Functionalized 2,5-Disubstituted Benzazepines: Stereoselective Synthesis of 3-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carbonitrile and Related Derivatives

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This paper is dedicated to the career of Clayton H. Heathcock for 40 years of scholarship and teaching at UC Berkeley

Abstract: A stereoselective synthesis of 2-carbonitrile and 2-aminomethyl-substituted 5-phenylbenzazepine derivatives was developed starting from [4-hydroxy-3-(methyloxy)phenyl]acetic acid. The key step in the synthesis is a stereoselective addition of cyanide to 3-methyl-1-phenyl-2,3-dihydro-1*H*-3-benzazepine (**4**) to give a 15:1 *trans*/*cis* mixture of 2-carbonitrile-5-phenyl benzazepine diastereomers **5a**/**5b** in 83% yield. The stereochemistry of the major product was deduced by ^{1}H NMR NOESY analysis. The carbonitrile diastereomers could be separated and further manipulated by reduction to the corresponding aminomethyl derivatives **3a** and **3b** in a stereoselective manner. The aminomethyl benzazepine template **3** has potential to serve as a handle for the synthesis of a variety of derivatives modified at the 2-position of the benzazepine scaffold, as illustrated by an acylation of the primary amine of **3** followed by mild deprotection of the 7-phenol functionality.

Key words: 2,5-*trans*-disubstituted 2-aminomethyl 3-benzazepine, cyanide addition, stereoselective synthesis

2,3,4,5-Tetrahydro-1*H*-3-benzazepines (e.g. compound **1**) are of significant interest due to their pharmacological activity against dopamine and other biological receptors.[2] Nearly all examples that contain a 1-phenyl substituent that have been disclosed are unsubstituted on methylene groups adjacent to the nitrogen (positions 2 and 4) on the benzazepine scaffold.[3] A few years ago we reported the synthesis of 2-alkyl-5-phenyl benzazepines **2** (Figure 1). In one of the routes disclosed, high *cis* selectivity could be obtained, particularly when R was benzyl.[4] In order to extend our understanding of the biological properties of 3-benzazepines substituted within the 7-membered ring, we sought to develop syntheses of the 1-phenyl-3-benzazepine scaffold substituted at the 2-position[5] with functionalized amine substituents as represented by structure **3**. In addition, we sought to develop a route that would generate a free phenol for possible further derivatization. Herein, we wish to report a general method for synthesis of 2,5-disubstituted benzazepines with a nitrile group at the 2-position. Because this route selectively delivers the *trans* configuration between the 5-phenyl and 2-nitrile substituents, this methodogy complements the previous approach that delivers the *cis* stereochemistry as the favored diastereomer.

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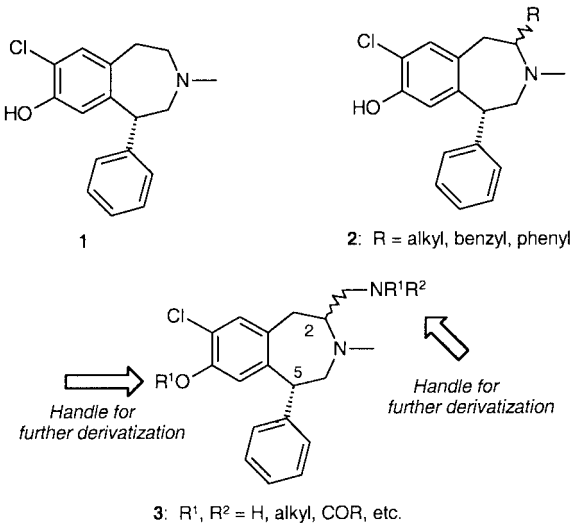
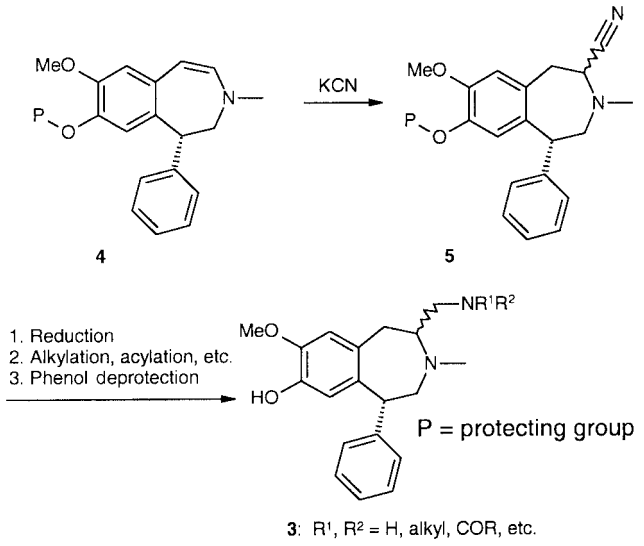


