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Two General Routes to 1,4-Disubstituted-2,3,4,5-tetrahydro-1*H*-3-benzazepines

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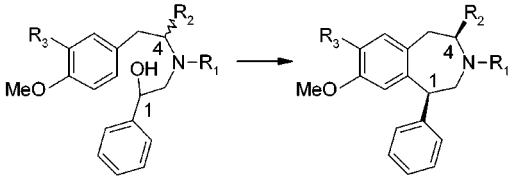
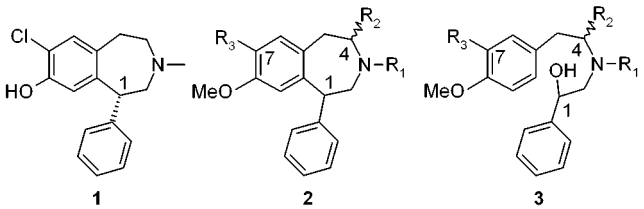
ABSTRACT



Two general routes to 1,4-disubstituted-2,3,4,5-tetrahydro-1*H*-3-benzazepines are described. Both routes utilize an appropriately functionalized phenethylamino alcohol as the penultimate intermediate: the first route makes use of the reductive amination of a benzyl alkyl ketone with α-(aminomethyl)benzyl alcohol, while the second route utilizes the addition of a Grignard reagent to the oxazolidine derived from a substitued phenylacetaldehyde and α-(methylaminomethyl)benzyl alcohol. In all cases studied, the *cis*-1,4-disubstituted-2,3,4,5-tetrahydro-1*H*-3-benzazepine was obtained as the major product.

Chemical entities based on the 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine[1] nucleus have been shown to bind to the dopaminergic family of G-protein-coupled receptors (GPCRs).[2] For example, SCH 23390 (**1**) is a 300 picomolar antagonist of the dopamine D_1 receptor.[2c] As part of a drug discovery effort seeking small molecule ligands for other GPCRs, we became interested in the preparation of 1-phenyl-4-alkyl-3-benzazepines as exemplified by **2** (R_2 = alkyl). Despite the large number of known analogues[2,3] of **1**, a general route to 1,4-disubstituted-3-benzazepines has not been reported.[4]



1 **2** **3**

Typically, 1-phenyl-3-benzazepines (**2**, R_2 = H) have been synthesized via the acid-mediated electrophilic cyclization of an amino alcohol precursor (**3**, R_2 = H).[2] These amino alcohol precursors are readily prepared by the reaction of styrene oxide with the appropriate *N*-methylphenethylamine. The logical extension of this approach for the preparation of 1,4-disubstituted-3-benzazepines (**2**, R_2 = alkyl) was unsuccessful because the requisite *N*-methyl-1-alkyl-2-phenethylamines provided poor yields (<30%) of **3** (R_2 = alkyl) upon reaction with styrene oxide.[5] To circumvent this

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(1) For the remainder of this Letter, we will refer to 2,3,4,5-tetrahydro-1*H*-3-benzazepines as 3-benzazepines.

(2) Reviews: (a) Weinstock, J.; Hieble, J. P.; Wilson, J. W., III. *Drugs Future* **1985**, *10*, 645. (b) Barnett, A.; Gold, E. H.; Chipkin, R. E.; Iorio, L. C. *Adv. Biosci.* **1990**, *77*, 1. (c) Iorio, L. C.; Barnett, A.; Billard, W.; Gold, E. H. *Adv. Exp. Med. Biol.* **1986**, *204*, 1.

(3) (a) Walter, L. A.; Chang, W. K. U.S. Patent 3393192, 1968; *Chem. Abstr.* **1969**, 96507. (b) Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45. (c) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipkin, R. E.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1913. (c) Chumpradit, S.; Kung, M. P., Billings, J. J.; Kung, H. F. *J. Med. Chem.* **1991**, *34*, 877.

(4) The synthesis of a 1-phenyl-4-methyl-3-benzazepine is described in ref 3a, but no additional 4-position substituents were reported.

