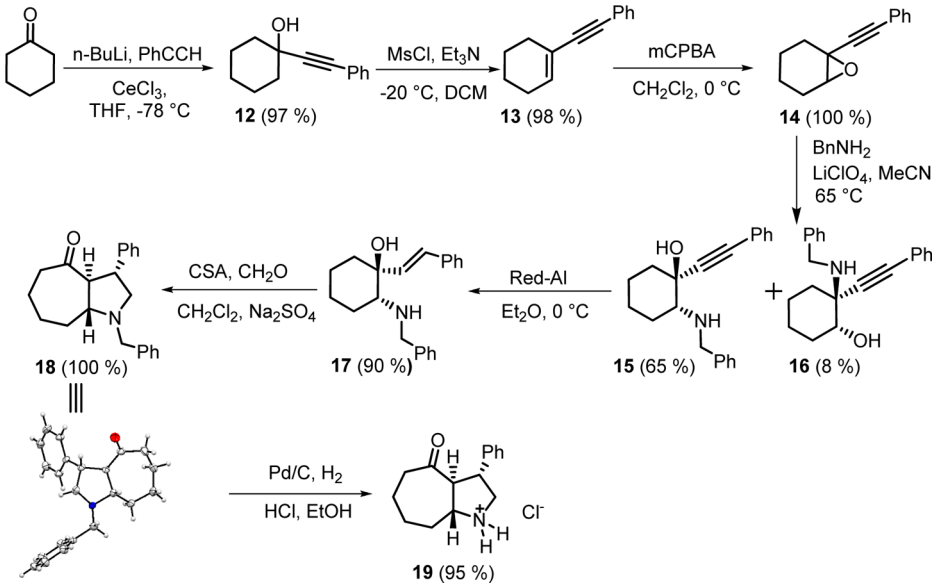
Scheme 3

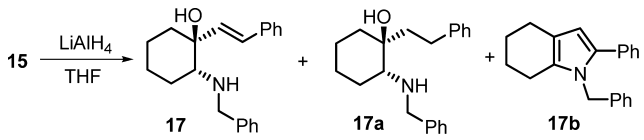


epoxidation of **13** with mCPBA in dichloromethane at 0 °C furnished epoxide **14** in quantitative yield (67% overall yield from the starting cyclohexanone). Using a cerium(III)-mediated addition in the first step[16] and MsCl-Et_3N[17] for dehydration in the second step allowed us to increase the overall yield of **14** to 95% (Scheme 3).

The $LiClO_4$-meditated epoxide ring-opening[15] of **14** using 2 equiv of benzylamine gave amino cyclohexanol **15** and a small amount of regioisomeric product **16** (8−10%). Pure **15** was isolated in 65% yield following the recrystallization of its HBr salt from ethanol:methyl *tert*-butyl ether (MTBE) 1:1 mixture.

Initial attempts to reduce propargyl alcohol **15** using $LiAlH_4$ in THF resulted in a mixture containing the desired product **17**, overreduced product **17a** and pyrrole **17b**, the product of 5-*endo-dig* cyclization (Scheme 4). Alternatively, employing $NaAlH_2(OCH_2OCH_3)_2$ (Red-Al) in Et_2O gave *E*-alkene **17** in a 90% yield after chromatographic purification (Scheme 3).[18]

Scheme 4



For large-scale preparations of **17** (>10 g), this two-step procedure was simplified to avoid column chromatography. The crude mixture containing **15** was separated from the benzylamine using a short silica pad and subsequently reduced using Red-Al (Et_2O, −10 °C). Following an aqueous workup, the crude residue was dissolved in ethanol−MTBE (1:1) and acidified with aqueous HBr to pH 5. Pure **17** (>95%) was crystallized out as its HBr salt with a 65% yield in two steps. Thus, the final optimized route to **17**, the starting material for the aza-Cope−Mannich rearrangement, furnished the target compound in five steps from cyclohexanone with only one chromatographic purification step in 61% overall yield. The experimental simplicity of this route allowed us to prepare **17** on a half-mole scale.

The reaction of **17** with an excess of formalin and 0.9 equiv of camphorsulfonic acid (CSA) in methylene chloride at room temperature gave **18** in a quantitative yield as the sole product (Scheme 3). The structure of **18** was unambiguously confirmed by X-ray crystallographic analysis.[19] Reducing the amount of CSA to 0.3 equiv increased the reaction time only slightly and did not change the yield. After the addition of all the reactants, TLC indicates the immediate consumption of the starting material **17** and only a slow formation of **18**. This result led us to propose an open hemiaminal as the intermediate, in contrast to the stable oxazolidine, which is formed with *cis*-amino alcohols.[3b,8] Debenzylation under hydrogenolytic conditions furnished *β*-amino ketone **19** as HCl salt.

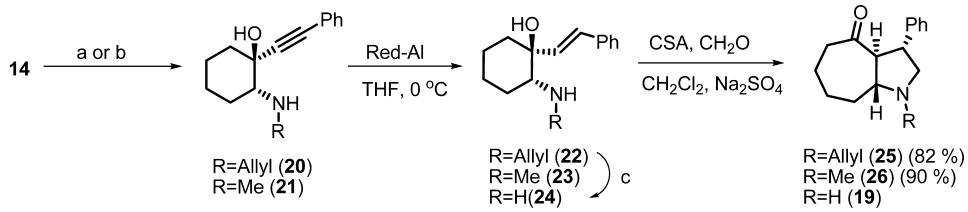
We next examined various factors that may influence the stereochemical outcome of the aza-Cope−Mannich reaction. The nature of the solvent affects the stereoselection in this type of a molecular rearrangement.[6c,e,7c] However, **18** was the only product formed in polar, aprotic solvents (CH_2Cl_2, DMSO, DMF and THF). Running the reaction in solvents with low dielectric conductivity (benzene, dioxane, EtOAc) or EtOH resulted in complex mixtures containing varying amounts of the starting material and the products of its dehydration.

We further investigated whether the stereochemical outcome of the reaction could be controlled by the size of the substituent on nitrogen[6c,7c] (Scheme 2). *N*-Allyl and *N*-Me **22** and **23** amino alcohols were prepared by the epoxide ring-opening of **14** followed by alkyne reduction (Scheme 5). Amino alcohol **24**, containing an unsubstituted nitrogen functionality, was prepared by the Pd-catalyzed deallylation[20] of **22** in 80% yield.

The aza-Cope−Mannich rearrangement of **22** under the same conditions as for **17** (0.3 equiv of CSA, CH_2O, DCM) gave *trans*-amino ketone **25** in an 82% yield. *N*-Me amino alcohol **23** could be completely consumed only after using 0.9 equiv of CSA, furnishing pure *N*-Me amino ketone **26** in 90% yield. N-Unsubstituted amino alcohol **24** produced a complex mixture under the reaction conditions (0.9 equiv of CSA, CH_2O, CH_2Cl_2 or HBr salt, CH_2O, DMSO), which contained a small amount of *trans*-ketone **19** (LC−MS and ^{13}C NMR). The formation of the *trans*-fused product was confirmed by a comparison of the NMR spectra of **25** and **26** with those of **18**

dx.doi.org/10.1021/jo301762a | J. Org. Chem. 2012, 77, 10125−10134

Scheme 5[a]



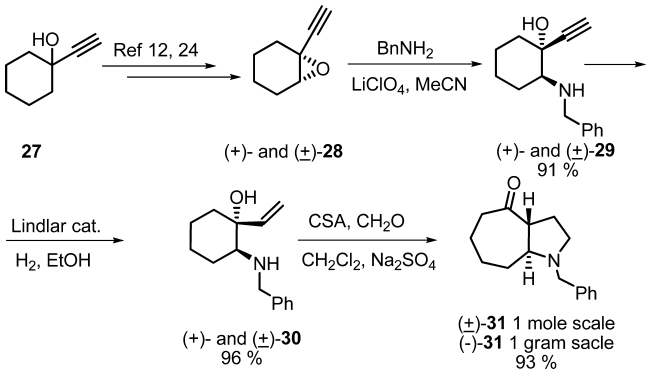
[a]Reagents and conditions: (a) $AllylNH_2$, $LiClO_4$, MeCN, 65 °C, 87%; (b) $MeNH_2$, MeOH–H_2O, 50 °C, 92%; (c) $[Pd(PPh_3)_2]Cl_2$ 1%, *N,N′*-dimethylbarbituric acid, CH_2Cl_2, 61%.

and **19**. In particular, the ^1H NMR spectra displayed characteristic signals at ~3.2 ppm (dd, H-3a), ~3.9 ppm (ddd, H-3) and 2.0–2.6 ppm (ddd, H-8a) with typical coupling constant values of 9.6–10.8 Hz for H-3a–H-8a and 5.5–6.9 Hz for the H-3–H-3a pair. Additionally, the reductive amination (CH_2O, HCOOH) of **19** gave **26** as the only product.