Figure 1 Benzazepines derivatives of interest

Because nitrile addition to 1,2,3,4-tetrahydropyridine systems to afford cyanamines is a well-known process (Equation 1),[6] we envisioned accessing compounds of structure **3** via nitrile addition to the 1-phenyl-2,3-dihydro-1*H*-3-benzazepine system, followed by reduction (Scheme 1). However, in contrast to the 6-membered ring system, little precedent exists for the analogous reaction in benzazepine systems.[7] In addition to testing the efficiency of the nitrile addition reaction itself, we also sought to understand if the features resident in the 3-benzazepine ring system would govern a stereochemical preference for *cis* vs *trans* addition.

Equation 1 Reaction of 1,2,3,4-tetrahydropyridine systems with cyanide

In order to address the foregoing questions, we developed the route to intermediate **4** shown in Scheme 2. This sequence began with commercially available [4-hydroxy-3-(methyloxy)phenyl]acetic acid (**6**) and racemic 2-(methylamino)-1-phenylethanol (**7**), which were coupled under standard conditions to afford hydroxy amide **8** in

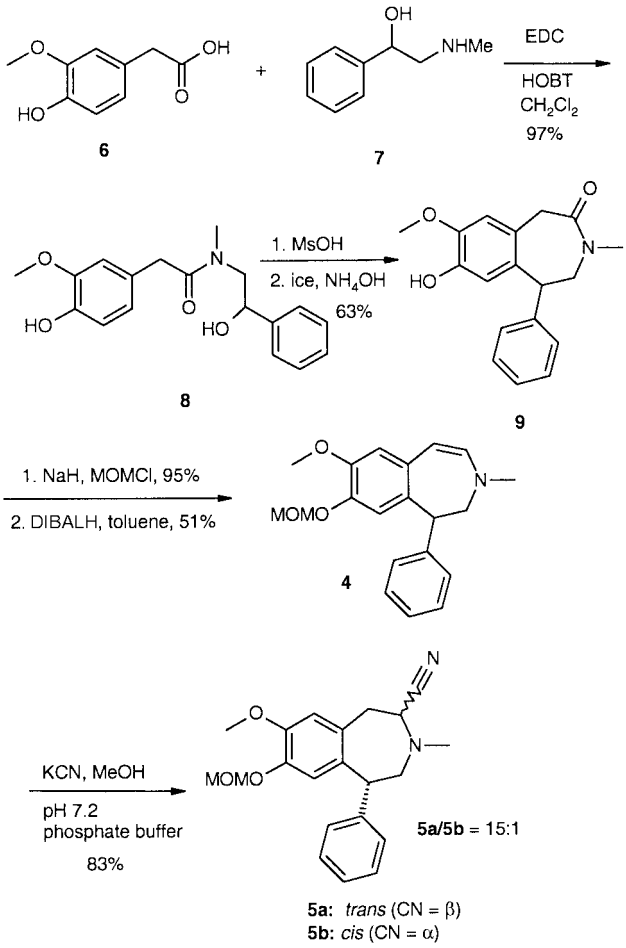


Scheme 1 Proposed route to benzazepine derivatives **3**

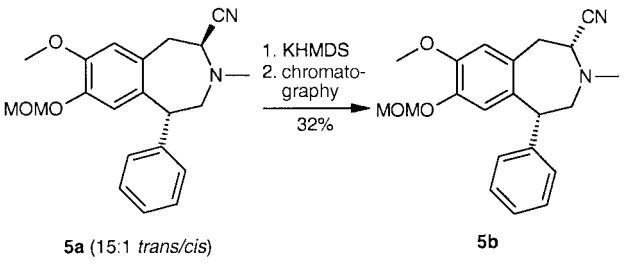
high yield. Subjecting **8** to neat methanesulfonic acid for 3 hours provided the 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one derivative **9** (Scheme 2),[8] which was protected as its MOM ether. The lactam functionality was then reduced with DIBALH in toluene to give, after silica gel chromatography, the novel targeted intermediate 2,3-dihydro-1*H*-3-benzazepine **4**.[9]

With **4** in hand, we proceeded to investigate the nitrile addition to obtain **5**. After experimenting with various conditions that gave sub-optimal yields, we found that treatment of **4** with KCN in methanol in the presence of pH 7.2 phosphate buffer provided the nitrile adduct isolated in 83% yield as a 15:1 mixture of *trans*/*cis* diastereomers **5a**/**5b** (Scheme 2).