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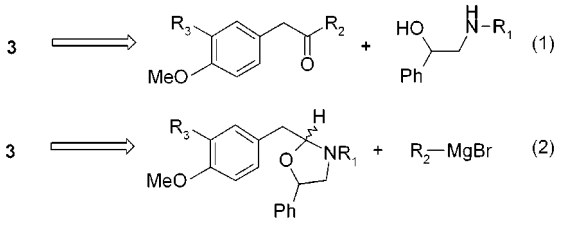
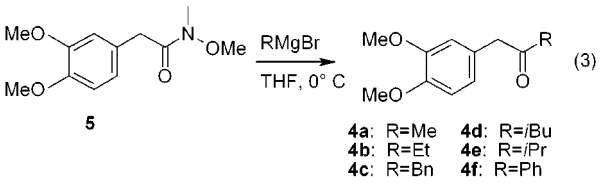
limitation, we have developed two novel and complementary routes to **3** (R_2 = alkyl). The first route is outlined in eq 1,



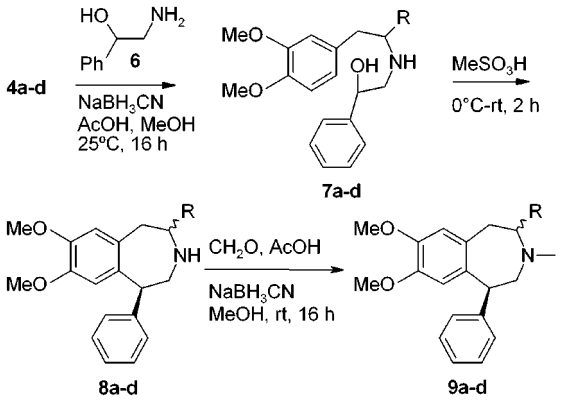
in which **3** (R_2 = alkyl) arises from the reductive amination of an alkyl benzyl ketone. The retrosynthesis described in eq 2 utilizes a Grignard addition to an appropriately substituted oxazolidine to afford **3** (R_2 = alkyl). The successful application of these approaches to the synthesis of 1,4-disubstituted-3-benzazepines is reported herein.

Initially, we focused on the "reductive amination" route described in eq 1, and our synthesis commenced with the preparation[6] of benzyl ketones **4a**−**f**. The conversion of commercially available 3,4-dimethoxyphenylacetic acid to its corresponding Weinreb amide[7] **5** proceeded smoothly under standard conditions. As described in eq 3, addition of methylmagnesium bromide to **5** provided ketone **4a** in a 93% yield. The generality of this method allowed the synthesis of ketones **4b**−**f** with comparable yields.



As described in Scheme 1, ketone **4a** was reacted with α-(aminomethyl)benzyl alcohol (**6**) under standard reductive amination conditions[8] to afford amino alcohol **7a** as a 1:1 mixture of diastereomers. Upon treatment with neat methanesulfonic acid at 0 °C, **7a** cyclized to provide the desired 4-methyl-1-phenyl-3-benzazepine **8a** as an inseparable mixture of diastereomers. Reductive alkylation of N(3) of **8a** with formaldehyde afforded **9a** as a 3:1 mixture of readily separable *cis* and *trans* diastereomers in a 59% yield over three steps. The relative stereochemistry was assigned by NOESY analysis as summarized in Figure 1. The expected pseudoequatorial orientation of the phenyl substituent at C(1) of *cis*- and *trans*-**9a** was confirmed by the observation of an NOE between the pseudoaxial C(1) hydrogen and the pseudoequatorial hydrogen at C(2). The relative stereochemistry of the C(1) and C(4) substituents of *cis*-**9a** was assigned through the observation of an NOE between the pseudoaxial

Scheme 1



C(4) methyl group and the pseudoaxial C(2) hydrogen of *cis*-**9a**. Conversely, the observation of an NOE between the pseudoaxial C(4) and C(2) hydrogens of *trans*-**9a** is consistent with a 1,4-*trans* stereochemical relationship. We subsequently confirmed the relative stereochemistry of *cis*-**9a** via X-ray crystallography of a closely related analogue.

To eliminate the N(3) reductive alkylation step, we explored the use of α-(methylaminomethyl)benzyl alcohol in place of **6**, but we found that only ketone **4a** underwent successful reductive amination with the more hindered amino alcohol. While the use of **6** in the reductive amination step adds a step to the overall synthetic scheme, it does facilitate the introduction of a variety of N(3) substituents at a late stage in the synthesis. We have successfully utilized aldehydes and simple ketones (i.e., acetone) for the reductive alkylation of **8a**−**d**.

Entries 1−8 of Table 1 summarize the 3-benzazepines synthesized via reductive amination of **4a**−**d** with **6**. In all cases, a 3:1 ratio of *cis*:*trans* 3-benzazepines was obtained, suggesting that the C(4) substituent plays a minor role in controlling the stereochemical outcome of the acid-mediated cyclization.