These results indicate that the nature of the solvent or the substituent at the nitrogen atom has little impact on the stereochemical outcome of the aza-Cope–Mannich reaction (Scheme 2, Path A). However we show that bulky alkyl groups greatly simplify the purification of amino ketones and increase their stability (e.g., pure **18** was obtained on the 0.5 molar scale following an aqueous 5% K_2CO_3 workup of the reaction mixture). Also benzyl N-protecting group was chosen because of the ease of its installation and removal.

To test the versatility of our approach, we synthesized amino ketone **31** without the C3 phenyl group (Scheme 6). The ring-

Scheme 6



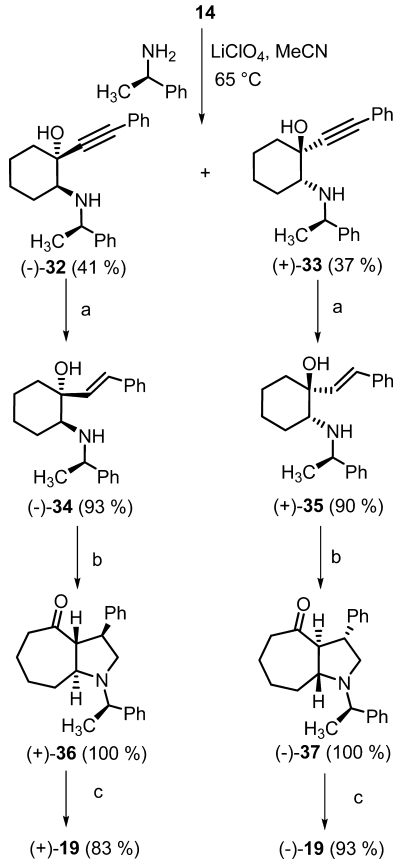
opening of the commercially available oxirane **28** furnished amino alcohol **29** in 80% yield. The Red-Al[18] reduction of **29** in THF resulted in **30**, albeit in low yield (10–15%). Hydrogenation using the Lindlar catalyst significantly improved the yield of **30**. Treatment of **30** with formalin in the presence of CSA (0.9 equiv) gave the desired *trans*-amino ketone **31** in a 93% yield. A comparison of the ^1H NMR spectrum of crude **31** and a separately prepared *cis*-isomer[21] of **31** indicated that no *cis*-isomer is formed during the aza-Cope–Mannich rearrangement of **30**. These transformations (**28** to **31**) were routinely performed on a 1 molar scale.

In addition, amino ketones **31** and **18** do not epimerize under the reaction conditions or upon storage. However, under the action of strong base (NaOMe in MeOH), enantiopure **31** was converted to a 5:2 mixture of its *cis*/*trans*-isomers.[7e] Compound **18** was recovered unchanged under the same conditions, likely as a result of the steric shielding of the C3a α-ketone center by the neighboring phenyl group.

Preparation of Enantiomerically Pure *trans*-3a-Phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one Derivatives. Since in natural products and drug synthesis, it is often necessary to access single enantiomers, stereoselective routes are highly desirable.

The epoxide ring-opening of **14** by chiral (*R*)-1-phenylethylamine[3b,22] resulted in a ~1:1 mixture of diastereomers **32** and **33** in a 78% combined yield (Scheme 7), which were readily separable by column chromatography and were characterized by X-ray crystallographic analysis (as HBr salts).[23] In cases of incomplete chromatographic separation, pure **32** and **33** could be obtained following recrystallizations of

Scheme 7. Stereoselective Synthesis Using a Chiral Auxiliary[a]



[a]Reagents and conditions: (a) $NaAlH_2(OCH_2OCH_3)_2$, THF, 0 °C; (b) CSA, 2.2 equiv CH_2O, CH_2Cl_2, Na_2SO_4; (c) H_2, 1 atm, 10% Pd/C, EtOH, HCl.

dx.doi.org/10.1021/jo301762a | J. Org. Chem. 2012, 77, 10125–10134

their HBr salts from ethanol-MTBE (1:1). Additionally, no product of the C-1 epoxide ring-opening was observed, which is attributed to the increased steric bulk surrounding the amine. The reduction of **32** and **33** using Red-Al furnished allyl alcohols **34** (93%) and **35** (90%), which were readily crystallized from ethanol−MTBE as their HBr salts. A subsequent aza-Cope−Mannich reaction gave ketones **36** and **37** in a quantitative yield. Their configurations were verified by X-ray analysis and matched those predicted by the mechanism.[24,25] The hydrogenation of **36** and **37** under acidic conditions completed the preparation of enantiopure ketones **19** in 83 and 93% yields after recrystallization (ee >95%, as determined by ^{19}F NMR of (*R*)-Mosher amide). These compounds exhibit opposite signs of optical rotations with the same magnitude ($[\alpha]_D^{23} = \pm 2.3$, c = 1, MeOH).

Thus, the routes to both enantiomers of **19** consist of 7 steps from the starting cyclohexanone with only one chromatographic purification to furnish the desired products with 18−19% overall yields. The bottleneck of this sequence is the epoxide ring-opening and subsequent separation of the diastereomers; however, it was routinely performed on a 100 mM scale.

Next we investigated the preparation of the enantiopure ketone **31**. Initial attempts to use the same method as for **19** failed. The epoxide opening of **28** followed by reduction using a Lindlar catalyst and the aza-Cope−Mannich reaction produced a 1:1 mixture of inseparable diastereomers for all three steps. However, epoxide **28** could be readily accessed by an asymmetric Shi epoxidation of the respective alkene in 98% ee,[26] which in turn arose from the commercially available propargyl alcohol **27** (Scheme 6).[14] Employing the reaction conditions used for *rac*-**31** synthesis resulted in (−)-**31** without loss of optical purity. This method allows only moderate scaling up of the reaction (up to several grams of (−)-**31**), as Shi epoxidation requires high dilution and long reaction times to reach full conversion.[27]

CONCLUSION

Thus, we developed a simple high stereoselectivity and high efficiency synthesis of *trans*-fused octahydrocyclohepta[*b*]-pyrrol-4(1*H*)-ones. Its key processes are as follows: (1) high efficiency 3−5 step preparation of *N*-benzyl-*trans*-1-alkenyl-2-aminocyclohexanones from commercially available reagents via 1-alkynyl-oxirane ring-opening with appropriate amines followed by partial reduction of the triple bond (61−75% overall yield with one chromatographic purification for all the steps); and (2) the aza-Cope−Mannich reaction of these compounds with formalin proceeding in very high yields and complete stereoselectivity. All the steps of this synthesis are simple and easily scalable up to 0.5−1 mol with the use of standard laboratory equipment. We showed the possibility of applying this technology for obtaining individual enantiomers with the use of chiral 1-phenylethylamine at the epoxide ring-opening step followed by chromatographic separation of the diastereomeric alcohols. In cases where using the chiral 1-phenylethylamine is ineffective due to inseparability of the diastereomeric mixtures of the intermediate amino alcohols, the developed approach enables obtaining small amounts (up to several grams) of individual enantiomers by using the Shi asymmetric epoxidation. To the best of our knowledge, this is the only example of a completely trans-selective aza-Cope−Mannich reaction.

EXPERIMENTAL SECTION

Compounds **12**−**14** were synthesized using procedures from ref 13. For modified procedures, see ref 8 ($CeCl_3$) and ref 17 ($MsCl-Et_3N$).

1-(Phenylethynyl)cyclohexanol (12). Data: mp = 61.0−61.6 °C (hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.22−1.36 (m, 1H), 1.54−1.79 (m, 7H), 1.96−2.07 (m, 2H), 2.18 (br. s., 1H), 7.26−7.36 (m, 3H), 7.40−7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.4 (2 C), 25.2, 40.1 (2C), 69.1, 84.4, 92.8, 122.9, 128.2 (2 C), 128.3, 131.7 (2C). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.25; H, 8.18.