[10] The structure of the major isomer, which was easily purified via recrystallization or column chromatography, was determined through NOESY experiments (Figure 2). It was found that re-exposure of the isolated minor isomer **5b** to the reaction conditions led to generation of **5a** as the major product (**5a**/**5b** = ca. 6:1), suggesting that the reaction is under a significant degree of thermodynamic control. Although conditions to preferentially generate **5b** were not identified, a ca. 1:1 mixture of nitrile epimers could be obtained by deprotonating the product **5a** with KHMDS and quenching with 2,6-di-*tert*-butyl-hydroxy toluene. The *cis* isomer **5b** could then be readily isolated by chromatography (Equation 2).[11] In this experiment, it is believed that the ca. 1:1 product ratio is a result of unselective kinetic protonation of the trigonal C-2 anionic center, given that under the conditions employed it is unlikely that there is an opportunity for subsequent equilibration following protonation by the phenol.

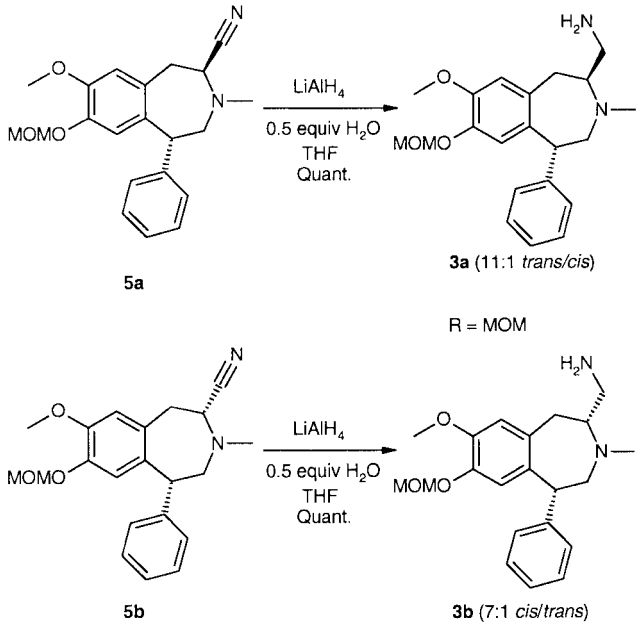
Subjecting either **5a** or **5b** to $LiAlH_4$ in THF led in high yield to the formation of primary amino methyl product **3**. In both instances however, erosion of the stereochemistry at the C-2 position with a ca. 1.5:1 mixture of product diastereomers (with the predominant diastereomer corresponding to that of the starting nitrile) was observed under strictly anhydrous conditions. Interestingly, however, it was found that deactivation of the $LiAlH_4$ by slow addition of 0.5 molar equivalents H_2O (relative to $LiAlH_4$) prior to addition of the nitrile afforded a good diasteomeric excess of either **3a** or **3b** (Scheme 3).[12] The explanation for the suppression of stereochemical erosion with the non-anhydrous conditions is not clear, but may be due to formation of a reducing complex with decreased Lewis acidity, which mitigates the tendency of the carbonitrile substituent to epimerize prior to reduction.[13] A variety of alternative conditions were also attempted to affect reduction of the nitrile [e.g. Raney-Ni, $LiAl(Ot\text{-}Bu)_3H$, $LiBH_4$,