Although this "reductive amination" route to 1,4-disubstituted-3-benzazepines approach is quite general, it has the significant disadvantage that it requires the installation of the R_2 group of **3** at an early stage in the synthesis. In addition, sterically or electronically demanding ketones (i.e., **4e** and **4f**) did not undergo reductive amination with **6**. To

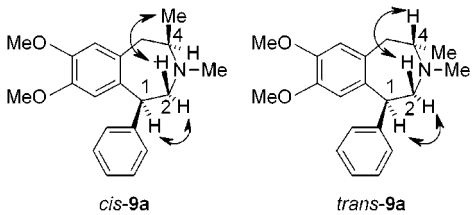
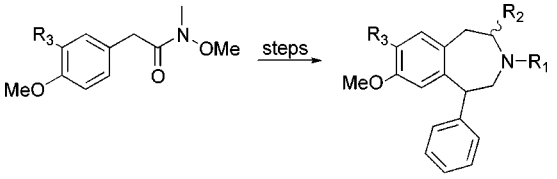


Figure 1. NOEs observed between the C(1), C(2), and C(4) substituents of *cis*- and *trans*-**9a**.

(5) This synthetic step is reported in ref 3a without yield information.
(6) All new compounds reported herein provided analytical data consistent with their proposed structures.
(7) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(8) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Table 1. Synthesis of 1,4-Disubstituted-3-benzazepines



entry	route[a]	R^1	R^2	R^3	*cis*:*trans* ratio	yield, %[b]
1	RA	Me	Me	OMe	3:1	54
2	RA	Me	Et	OMe	3:1	48
4	RA	Me	Bn	OMe	3:1	50
6	RA	Me	*i*Bu	OMe	3:1	52
7	RA	*i*Pr	Me	OMe	3:1	44
8	RA	Bn	Bn	OMe	3:1	49
9	OO	Me	Me	OMe	3:1	68
10	OO	Me	Et	OMe	3:1	72
11	OO	Me	Bn	OMe	3:1	66
12	OO	Me	*i*Bu	OMe	3:1	74
13	OO	Me	*i*Pr	OMe	n.d.[d]	49
14	OO	Me	Ph	OMe	n.d.	54
15	OO	Me	Me	H	*cis* only	42[c]
16	OO	Me	Et	H	*cis* only	38[c]
17	OO	Me	*i*Pr	H	*cis* only	42[c]
18	OO	Me	Bn	H	*cis* only	47[c]

[a] RA = reductive amination; OO = oxazolidine opening. [b] Yields calculated over 4 steps (RA route) or 3 steps (OO route). [c] Does not include the yield of spiropiperidine dione (approximately 20%). [d] n.d. = not determined.

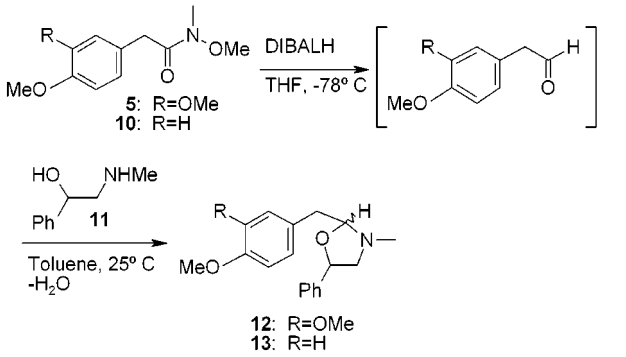
overcome these limitations, we devised the route shown in eq 2 in which the R_2 substituent of **4** is introduced via the addition of a Grignard reagent to the oxazolidine derived from α-(methylaminomethyl)benzyl alcohol and a substituted phenylacetaldehyde. The reaction of Grignard reagents with oxazolidines to afford amino alcohol derivatives is well precedented,[9] although this methodology has not been applied to the synthesis of 1,4-disubstituted-3-benzazepines.[10]

Our synthesis commenced with the conversion of Weinreb amide **5** to 3,4-dimethoxyphenylacetaldehyde with DIBALH in THF at −78 °C (Scheme 2). The unstable aldehyde was not isolated but instead, following a Rochelle's salt workup, was treated immediately with α-(methylaminomethyl)benzyl alcohol (**11**) in toluene and concentrated in vacuo to afford oxazolidine **12** as a 1.2:1 mixture of diastereomers. Oxazolidine **13** was synthesized in an analogous fashion from Weinreb amide **10**. Oxazolidines **12** and **13** were not stable to silica gel chromatography, but they would tolerate an aqueous workup and subsequent storage as a solution in toluene.

(9) (a) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515. (b) Goodson, L. H.; Christopher, H. *J. Am. Chem. Soc.* **1950**, *72*, 358. (c) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256. (d) Takahashi, H.; Niwa, H.; Higashiyama, K. *Heterocycles* **1988**, *27*, 2099. (e) Davidsen, S. K.; Chu-Moyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558.