(Cyclohex-1-en-1-ylethynyl)benzene (13). Data: bp = 130 °C (1 Torr.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.62−1.74 (m, 4H), 2.13−2.21 (m, 2H), 2.22−2.29 (m, 2H), 6.21−6.27 (m, 1H), 7.27−7.36 (m, 3H), 7.42−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.5, 22.4, 25.8, 29.3, 86.8, 91.3, 120.7, 123.8, 127.7, 128.2 (2C), 131.4 (2C), 135.2. Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.32; H, 7.63.

1-(Phenylethynyl)-7-oxabicyclo[4.1.0]heptane (14). Data: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.26−1.52 (m, 4H), 1.95−2.01 (m, 2H), 2.09−2.17 (m, 1H), 2.23−2.31 (m, 1H), 3.47 (t, J = 2.4 Hz, 1H), 7.29−7.34 (m, 3H), 7.44−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 18.9, 19.5, 24.2, 29.8, 50.7, 60.4, 82.0, 89.7, 122.3, 128.3 (2C), 128.5, 131.8 (2C). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.61; H 7.28.

General Procedure for Epoxide Opening (Procedure A). To a vigorously stirred solution of epoxide (**14** or **28**) (10 mmol) and amine (15−30 mmol) in MeCN (10 mL), $LiClO_4$ (15 mmol) was added in one portion. The reaction mixture was warmed at 50−60 °C until the consumption of the starting epoxide occurred (reaction monitored by TLC, typically 5−10 h). The reaction mixture was then allowed to cool to ambient temperature, poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (10:1 hexane−EtOAc) to give colorless or slightly yellow oils.

General Procedure for the Synthesis of HBr Salts of Aminoethanols. To a solution of compound **15** (**17** or **32**−**35**) (1 g) in ethanol (5 mL), aqueous HBr (48 wt %) was added until the pH was ∼4 (∼0.42 mL). The mixture was left undisturbed until the first crystallization occurred (0.5−1 h). Then, 15 mL of MTBE was added, and the resulting suspension was cooled in the freezer for 24 h. The precipitate was filtered and subsequently washed with 20 mL of MTBE:EtOH 10:1 mixture and 20 mL of MTBE. Yield 90−100%.

(1*RS*,2*SR*)- 2-(Benzylamino)-1-(phenylethynyl)cyclohexanol (15). Compound **15** was synthesized by the general procedure A from epoxide **14** (32.0 g) and benzylamine (2 equiv) at 60 °C, and isolated as yellow oil (38.5 g, 78%) alone with a small amount of **16** (8%, 3.9 g) and then recrystallized as as a HBr salt (40.5 g, 65%). R_f = 0.6 (hexane−EtOAc, 5:1). **Free base:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.23−1.47 (m, 3H), 1.52−1.63 (m, 1H), 1.65−1.89 (m, 3H), 2.23 (td, J = 13.6, 2.0 Hz, 1H), 2.49 (dd, J = 11.0, 3.3 Hz, 1H), 3.77 (d, J = 13.1 Hz, 1H), 4.07 (d, J = 13.1 Hz, 1H), 4.45 (br. s., 1H), 7.27−7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.4, 25.3, 29.0, 38.2, 50.8, 65.1, 72.3, 86.2, 90.4, 122.9, 127.1, 128.2 (2C), 128.3 (2C), 128.5 (2C), 131.7 (2C), 140.4; IR ν_{max} (KBr) 3464, 3060, 3028, 2933, 2856, 1490, 1452, 1371, 1070, 756, 694 cm^{-1}; m/z (I_{rel}, %) 305 (M+, 7), 129 (38), 115 (25), 92 (28), 91 (100), 65 (41).

HBr salt: mp = 194.2−194.6 °C (Ethanol); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.03−1.21 (m, 1H), 1.38−1.55 (m, 2H), 1.55−1.69 (m, 2H), 1.69−1.81 (m, 1H), 1.97−2.10 (m, 1H), 2.10−2.24 (m, 1H), 2.71 (d, J = 10.5 Hz, 1H), 4.27 (s, 2H), 6.50 (br.s., 1H), 7.35−7.51 (m, 6H), 7.51−7.68 (m, 4H), 8.70 (br.s., 1H), 9.02 (br.s., 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 23.2, 23.8, 25.8, 40.3, 48.7, 63.0, 69.8, 88.0, 88.2, 122.2, 129.1 (2C), 129.3 (2C), 129.5, 129.6, 130.8 (2C), 131.7, 132.2 (2C); m/z (I_{rel}, %) 305 (MH$^+$, 5), 258 (6), 214 (5), 196 (5), 132 (5), 129 (12), 115 (8), 92 (7), 91 (100), 77 (7), 65 (16), 56 (5), 41 (8), 39 (7); IR ν_{max} (KBr) 3325 (br.), 2935, 2864, 2808, 1564, 1425, 1404, 1070, 1034, 752, 702, 688 cm^{-1}. Anal. Calcd for $C_{21}H_{24}NOBr$: C, 65.29; H, 6.26; N, 3.63. Found: C, 65.23; H, 6.17; N, 3.70.

dx.doi.org/10.1021/jo301762a | J. Org. Chem. 2012, 77, 10125−10134

(1*RS*,2*SR*)-2-(Benzylamino)-2-(phenylethynyl)cyclohexanol (16). Data: ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.26−1.48 (m, 2H), 1.60−1.85 (m, 4H), 1.92−2.00 (m, 1H), 2.19 (br.s., 2H), 2.24−2.31 (m, 1H), 3.51 (dd, J = 11.2, 4.1 Hz, 1H), 3.90 (d, J = 12.1 Hz, 1H), 4.09 (d, J = 12.1 Hz, 1H), 7.24−7.56 (m, 10H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 22.7, 24.3, 32.1, 35.5, 48.0, 62.0, 65.0, 76.2, 88.0, 89.3, 123.0, 127.0, 128.3, 128.4 (2C), 128.5 (4C), 131.8 (2C), 140.8.

(1*RS*,2*SR*)-2-(Allylamino)-1-(phenylethynyl)cyclohexanol (20). Compound **20** was synthesized by the general procedure A from epoxide **14** (4.40 g) and allyl amine (3 equiv) at 50 °C, and isolated as colorless oil (4.90 g, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.12 (br.s., 1H), 1.27−1.36 (m, 2H), 1.56 (td, J = 12.2, 4.8 Hz, 1H), 1.66−1.87 (m, 3H), 2.07−2.19 (m, 1H), 2.24 (dq, J = 8.1, 3.0 Hz, 1H), 2.41 (dd, J = 11.1, 3.8 Hz, 1H), 3.22 (ddt, J = 14.3, 5.9, 1.4 Hz, 1H), 3.51 (ddt, J = 14.3, 5.9, 1.4 Hz, 1H), 4.41 (br.s., 1H), 5.12 (dq, J = 10.2, 1.4 Hz, 1H), 5.23 (dq, J = 17.2, 1.6 Hz, 1H), 5.93 (dddd, J = 17.1, 10.3, 6.0, 6.0 Hz, 1H), 7.30−7.35 (m, 3H), 7.43−7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.4, 25.2, 29.1, 38.1, 49.4, 65.0, 72.7, 86.1, 90.3, 115.9, 122.9, 128.2 (2 C), 128.2 (2 C), 131.7, 137.3; IR ν_{max} (KBr) 3437 (br), 2933, 2858, 1489, 1444, 1369, 1072, 918, 756, 692 cm^{-1}; m/z (I_{rel}, %) 255 (M+, 19), 214 (25), 196 (50), 129 (50), 115 (43), 96 (42), 83 (30), 82 (44), 70 (65), 68 (87), 56 (52), 55 (33), 41 (100), 39 (50). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.01; H, 8.01; N, 5.50.