Scheme 2 Synthesis of nitrile derivative **5**



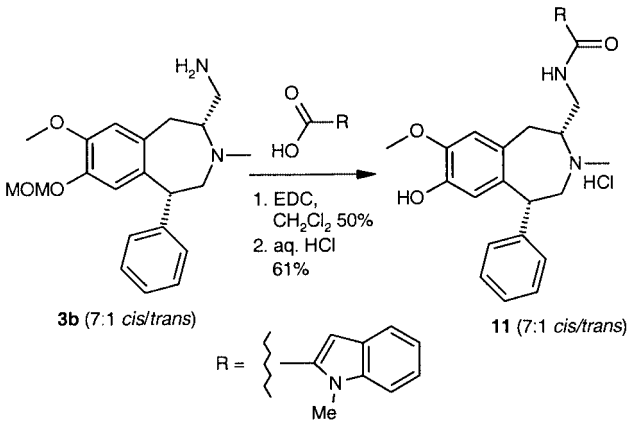
Equation 2 Epimerization to prepare *cis* nitrile **3b**



Scheme 3 Reduction of *cis* and *trans* nitriles **3a** and **3b**

DIBAL]. These conditions afforded either poor yields or a high degree of scrambling at the C-2 stereocenter.

With the benzazepine **3** in hand, we exemplified its utility as a scaffold for further derivatization through coupling it with an amide and liberation of the phenol. In the representative example, the *cis* diastereomer **3b** was coupled with 1-methyl-1*H*-indole-2-carboxylic acid to give the corresponding amide derivative in high yield (Equation 3).[14] The MOM protecting group could then be readily removed to give the corresponding phenol. Similar reactions with the *trans* derivative as well as transformations to related derivatives using other electrophilic moieties [e.g. $(Boc)_2O$, Ac_2O, etc.] have been successfully carried out in good (>80%) yield.



Equation 3 Acylation and deprotection of amine derivative **3b**

In summary, we have developed a synthetic route to the novel 2-aminomethyl substituted benzazepine scaffold **3**. The synthesis of this class of derivatives is accomplished via a nitrile addition reaction to the novel unsaturated benzazepine derivative **4**. In the process of developing this reaction, we observed a high degree of selectivity to preferentially generate the *trans* carbonitrile **5a**. The stereoselectivity of this reaction sequence complements the *cis*-selective approach reported previously.[4] In addition, through our ability to epimerize and readily purify the *cis* derivative **5b**, we are able to access in preparative fashion analogues that are enriched in either diastereomer. The versatility of this chemistry through the synthesis of further analogues in a parallel chemistry format has been explored and will be described in the future.