(1*RS*,2*SR*)-2-(Methylamino)-1-(phenylethynyl)cyclohexanol (21). Epoxide **14** (1.00 g) was dissolved in methanol (10 mL), and aqueous methylamine was added (10 mL). The reaction mixture was warmed at 50 °C until the consumption of the starting epoxide occurred (reaction monitored by TLC, 10 h). The reaction mixture was evaporated and purified via silica gel flash column chromatography using DCM:EtOH (20:1). Yield: 92%, 1.06 g (sum of regioisomers, ∼5:1 in favor to desired); mp = 82−83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20−1.33 (m, 2 H), 1.51−1.85 (m, 4 H), 2.10−2.25 (m, 2 H), 2.49 (s, 3 H), 2.51 (CH_3 signal of minor isomer), 3.45 (br. s., 1 H), 7.23−7.33 (m, 3 H), 7.40−7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.4, 25.1, 28.2, 33.5, 38.5, 67.5, 72.1, 86.2, 90.1, 122.8, 128.2 (3C), 131.7 (2C); IR ν_{max} (KBr) 3062, 2937, 2856, 2802, 1488, 1452, 1103, 1072, 752, 690 cm^{-1}; m/z (I_{rel}, %) 229 (M+, 16), 183 (59), 170 (36), 70 (56), 57 (100), 44 (68), 42 (41). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.23; H, 8.22; N, 5.96.

(1*RS*,2*SR*)-2-(Benzylamino)-1-ethynylcyclohexanol (29). Compound **29** was synthesized by the general procedure A from epoxide **28** (20.0 g) and benzylamine (2 equiv) at 60 °C, and isolated as colorless oil (34.0 g, 91%). For (1*R*,2*S*)-2-(benzylamino)-1-ethynylcyclohexanol: $[\alpha]_D^{23}$ = +31.1 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.18−1.52 (m, 4H), 1.55−1.82 (m, 3H), 2.09−2.21 (m, 2H), 2.38 (dd, J = 11.3, 3.8 Hz, 1H), 2.45 (s, 1H), 3.71 (d, J = 13.0 Hz, 1H), 4.01 (d, J = 13.0 Hz, 1H), 4.33 (br. s., 1H), 7.24−7.29 (m, 1H), 7.31−7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.1, 25.1, 28.7, 37.8, 50.8, 64.7, 71.8, 74.1, 85.2, 127.2, 128.2 (2C), 128.5 (2C), 140.3; IR ν_{max} (KBr) 3465 (br), 3296, 2935, 2858, 1452, 1369, 1095, 1072, 1032, 741, 700 cm^{-1}; m/z (I_{rel}) 229(2 MH$^+$), 138 (9), 132 (11), 120 (9), 92 (12), 91 (100), 65 (26), 53 (18), 53 (18), 41 (14), 39 (18%). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.47; H, 8.17; N, 6.00.

Compounds **32** and **33** were synthesized by the general procedure A from epoxide **14** (10.0 g) and (1*R*)-1-phenylethanamine (1.5 equiv) at 65 °C, and isolated by means of column chromatography (eluent: hexane−EtOAc 30:1) as white solid and colorless oil (6.60 g, 41%; 5.97 g, 37%), respectively.

(1*R*,2*S*)-2-{[(1*R*)-1-Phenylethyl]amino}-1-(phenylethynyl)-cyclohexanol (32). Free base: mp = 85−87 °C; $[\alpha]_D^{23}$ = −41.9 (c = 0.96, MeOH); R_f 0.65 (hexane−EtOAc, 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.11−1.22 (m, 1H), 1.26−1.46 (m, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.61−1.71 (m, 2H), 1.72−1.80 (m, 1H), 2.12−2.23 (m, 3H), 4.04 (q, J = 6.5 Hz, 1H), 4.31 (br. s., 1H), 7.26−7.31 (m, 1H), 7.33−7.38 (m, 7H), 7.48−7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.3, 25.1, 25.8, 28.8, 37.9, 54.0, 62.1, 72.2, 86.2, 90.5, 123.0, 126.9 (2C), 127.2, 128.25, 128.29 (2C), 128.6 (2C), 131.8 (2C), 145.10; m/z (I_{rel}, %) 319 (M$^+$, 18), 304 (11), 214 (17), 197 (11), 196 (23), 169 (31), 156 (12), 129 (26), 115 (13), 105 (100), 103 (15), 91 (13), 79 (20), 77 (24); IR ν_{max} (KBr) 3456, 2931, 1491, 1450, 1369, 1117, 1063, 756, 704 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.92; H, 8.14; N, 4.44.

HBr salt: mp = 258.9−259.6 °C; $[\alpha]_D^{23}$ = −75.5 (c = 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 0.96−1.12 (m, 1H), 1.29−1.40 (m, 1H), 1.55−1.78 (m, 3H), 1.68 (d, J = 6.7 Hz, 3H), 2.03 (d, J = 12.3 Hz, 1H), 2.09−2.19 (m, 1H), 2.50−2.56 (m, 1H), 3.35 (s, 1H), 4.60−4.71 (m, 1H), 6.37 (s, 1H), 7.40−7.50 (m, 6H), 7.54−7.60 (m, 2H), 7.61−7.66 (m, 2H), 8.63 (br. s, 1H), 8.79 (br. s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 20.4, 23.2, 24.0, 25.8, 40.4, 56.2, 63.4, 69.6, 87.9, 88.3, 122.3, 128.4 (2 C), 129.1 (2 C), 129.5 (2 C), 132.2 (2 C), 137.4. Anal. Calcd for $C_{22}H_{26}NOBr$: C, 66.00; H, 6.55; N, 3.50. Found: C, 66.02; H, 6.48; N, 3.55.

(1*S*,2*R*)-2-{[(1*R*)-1-Phenylethyl]amino}-1-(phenylethynyl)-cyclohexanol (33) Free base. Colorless viscous oil: $[\alpha]_D^{23}$ = +33.6 (c = 0.72, MeOH); R_f 0.55 (hexane−EtOAc, 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.86−0.95 (m, 1H), 1.23−1.35 (m, 3H), 1.39 (d, J = 6.2 Hz, 3H), 1.55−1.84 (m, 4H), 1.90−2.00 (m, 1H), 2.22−2.33 (m, 1H), 2.50−2.65 (m, 1H), 3.98 (q, J = 6.4 Hz, 1H), 7.25−7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.4, 23.6, 25.4, 29.7, 38.3, 55.1, 63.7, 72.3, 86.2, 90.4, 122.9, 126.5 (2C), 127.2, 128.2 (2C), 128.6 (2C), 131.8 (2C), 146.6; m/z (I_{rel}, %) 319 (M$^+$, 18), 304 (10), 301 (16), 214 (16), 197 (27), 196 (24), 169 (37), 129 (31), 115 (15), 105 (100), 103 (22), 91 (16), 79 (29), 77 (34), 56 (12); IR ν_{max} (KBr) 3456 (br), 2931 (br), 2856, 1491, 1444, 1371, 1109, 1057, 756, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.65; H, 7.95; N, 4.29.

HBr salt: mp = 193.3−193.7 °C; $[\alpha]_D^{23}$ = +33.8 (c = 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.03−1.19 (m, 1H), 1.41−1.57 (m, 1H), 1.57−1.73 (m, 5H), 1.70 (d, J = 6.8 Hz, 3H), 2.10 (d, J = 12.5 Hz, 1H), 3.01−3.10 (m, 1H), 3.36 (s, 1H), 4.52 (q, J =6.1 Hz, 1H), 6.42 (s, 1H), 7.38−7.48 (m, 6H), 7.51−7.55 (m, 1H), 7.68−7.73 (m, 2H), 8.64 (br. s, 1H), 8.93 (br. s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 19.9, 23.2, 24.0, 27.9, 40.5, 59.3, 65.9, 70.2, 88.0, 88.3, 122.3, 128.9 (2C), 129.1 (2C), 129.2 (2C), 129.4, 129.5, 132.1 (2C), 138.1. Anal. Calcd for $C_{22}H_{26}NOBr$: C, 66.00; H, 6.55; N, 3.50. Found: C, 66.25; H, 6.40; N, 3.42.

General Procedure for Alkyne Reduction (Procedure B). A mixture of the amino alcohol **15** (**20**, **21**, **32** or **33**) (10 mmol) and 25 mL of Et_2O was added dropwise to a solution of RedAl (8.6 mL, 30 mmol) in 25 mL of Et_2O at 0 °C. After gas evolution subsided, the mixture was allowed to warm to room temperature and stirred for 2 h. Excess hydride was quenched by successive dropwise addition 1 mL of water, 1.5 mL of 10% NaOH and 1 mL of water to reaction mixture at −10 °C. The reaction was allowed to warm to room temperature, stirred for an hour and filtered through a thin pad of silica gel. The precipitate was washed with THF. The organic layer was then concentrated to give an oil, which was purified by column chromatography or redissolved in EtOH to be precipitated as the HBr salt (see above procedure).

(1*RS*,2*SR*)-2-(Benzylamino)-1-[(*E*)-2-phenylethenyl]-cyclohexanol (17). Compound **17** was synthesized by the general procedure B from propargyl alcohol 15 (38.48 g), and isolated as colorless oil (33.25 g, 86%) or as a white solid (HBr salt, 44.0 g, 90%). **HBr salt:** mp = 194.2−194.6 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.10−1.24 (m, 1H), 1.45−1.68 (m, 4H), 1.73−1.86 (m, 2H), 2.03−2.13 (m, 1H), 2.74−2.86 (m, 1H), 4.21 (s, 2H), 5.66 (s, 1H, OH), 6.68 (d, J = 15.8 Hz, 1H), 6.90 (d, J = 15.8 Hz, 1H), 7.22−7.31 (m, 1H), 7.31−7.48 (m, 5H), 7.51−7.63 (m, 4H), 8.17 (br.s., 1H, NH), 8.81 (br.s., 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 22.4, 24.4, 24.7, 40.4, 48.3, 63.8, 72.6, 127.4 (2C), 128.16, 128.22, 129.0 (2 C), 129.2 (2 C), 129.5, 130.8 (2 C), 131.8 (2 C), 137.10; m/z (I_{rel}, %) 307 (MH, 5), 198 (13), 146 (18), 132 (16), 131 (33), 120 (34), 115 (12), 106 (44), 92 (23), 91 (100), 82 (15), 80 (16), 79 (12), 77 (29), 65 (46), 56 (22), 55 (13), 51 (14), 43 (15), 41 (21), 39 (20); IR ν_{max} (KBr) 3330 (br.), 2943, 2910, 2871, 2802, 1568, 1452, 1425, 978, 970, 746, 702, 688 cm^{-1}. Anal. Calcd for $C_{21}H_{26}NOBr$: C, 64.95; H, 6.75; N, 3.61. Found: C, 65.11; H, 6.77; N, 3.75.

Free base: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.16−1.33 (m, 2H), 1.35−1.48 (m, 1H), 1.54−1.67 (m, 2H), 1.67−1.77 (m, 1H), 1.86−1.95 (m, 1H), 1.95−2.02 (m, 1H), 2.13−2.21 (m, 1H), 2.57 (dd, J = 11.7, 3.9 Hz, 1H), 3.70 (d, J = 13.1 Hz, 1H), 3.74 (br.s., 1H), 3.97 (d, J = 13.1 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.86 (d, J = 15.9 Hz, 1H), 7.21−7.29 (m, 2H), 7.30−7.37 (m, 6H), 7.40−7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 25.4, 28.3, 38.6, 50.9, 65.1, 74.0, 126.6 (2C), 127.1, 127.4, 128.1 (2C), 128.5 (2C), 128.6 (2C), 130.40, 130.45, 137.3, 140.6.

(1*RS*,2*SR*)-2-(Benzylamino)-1-(2-phenylethyl)cyclohexanol (17a). Data: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.08−1.95 (m, 10H), 2.04−2.12 (m, 2H), 2.49 (dd, J = 11.5, 3.9 Hz, 1H), 2.61 (td, J = 12.8, 5.1 Hz, 1H), 2.83 (dd, J = 12.8, 4.1 Hz, 1H), 3.68 (d, J = 12.7 Hz, 1H), 3.97 (d, J = 12.7 Hz, 1H), 7.18−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.3, 25.2, 28.1, 29.0, 34.2, 34.4, 52.2, 65.9, 73.3, 125.7, 127.1, 128.2 (2C), 128.4 (2C), 128.5 (4C), 140.7, 143.3.

(1*RS*,2*SR*)-1-[(*E*)-2-Phenylethenyl]-2-(prop-2-en-1-ylamino)-cyclohexanol (22). Compound **22** was synthesized by the general procedure B from propargyl alcohol **20** (3.11 g), and isolated as slightly yellow solid (2.43 g, 78%): mp = 71−72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.75 (br.s., 1H), 1.16 (ddd, J = 24.9, 12.9, 3.9 Hz, 1H), 1.35−1.48 (m, 1H), 1.54−1.69 (m, 2H), 1.69−1.77 (m, 1H), 1.84−1.93 (m, 1H), 1.95−2.02 (m, 1H), 2.07−2.15 (m, 1H), 2.51 (dd, J = 11.7, 3.9 Hz, 1H), 3.16 (ddt, J = 13.9, 5.9, 1.4 Hz, 1H), 3.43 (ddt, J = 13.9, 5.9, 1.4 Hz, 1H), 3.78 (br.s., 1H), 5.07 (dq, J = 10.2, 1.4 Hz, 1H), 5.19 (dq, J = 17.2, 1.8 Hz, 1H), 5.88 (dddd, J = 17.1, 10.3, 6.0, 6.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 15.9 Hz, 1H), 7.22−7.28 (m, 1H), 7.31−7.36 (m, 2H), 7.42−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 25.4, 28.4, 38.6, 49.5, 65.0, 73.9, 115.7, 126.5 (2C), 127.4, 128.5 (2C), 130.29, 130.34, 137.28, 137.35; IR ν_{max} (KBr) 3435 (br), 3303 (br), 2931, 2860, 1450, 974, 920, 748, 694 cm^{-1}; m/z (I_{rel}, %) 257 (M+, 32), 198 (44), 131 (91), 115 (46), 109 (41), 105 (35), 103 (67), 96 (99), 91 (77), 82 (36), 77 (43), 70 (91), 68 (51), 56 (48), 41 (100). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.19; H, 8.82; N, 5.33.

(1*RS*,2*SR*)-2-(Methylamino)-1-[(*E*)-2-phenylvinyl]cyclohexanol (23). Compound **23** was synthesized by the general procedure B from propargyl alcohol **21** (1.00 g), and isolated as slightly yellow solid (0.82 g, 81%): mp = 117−8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.14 (dq, J = 12.8, 3.6 Hz, 1 H), 1.20−1.48 (m + br. s., 2 H), 1.49−1.70 (m, 3 H), 1.70−1.78 (m, 1 H), 1.85−1.93 (m, 1 H), 1.94−2.01 (m, 1 H), 2.10−2.19 (m, 1 H), 2.40 (dd, J = 11.9, 3.9 Hz, 1 H), 2.43 (s, 3 H), 6.59 (d, J = 15.9 Hz, 1 H), 6.83 (d, J = 15.9 Hz, 1 H), 7.21−7.27 (m, 1 H), 7.30−7.37 (m, 2 H), 7.40−7.46 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 25.3, 27.5, 33.7, 38.7, 67.6, 74.0, 126.5 (2C), 127.4, 128.5 (2C), 130.2, 130.3, 137.2; IR ν_{max} (KBr) 3057, 2931, 2858, 1467, 1448, 1109, 968, 856, 746, 694 cm^{-1}; m/z (I_{rel}, %) 231 (M+, 11), 96 (15), 91 (11), 83 (32), 77 (13), 70 (59), 57 (50), 56 (15), 44 (100), 42 (21). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.60; H, 9.06; N, 6.03.

(1*RS*,2*SR*)-2-Amino-1-[(*E*)-2-phenylethenyl]cyclohexanol (24). To a solution containing 3.74 g of **22** (14.5 mmol) and 4.50 g of *N*,*N*′-dimethylbarbituric acid (29.0 mmol, 2 equiv) in 140 mL of CH_2Cl_2, 0.16 g of $[Pd(PPh_3)_2]Cl_2$ (1 mol. %) was added under argon. The mixture was stirred for 2−4 h under reflux (reaction monitored by TLC). After cooling, the CH_2Cl_2 was extracted twice with 5% aqueous K_2CO_3 to remove the unreacted NDMBA. The organic phase was dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (20:1 CH_2Cl_2:MeOH) gave an oil, which solidified upon standing (1.92 g, 61%): mp = 118−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.25−2.03 (m, 11H), 2.70 (dd, J = 11.4, 3.9 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 6.84 (d, J = 16.0 Hz, 1H), 7.23−7.30 (m, 1H), 7.31−7.38 (m, 2H), 7.41−7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.3, 25.2, 33.6, 38.7, 59.2, 75.0, 126.5 (2C), 127.5, 128.6 (2C), 129.7, 130.9, 137.2; m/z (I_{rel}, %) 217 (7 MH$^+$), 73 (15), 69 (46), 56 (58), 43 (73), 32 (38), 30 (100%); IR ν_{max} (KBr) 3176 (br.), 2933, 2862, 1595, 1460, 1446, 1333, 1103, 1065, 976, 933, 750, 696 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 76.92; H, 8.42; N, 6.23.