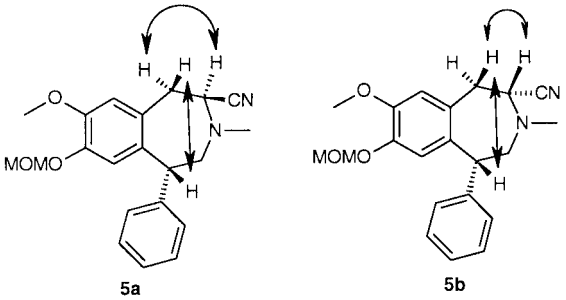


Figure 2 NOE interactions observed for *cis*- and *trans*-**5**

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(9) **Synthesis of 3-Methyl-7-(methyloxy)-8-{[(methyloxy)methyl]oxy}-1-phenyl-2,3-dihydro-1*H*-3-benzazepine (4)**: To a –78 °C solution of lactam **9** (2.63 g, 7.72 mmol) in anhyd THF (50 mL) under N_2 was added via syringe 1.5 M DIBALH in toluene (6.69 mmol, 10.04 mmol). The mixture was stirred at –78 °C for 2 h, allowed to warm to ambient temperature and stirred for 16 h. The mixture was quenched by slow addition of sat. aq NH_4Cl (75 mL). The mixture was extracted with 1:1 hexane–EtOAc (150 mL). The organic layer was separated and stirred rapidly for 2 h with sat. aq sodium potassium tartrate. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to afford a yellow oil. Purification by silica gel chromatography (2:1 hexanes–EtOAc as eluant) gave 1.29 g (51%) of product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 3.43 (s, 3 H), 3.49–3.56 (m, 2 H), 3.85, (s, 3 H), 4.42 (d, 1 H, *J* = 5.2 Hz), 5.02 (d, 1 H, *J* = 11.2 Hz), 5.06 (d, 1 H, *J* = 6.4 Hz), 5.10 (d, 1 H, *J* = 6.4 Hz), 5.88 (d, 1 H, *J* = 11.2 Hz), 6.63 (s, 1 H), 6.73 (s, 1 H), 7.08 (d, 2 H, *J* = 7.6 Hz), 7.16 (t, 1 H, *J* = 7.2 Hz), 7.25 (d, 2 H, *J* = 7.6 Hz).

(10) **Synthesis of *trans*-3-Methyl-8-(methyloxy)-7-{[(methyloxy)methyl]oxy}-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carbonitrile (5a):** To a solution of enamine **4** (1.29 g, 3.96 mmol) in MeOH (70 mL) was added KCN (1.29 g, 19.8 mmol) followed by pH 7.2 phosphate buffer (15 mL). The mixture was stirred at ambient temperature for 3 d. The solvent was removed and the mixture was partitioned between H_2O (50 mL) and 2:1 hexane–EtOAc (75 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to afford 1.16 g (83%) of product as a pale yellow solid judged to be a >15:1 mixture of **5a**:**5b** by ^{1}H NMR. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.29; H, 7.09; N, 7.55. A sample of diastereomerically pure **5a** (0.63 g) was obtained by recrystallization from Et_2O as a white solid, mp 157–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 2.71 (dd, 1 H, *J* = 15.0, 6.1 Hz), 3.02 (t, 2 H, *J* = 6.7 Hz), 3.48 (m, 1 H), 3.50 (s, 3 H), 3.87 (m, 1 H), 3.88 (s, 3 H), 4.15 (d, 1 H, *J* = 4.8 Hz), 5.18 (d, 1 H, *J* = 6.9 Hz), 5.21 (d, 1 H, *J* = 6.9 Hz), 6.69 (s, 1 H), 6.98 (s, 1 H), 7.08 (d, 2 H, *J* = 7.5 Hz), 7.17 (t, 1 H, *J* = 7.6 Hz), 7.24–7.28 (m, 2 H). ^{1}H NMR NOESY analysis indicated that **5a** is the *trans* diastereomer as assigned.

(11) ***cis*-3-Methyl-8-(methyloxy)-7-{[(methyloxy)methyl]oxy}-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carbonitrile (5b)**: The foregoing 15:1 mixture of *trans*/*cis* benzazepines **5a** and **5b** (1.40 g, 3.97 mmol) was dissolved in anhyd THF (60 mL) and the solution was cooled under N_2 to –78 °C. A solution of KHMDS in toluene (11.9 mL of 0.5 M solution, 5.96 mmol) was added and the mixture was stirred for 20 min. A solution of 2,6-*tert*-butylhydroxytoluene (1.54 g, 7.0 mmol) in THF (10 mL) was added slowly via syringe. The mixture was stirred for 1 h at –78 °C, allowed to warm to 0 °C, and partitioned between sat. aq $NaHCO_3$ and 1:1 hexane–EtOAc. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (2:1 hexane–EtOAc) afforded in order of mobility **5a** (0.76 g, 2.15 mmol) and **5b** (mp 137–138 °C) (0.44 g, 1.25 mmol). Compound **5b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 2.92 (dd, 1 H, *J* = 12.4, 9.6 Hz), 2.99–3.08 (m, 2 H), 3.28 (s, 3 H), 3.48 (d, 1 H, *J* = 14.8 Hz), 3.84 (s, 3 H), 4.06 (d, 1 H, *J* = 4.8 Hz), 4.18 (d, 1 H, *J* = 9.6 Hz), 4.89 (s, 2 H), 6.27 (s, 1 H), 6.73 (s, 1 H), 7.17 (s, 1 H), 7.19 (s, 1 H), 7.29 (t, 1 H, *J* = 7.2 Hz), 7.35–7.39 (m, 2 H). ^{1}H NMR NOESY analysis indicated that **5b** is the assigned *cis* diastereomer.

(12) **Reduction of Nitrile 5a or 5b to Give Aminomethyl Benzazepines 3a and 3b. Compound 3a as major diastereomer**: To a solution of 50 mg of **5a** (0.142 mmol) in THF (2.0 mL) was added 4 μL H_2O, followed by 15 mg (0.395 mmol) $LiAlH_4$. The mixture was stirred for 45 min and an additional 17 mg (0.45 mmol) of $LiAlH_4$ was added. The mixture was stirred for 30 min and, after cooling to 0 °C quenched by addition of 30 μL H_2O, 30 μL 15% NaOH and 60 μL H_2O. The mixture was filtered through a pad of Celite and concentrated to afford a quantitative yield of product **3** judged by ^{1}H NMR to be an 11:1 mixture of **3a** and **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.60–2.73 (m, 2 H), 2.75–2.84 (m, 2 H), 3.10 (dd, 1 H, *J* = 14.0, 10.0 Hz), 3.20–3.30 (m, 4 H), 3.38 (s, 3 H), 3.75 (t, 1 H, *J* = 4.5 Hz), 3.85 (s, 3 H), 4.40 (dd, 1 H, *J* = 8.0, 3.0 Hz), 4.98 (d, 1 H, *J* = 6.4 Hz), 5.01 (d, 1 H, *J* = 6.4 Hz), 6.48 (s, 1 H), 6.67 (s, 1 H), 7.15 (d, 2 H, *J* = 7.0 Hz), 7.25 (t, 1 H, *J* = 7.0 Hz), 7.32 (t, 1 H, *J* = 7.0 Hz). **Compound 3b as major diastereomer:** The same procedure as was employed above was carried out on **5b** (101.4 mg, 0.288 mmol) using 6 μL H_2O (0.33 mmol) and 27 mg (0.71 mmol) $LiAlH_4$ in 4 mL THF to supply a quantitative yield of **3** judged to be a 1:7 mixture of **3a**:**3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 2.63–2.81 (m, 4 H), 2.99 (dd, 1 H, *J* = 14.4, 3.2 Hz), 3.21 (d, 1 H, *J* = 14.1 Hz), 3.32 (s, 3 H), 3.47 (dd, 1 H, *J* = 14.4, 10.0 Hz), 3.71–3.74 (m, 2 H), 3.83 (s, 3 H), 4.46 (dd, 1 H, *J* = 10.0, 2.8 Hz), 4.91 (d, 1 H, *J* = 6.4 Hz), 4.93 (d, 1 H, *J* = 6.4 Hz), 6.38 (s, 1 H), 6.62 (s, 1 H), 7.11 (d, 2 H, *J* = 6.8 Hz), 7.23 (t, 1 H, *J* = 6.8 Hz), 7.31 (t, 2 H, *J* = 7.2 Hz).