(1*RS*,2*SR*)-2-(Benzylamino)-1-ethenylcyclohexanol (30). To an ethanolic solution of **29** (10.10 g), Lindlar catalyst was added (1.00 g), and the resulting mixture was degassed and stirred under 1 atm of hydrogen until the complete consumption of the starting material occurred (reaction was monitored by TLC every 30 min, hexane:EtOAc 1:1, typically 2 h). The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure to give a colorless oil (9.83 g, 96%). The product usually contains 5−10 mol % inseparable overreduced product ((1*RS*,2*SR*)-2-(benzylamino)-1-ethylcyclohexanol). For (1*R*,2*S*)-2-(benzylamino)-1-ethenylcyclohexanol: $[\alpha]_D^{23}$ = +34.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.06−1.19 (m, 1H), 1.33−1.41 (m, 1H), 1.45−1.60 (m, 2H), 1.54−1.73 (m, 1H), 1.81−1.92 (m, 2H), 2.09−2.16 (m, 1H), 2.51 (dd, J =11.7, 3.9 Hz, 1H), 3.53 (br.s., 1H), 3.68 (d, J = 13.1 Hz, 1H), 3.97 (d, J = 13.1 Hz, 1H), 5.25 (dd, J = 10.8, 2.0 Hz, 1H), 5.49 (dd, J = 17.0, 2.0 Hz, 1H), 6.24 (dd, J = 17.0, 10.8 Hz, 1 H), 7.24−7.31 (m, 1H), 7.31−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.8, 25.3, 28.2, 38.2, 50.8, 64.6, 73.9, 115.4, 127.0, 128.1 (2 C), 128.4 (2 C), 138.6, 140.6; IR ν_{max} (KBr) 3473 (br), 2933, 2860, 1454, 1119, 926, 739, 698 cm^{-1}; m/z (I_{rel}) 231 (4 MH$^+$), 146 (26), 133 (19), 120 (17), 105 (25), 91 (100), 65 (33), 55 (44), 41 (25), 39 (24%). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.02; H, 9.17; N, 6.24.

(1*R*,2*S*)-2-{[(1*R*)-1-Phenylethyl]amino}-1-[(*E*)-2-phenylethenyl]cyclohexanol (34). Compound **34** was synthesized by the general procedure B from propargyl alcohol **32** (1.00 g), and isolated as slightly yellow oil (0.94 g, 93%). **Free base:** Colorless viscous oil; yield 93%; $[\alpha]_D^{23}$ = −97.3 (c = 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.79−0.95 (m, 1H), 1.02−1.52 (m, 6H), 1.22 (d, J = 6.7 Hz, 3H), 1.54−1.61 (m, 1H), 1.72−1.86 (m, 2H), 2.03−2.12 (m, 1H), 2.21 (dd, J = 10.1, 4.0 Hz, 1H), 3.60 (br.s., 1H), 3.90 (q, J = 6.6 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 6.83 (d, J = 15.8 Hz, 1H), 7.15−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 25.3, 25.8, 28.0, 38.5, 54.0, 62.0, 73.8, 126.7 (2C), 126.9 (2C), 127.2, 127.5, 128.7 (4C), 130.5, 130.6, 137.5, 145.3; m/z (I_{rel}, %) 321 (MH, 13), 216 (17), 198 (24), 131 (44), 120 (21), 105 (100), 104 (12), 103 (30), 91 (22), 84 (17), 79 (23), 77 (28), 69 (14), 56 (18), 43 (12); IR ν_{max} (KBr) 3469 (br.), 3026, 2931, 2860, 1493, 1450, 1369, 1120, 975, 733, 700, 519 cm^{-1}.

HBr salt: $[\alpha]_D^{23}$ = −121.3 (c = 1.0, MeOH); mp = 205−210 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 0.97−1.13 (m, 1H), 1.36−1.56 (m, 3H), 1.64 (d, J = 6.7 Hz, 3H), 1.67−1.83 (m, 3H), 2.09−2.19 (m, 1H), 2.52−2.62 (m, 1H), 4.61−4.70 (m, 1H), 5.61 (br. s., 1H), 6.73 (d, J = 15.9 Hz, 1H), 6.92 (d, J = 15.9 Hz, 1H), 7.25−7.31 (m, 1H), 7.34−7.48 (m, 5 H), 7.57−7.64 (m, 4H), 8.12 (br. s., 1H), 8.69 (br. s., 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 20.3, 22.4, 24.47, 24.51, 40.7, 55.4, 63.8, 72.5, 127.4 (2C), 128.2, 128.3 (2C), 128.5, 129.0 (2C), 129.44, 129.48 (2C), 131.6, 137.2, 137.4; IR ν_{max} (KBr) 3342, 2981, 2949, 2829, 1556, 1454, 1350, 1088, 1065, 970, 756, 754, 700 cm^{-1}; m/z (I_{rel}, %) 321 (9 MH$^+$), 198 (17), 131 (32), 105 (100), 103 (35), 79 (28), 77 (32%). Anal. Calcd for $C_{22}H_{28}NOBr$: C, 65.67; H, 7.01; N, 3.48. Found: C, 65.67; H, 6.90; N, 3.43.

(1*S*,2*R*)-2-{[(1*R*)-1-Phenylethyl]amino}-1-[(*E*)-2-phenylethenyl]cyclohexanol (35). Compound **35** was synthesized by the general procedure B from propargyl alcohol **33** (1.00 g), and isolated as slightly yellow oil (0.91 g, 90%). **Free base:** Colorless viscous oil; yield 90%; $[\alpha]_D^{23}$ = +34.3 (c = 0.82, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.91−1.20 (br. s., 1H), 1.12 (dq, J = 12.7, 3.7 Hz, 1H), 1.84 (d, J = 6.5 Hz, 3H), 1.34−1.48 (m, 1H), 1.48−1.62 (m, 1H), 1.63−1.78 (m, 2H), 1.80−1.89 (m, 1H), 1.91−1.99 (m, 1H), 1.99−2.07 (m, 1H), 2.66 (dd, J = 11.9, 3.9 Hz, 1H), 3.87 (br. s., 1H), 3.93 (q, J = 6.5 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.87 (d, J = 15.9 Hz, 1H), 7.21−7.29 (m, 2H), 7.29−7.38 (m, 6H), 7.40−7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 23.6, 25.7, 29.0, 38.7, 55.0, 63.5, 73.8, 126.4 (2C), 126.5 (2C), 127.1, 127.3, 128.5 (4C), 130.45, 130.53, 137.4, 146.8; IR ν_{max} (KBr) 3467 (br), 3026, 2931, 2860, 1493, 1450, 1367, 1119, 1063, 972, 748, 700, 544 cm^{-1}; m/z (I_{rel}, %) 321 (M$^+$, 29), 306 (24), 223 (18), 216 (48), 199 (14), 198 (58), 173 (17), 160 (13), 134 (16), 132 (13), 131 (74), 120 (30), 105 (100), 104 (19), 103 (38), 91 (33), 84 (17), 79 (24), 77 (30), 69 (14), 56 (16), 43 (12).

dx.doi.org/10.1021/jo301762a | J. Org. Chem. 2012, 77, 10125−10134

HBr salt: mp = 185−7 °C; $[\alpha]_D^{23}$ = +56.2 (*c* = 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.21−1.35 (m, 1H), 1.41−1.79 (m, 5H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.86−1.96 (m, 2H), 3.06−3.15 (m, 1H), 4.47−4.55 (m, 1H), 5.71 (br. s., 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.90 (d, *J* = 15.9 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 H, 2H), 7.38−7.46 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.65 (d, *J* = 6.8 Hz, 2H), 8.00 (br., 1H), 8.59 (br., 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 19.5, 22.7, 24.6, 26.0, 40.7, 57.7, 66.0, 72.8, 127.2 (2C), 128.1, 128.4, 128.8 (2C), 129.0 (2C), 129.2 (2C), 129.4, 131.5, 137.2, 138.4; IR ν_{max} (KBr) 3321, 3194, 2945, 2887, 2870, 2756, 2692, 1554, 1450, 1390, 1020, 972, 762, 752, 702, 607 cm^{-1}; *m*/*z* (I_{rel}, %) 321 (6 MH$^+$), 198 (20), 131 (40), 105 (100), 103 (33), 79 (32), 77 (37%). Anal. Calcd for $C_{22}H_{28}NOBr$: C, 65.67; H, 7.01; N, 3.48. Found: C, 66.12; H, 7.24; N, 3.46.

General Procedure for Aza-Cope−Mannich Reaction (Procedure C). To a vigorously stirred mixture of **6** (10 mmol), anhydrous Na_2SO_4 (70 mmol), camphorsulfonic acid (3 mmol) and CH_2Cl_2 (50 mL), 1.64 mL of formalin (37% in water, 22 mmol) was rapidly added at room temperature. The reaction mixture was vigorously stirred overnight. The mixture was washed with saturated $NaHCO_3$ solution (50 mL) and dried over Na_2SO_4. The concentration yields products that are usually pure; however, when necessary, the products were purified via silica gel flash column chromatography using petroleum/EtOAc (10:1) or recrystallized as a free bases or as the HBr salts.

(3*RS*,3a*SR*,8a*RS*)-1-Benzyl-3-phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (18). Compound **18** was synthesized by the general procedure C from **17** (10.0 g), and isolated as white solid (10.4 g, 100%): mp = 106.2−106.7 °C; R_f 0.55 (Hexane:EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.29−1.44 (m, 1H), 1.57−1.80 (m, 2H), 1.86−1.98 (m, 1H), 2.06−2.15 (m, 1H), 2.26 (td, *J* = 10.3, 2.8 Hz, 1H, $C_{(8a)}\underline{H}$), 2.33−2.48 (m, 2H), 2.52−2.60 (m, 2H), 3.05 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.18 (d, *J* = 13.2 Hz, 1H), 3.23 (dd, *J* = 9.9, 6.0 Hz, 1H, $C_{(3a)}\underline{H}$), 3. 89 (ddd, *J* = 8.6, 6.0, 2.2 Hz, 1H, $C_{(3)}\underline{H}$), 4.15 (d, *J* = 13.1 Hz, 1H), 7.13−7.19 (m, 1H), 7.21−7.29 (m, 3H), 7.29−7.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.2, 26.8, 35.1, 40.7, 43.7, 58.1, 60.9, 67.4, 68.7, 126.0, 126.9, 127.5 (2C), 128.3 (2C), 128.5 (2C), 128.6 (2C), 139.3, 147.4, 210.4; IR ν_{max} (KBr) 3369 (br.), 3032, 2933, 2912, 2777, 1693, 1495, 1452, 1136, 760, 742, 700 cm^{-1}; *m*/*z* (I_{rel}, %) 333 (3, MH), 277 (7), 144 (3), 131 (3), 129 (5), 128 (4), 117 (4), 115 (10), 104 (5), 103 (3), 92 (8), 91 (100), 77 (4), 65 (15), 55 (11), 43 (4), 44 (10), 41 (12), 40 (6), 39 (7). Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.97; H, 7.88; N, 4.35.

(3*RS*,3a*SR*,8a*RS*)-3-Phenyl-1-prop-2-en-1-yloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (25). Compound **25** was synthesized by the general procedure C from **22** (0.50 g), and isolated as colorless oil (0.43 g, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24−1.38 (m, 1H), 1.49−1.60 (m, 1H), 1.66−1.79 (m, 1H), 1.84−1.95 (m, 1H), 2.02−2.13 (m, 1H), 2.18 (td, *J* = 10.3, 2.9 Hz, 1H, $C_{(8a)}\underline{H}$), 2.33−2.44 (m, 2H), 2.51−2.61 (m, 1H), 2.62 (t, *J* = 9.6 Hz, 1H), 2.73 (dd, *J* = 13.5, 7.8 Hz, 1H), 3.20 (dd, *J* = 10.2, 6.4 Hz, 1H, $C_{(3a)}\underline{H}$), 3.23 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.56−3.63 (m, 1H), 3.91 (ddd, *J* = 9.1, 6.4, 2.7 Hz, 1H, $C_{(3)}\underline{H}$), 5.13 (d, *J* = 9.4 Hz, 1H), 5.24 (d, *J* = 17.0 Hz, 1H), 5.93 (dddd, *J* = 17.0, 10.2, 7.7, 4.9 Hz, 1H), 7.17−7.23 (m, 1H), 7.27−7.33 (m, 2H), 7.37−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.1, 26.6, 34.9, 40.7, 43.7, 56.6, 60.7, 67.2, 68.3, 117.0, 126.1, 127.5, 128.5, 135.5, 147.0, 210.4; IR ν_{max} (KBr) 2929, 2858, 2789, 1703, 1493, 1454, 1371, 1346, 1219, 1163, 1134, 920, 762, 702 cm^{-1}; *m*/*z* (I_{rel}, %) 269 (5 MH$^+$), 115 (34), 91 (67), 77 (24), 70 (24), 56 (20), 55 (33), 43 (24), 42 (33), 39 (31%). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 79.94; H, 8.44; N, 5.15.

(3*RS*,3a*SR*,8a*RS*)-1-Methyl-3-phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (26). The title compound was prepared by general procedure C from **23**, but using 0.90 equiv of CSA (0.10 g scale). Chromatography CH_2Cl_2:EtOH 10:1. Yield: 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24−1.39 (m, 2 H), 1.46−1.58 (m, 1 H), 1.65−1.78 (m, 1 H), 1.84−1.94 (m, 1 H), 1.95 (td, *J* = 10.6, 2.9 Hz, 1 H, $C_{(8a)}\underline{H}$), 2.03−2.14 (m, 1 H), 2.30−2.43 (m+s, 2 + 3 H), 2.50−2.60 (m, 1 H), 2.63 (t, *J* = 9.6 Hz, 1 H), 3.17 (dd, *J* = 9.8, 2.2 Hz, 1 H), 3.19 (dd, *J* = 10.0, 6.1 Hz, 1 H, $C_{(3a)}\underline{H}$), 3.94 (ddd, *J* = 9.2, 6.1, 2.2 Hz, 1 H, $C_{(3)}\underline{H}$), 7.17−7.23 (m, 1 H), 7.26−7.33 (m, 2 H), 7.36−7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.1, 26.7, 34.7, 40.5, 40.8, 43.7, 63.9, 67.7, 70.4, 126.1, 127.5 (2C), 128.5 (2C), 147.3, 210.3; IR ν_{max} (KBr) 2929, 2854, 2775, 1703, 1454, 702 cm^{-1}; *m*/*z* (I_{rel}, %) 243 (M+, 31), 201 (37), 159 (37), 158 (52), 82 (44), 70 (38), 55 (39), 42 (100), 41 (50%). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.87; H, 8.73; N, 5. 63.

(3a*RS*,8a*SR*)-1-Benzyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (31). Compound **31** was synthesized by the general procedure C from **30** (10.00 g), and isolated as colorless oil (9.78 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.30−1.45 (m, 1H), 1.49−1.62 (m, 1H), 1.63−1.78 (m, 1H), 1.75−1.88 (m, 1H), 1.89−2.00 (m, 1H), 2.00−2.18 (m, 3H), 2.30−2.46 (m, 3H), 2.58−2.67 (m, 1H), 2.93 (td, *J* = 9.1, 1.8 Hz, 1H), 3.10 (d, *J* = 12.7 Hz, 1H), 3.24 (td,, *J* = 10.2, 5.5 Hz, 1H), 3.10 (d, *J* = 12.7 Hz, 1H), 7.23−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.8, 23.4, 27.1, 34.8, 43.6, 53.2, 56.5, 58.3, 67.9, 127.0, 128.3 (2C), 129.0 (2C), 138.8, 211.6; IR νmax (KBr) 2929, 2858, 2790, 1703, 1452, 1356, 1147, 735, 700 cm^{-1}; *m*/*z* (I_{rel}) 244 (10 MH$^+$), 201 (32), 186 (11), 159 (26), 91 (100), 65 (18), 55 (19), 42 (14), 41 (33), 39 (19), 29 (13%). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.73; H, 8.80; N, 5.50. For (3a*R*,8a*S*)-1-benzyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one: $[\alpha]_D^{23}$ = +44.2 (*c* = 1, $CHCl_3$).