(13) A possible explanation for the difference in the high diastereoselectivity of the cyanide addition to **4** (Scheme 2) compared to poor selectivity of the $LiAlH_4$ reduction under anhydrous conditions may be the fact that both are under thermodynamic control but involve distinct amine protonation states. At pH 7.2 there may be a strong thermodynamic preference for the protonated form of **5a** relative to the protonated form of **5b**, while under the conditions of the reduction there may be little thermodynamic bias between free base **5a** and **5b**. Experiments to further examine this question by attempting the epimerization of **5a** or **5b** under more basic conditions in the presence of a proton source have not been carried out.

(14) ***N*-{[(2*R**,5*R**)-7-Hydroxy-3-methyl-8-(methyloxy)-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-yl]methyl}-1-methyl-1*H*-indole-2-carboxamide Hydrochloride (11):** To a solution of 7:1 *cis*/*trans* benzazepines **3b**:**3a** obtained from the foregoing procedure (27.3 mg, 0.077 mmol) and *N*,*N*-diisopropylethylamine (27 μL, 0.154 mmol) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21.5 mg, 0.112 mmol), and *N*-methyl indole-2-carboxylate (21 mg, 0.12 mmol) followed by 1-hydroxybenzotriazole monohydrate (3 mg, 0.02 mmol). The solution was stirred at ambient temperature for 15 h. The mixture was partitioned between H_2O and EtOAc. The organic layer was separated, washed with sat. aq NaCl, filtered and concentrated to afford the crude product, which was purified by silica gel chromatography to give 26.0 mg (66% yield) of the pure MOM protected ether amide product as a 7:1 mixture of diastereomers by ^{1}H NMR. ^{1}H NMR (*major*, *cis diastereomer*) resonances include: δ = 2.67 (s, 3 H), 2.78 (dd, 1 H, *J* = 15.0, 7.2 Hz), 2.97 (br s, 1 H), 3.03 (d, 1 H, *J* = 14.4 Hz), 3.19 (dt, 1 H, *J* = 7.7, 3.6 Hz), 3.33 (s, 3 H), 3.53–3.61 (m, 2 H), 3.84 (s, 3 H), 4.04 (s, 2 H), 4.50 (d, 1 H, *J* = 8.4 Hz), 4.94 (s, 2 H), 6.41 (s, 1 H), 6.66 (s, 1 H), 6.74 (s, 1 H), 7.11–7.15 (m, 3 H), 7.24–7.38 (m, 5 H),

7.61 (d, 1 H, *J* = 7.9 Hz). This material was dissolved in MeOH (1.0 mL) and 1.0 N aq HCl was added (1.0 mL). The mixture was stirred at ambient temperature for 1.5 h. The solvent was removed and the mixture was resubjected to the above conditions and lyophilized to 24.6 mg of the product phenol hydrochloride salt **11** as a cream colored powder judged to be a 7:1 mixture of *cis*/*trans* diastereomers. Low res. MS = 470.2 [M + H]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.96 (s, 1.5 H), 3.00–3.10 (m, 3 H), 3.15 (s, 1.5 H), 3.40–3.60 (s, 1.5 H), 3.63 (s, 1.5 H), 3.63–3.80 (m, 1 H), 4.00 (s, 3 H), 4.00–4.10 (m, 1 H), 4.60 (d, 0.5 H, *J* = 8.0 Hz), 5.85 (s, 0.5 H), 5.95 (s, 0.5 H), 6.80–6.95 (m, 1 H), 7.05–7.70 (m, 11 H), 8.62–8.80 (m, 1 H), 8.80–8.81 (s, 0.5 H), 10.06 (br s, 1 H). Anal. Calcd. for $C_{29}H_{31}N_3O_3$·1.9HCl: C, 64.64; H, 6.15; N. 7.80. Found: C, 64.70; H, 6.10; N, 7.66.