(3*S*,3a*R*,8a*S*)-3-Phenyl-1-[(1*R*)-1-phenylethyl]octahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (36). Compound **36** was synthesized by the general procedure C from **36** (1.00 g), and isolated as colorless oil (1.04 g, 100%). Colorless viscous oil: R_f 0.55 (Hexane:EtOAc, 10:1); $[\alpha]_D^{23}$ = +1.03 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.25−1.37 (m, 1H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.57−1.68 (m, 1H), 1.68−1.79 (m, 1H), 1.84−1.94 (m, 1H), 2.06−2.16 (m, 1H), 2.21−2.37 (m, 2H), 2.45−2.57 (m, 1H), 2.57−2.69 (m, 1H), 2.81 (t, *J* = 9.1 Hz, 1H), 3.16−3.25 (m+dd, *J* = 9.9, 6.7 Hz, 2H, $C_{(3a)}\underline{H}$), 3.74 (ddd, *J* = 8.6, 6.7, 3.7 Hz, 1H, $C_{(3)}\underline{H}$), 4.23 (q, *J* = 7.0 Hz, 1H), 7.21−7.30 (m, 3H), 7.30−7.43 (m, 5H), 7.43−7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.7, 23.3, 26.6, 35.2, 40.5, 43.6, 53.7, 56.5, 64.0, 66.6, 126.1, 127.2, 127.6 (2C), 128.1 (2C), 128.3 (2C), 128.5 (2C), 138.9, 146.8, 210.7; IR ν_{max} (KBr) 2931, 1701, 1493, 1452, 1128, 910, 758, 733, 702 cm^{-1}; *m*/*z* (I_{rel}) 333 (9 MH$^+$), 318 (21), 291 (15), 144 (16), 115 (17), 105 (100), 103 (20), 79 (25), 77 (29), 41 (15%). Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.70; H, 8.02; N, 4.20.

(3*S*,3a*R*,8a*S*)-3-Phenyl-1-[(1*R*)-1-phenylethyl]octahydrocyclohepta[*b*]pyrrol-4(1*H*)-one (37). Compound **37** was synthesized by the general procedure C from **35** (1.00 g), and isolated as colorless oil (1.04 g, 100%). Colorless viscous oil. Yield: 100%; R_f 0.50 (Hexane:EtOAc, 10:1); mp = 60−61 °C; $[\alpha]_D^{23}$ = −24.4 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.23−1.34 (m, 1 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.47−1.64 (m, 1 H), 1.70−1.84 (m, 1 H), 1.84−1.97 (m, 1 H), 2.02−2.11 (m, 1 H), 2.27−2.36 (m, 1 H), 2.36−2.48 (m, 1 H), 2.50−2.60 (m, 1 H), 2.63 (td, *J* = 10.3, 3.0 Hz, 1 H, $C_{(8a)}\underline{H}$), 2.78 (dd, *J* = 9.7, 4.0 Hz, 1H), 3.01 (t, *J* =9.3 Hz, 1 H), 3.29 (dd, *J* = 9.7, 6.9 Hz, 1 H, $C_{(3a)}\underline{H}$), 3.84 (ddd, *J* = 8.8, 6.9, 4.0 Hz, 1H, $C_{(3)}\underline{H}$), 4.15 (q, *J* = 6.8 Hz, 1 H), 7.16−7.22 (m, 1 H), 7.24−7.31 (m, 3 H), 7.33−7.40 (m, 4 H), 7.49−7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.6, 23.1, 26.5, 35.5, 41.0, 43.8, 53.4, 55.9, 65.8, 66.6, 126.1, 126.6, 127.49 (2C), 127.53 (2C), 128.1 (2C), 128.4 (2C), 144.7, 146.5, 210.9; IR ν_{max} (KBr) 3475 (br.), 3059, 3028, 2968, 2922, 2856, 2802, 1705, 1697, 1603, 1450, 1375, 1219, 1165, 1134, 1082, 1032, 783, 760, 700, 526 cm^{-1}; *m*/*z* (I_{rel}, %) 333 (29, MH$^+$), 319 (24), 318 (98), 291 (36), 131 (26), 117 (22), 115 (26), 105 (100), 104 (24), 103 (34), 97 (25), 79 (27), 77 (47), 55 (30), 43 (28), 41 (37), 39 (20). Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.93; H, 8.31; N, 4.24.

(3*RS*,3a*SR*,8a*RS*)-3-Phenyloctahydrocyclohepta[*b*]pyrrol-4(1*H*)-one HCl salt (19). A suspension of 10.00 g of **18** in EtOH (100 mL) was acidified with aqueous HCl to pH ∼3 (approximately 2.6 mL needed). Pd/C (l0%, 1 g) was added, and the mixture was degassed and stirred under 1 atm of hydrogen gas for 2 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure. Recrystallization from ethanol gave white solid (7.91

dx.doi.org/10.1021/jo301762a | *J. Org. Chem.* 2012, 77, 10125−10134

g, 95%). **36** and **37** were debenzylated in a similar fashion: mp = 225−229 °C (MeOH); $[\alpha]_D^{23} = \pm 2.3$ (c = 0.5, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 1.18−1.37 (m, 1H), 1.70−1.89 (m, 2H), 1.89−2.06 (m, 1H), 2.06−2.26 (m, 2H), 2.26−2.40 (m, 1H), 2.40−2.63 (m, 1H), 3.12−3.28 (m, 1H), 3.28−3.52 (m, 1H) 3.52−3.72 (m, 2H), 3.72−3.88 (m, 1H), 7.16−7.26 (m, 1H), 7.26−7.36 (m, 2H), 7.36−7.48 (m, 2H), 9.90 (br., 1H), 10.20 (br., 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 22.0, 25.5, 32.5, 43.7, 44.3, 49.7, 61.0, 61.2, 127.4, 128.5 (2C), 128.9 (2C), 140.1, 207.7; IR ν_{max} (KBr) 3384 (br.), 3053, 2937, 2875, 2721, 2652, 1703, 1454, 1400, 1169, 762, 708, 515 cm^{-1}; m/z (I_{rel}, %) 229 (16, MH$^+$), 172 (13), 145 (11), 144 (20), 129 (11), 128 (11), 120 (10), 119 (100), 115 (17), 104 (13), 91 (21), 83 (29), 77 (12), 70 (27), 68 (19), 57 (13), 56 (26), 55(13), 41 (22), 39 (14), 38 (13), 36 (37). Anal. Calcd for $C_{15}H_{20}NClO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.42; H, 7.37; N, 5.03. Free base: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.25−1.40 (m, 1 H), 1.64 (qd, J = 13.1, 3.3 Hz, 1 H), 1.76 (qd, J = 12.3, 3.3 Hz, 1 H), 1.86−1.97 (m, 1 H), 2.00−2.11 (m, 1 H), 2.28−2.42 (m, 2 H), 2.48−2.48 (m, 1H), 2.94 (td, J = 10.6, 3.1 Hz, 1 H), 3.13 (dd, J = 9.7, 8.0 Hz, 1 H), 3.17 (dd, J = 10.8, 5.5 Hz, 1 H, $C_{(3a)}\underline{H}$), 3.37 (dd, J = 11.0, 8.2 Hz, 1 H), 3.98 (td, J = 8.5, 5.5 Hz, 1 H, $C_{(3)}\underline{H}$), 7.16−7.23 (m, 1 H), 7.29 (d, J = 4.50 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.2, 26.6, 37.3, 43.8, 45.7, 53.9, 64.2, 66.9, 126.3, 127.3 (2C), 128.6 (2C), 145.0, 210.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for new compounds and CIF files for **18**, **32**·HBr, **33**·HBr, *ent*-**32**, and **36**·HBr. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kurkin@direction.chem.msu.ru.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research (RFBR), Russia (Grant No. 11-03-00444a).

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