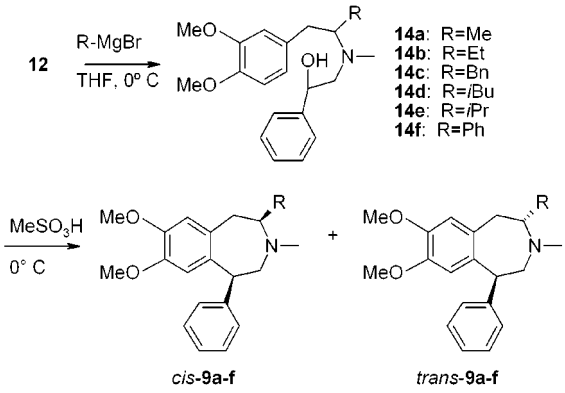
(10) It should be noted that analogous oxazolidines have been utilized for the synthesis of 1-phenyl-3-benzazepine (e.g., **3**, R_2 = H), although in this case the oxazolidines were simply reduced to amino alcohol **4** (R_2 = H) via borohydride reduction: (a) Labaw, C. S.; Tremper, A. W. Eur. Pat. Appl. 177326, 1985; *Chem. Abstr.* **1985**, 60593. (b) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron Lett.* **1989**, *30*, 3581.

Scheme 2



Our initial studies confirmed that addition of a Grignard reagent to **12** yielded the desired amino alcohol product. As described in Scheme 3, addition of methylmagnesium

Scheme 3



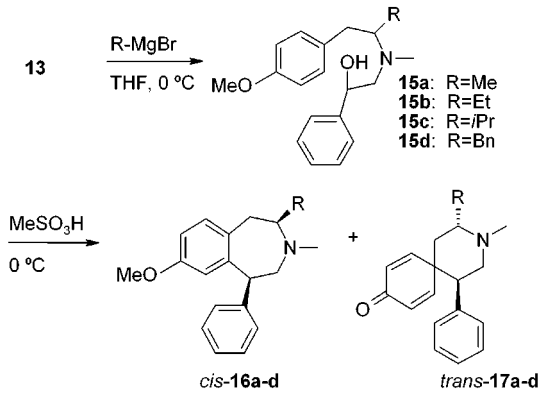
bromide to **12** provided the amino alcohol **14a** as a 1:1 mixture of diastereomers, which upon treatment with neat methanesulfonic acid readily cyclized to provide a 3:1 mixture of the aforementioned 4-methyl-1-phenyl-3-benzazepine diastereomers *cis*-**9a** and *trans*-**9a**. 3-Benzazepines **9b**−**d** were synthesized by analogy. These 3-benzazepines were previously synthesized by the reductive amination of **4a**−**d** (vide supra), a route which required four steps from Weinreb amide **5**. Even though the oxazolidine route saves only one linear step from **5**, the introduction of the C(4) substituent in the penultimate step greatly streamlines the synthesis of C(4) analogues. Moreover, C(4) substituents which were too sterically or electronically demanding (i.e., isopropyl or phenyl) to undergo reductive amination with α-(aminomethyl)benzyl alcohol were easily introduced via the oxazolidine route, affording **9e** and **9f**, respectively. Unfortunately, we were not able to unambiguously assign the stereochemistry of **9e** and **9f**, and so the ratio of *cis* to *trans* diastereomers is unknown. Entries 9−14 of Table 1 summarize the 3-benzazepines synthesized via the opening of oxazolidine **5**.

The cyclization of **14a**−**d** (and **8a**−**d**) to **9a**−**d** consistently provided a 3:1 mixture of *cis* and *trans* 3-benzazepines.

Because amino alcohol **8** is a 1:1 mixture of diastereomers, the 3:1 ratio of *cis*-**9** to *trans*-**9** must result from the equilibration of the C(1) or C(4) center at some point in the acid-mediated cyclization. The available evidence indicates that this occurs via formation of the benzylic cation at C(1), followed by cyclization to form the product 3-benzazepine, rather than via epimerization of the C(1) or C(4) center after cyclization. First, resubjecting *cis*-**9** to cyclization conditions provides no trace of *trans*-**9**, thereby ruling out the possibility of a postcyclization C(1) or C(4) epimerization. A second piece of supporting evidence is a previous study[10b] of the formation of 1-phenyl-3-benzazepines (e.g., **3**, where R_2 = H) from the corresponding amino alcohol precursor. In that case, an enantiomerically pure (>95% ee) amino alcohol (e.g., **4**, R_2 = H) was subjected to the standard cyclization conditions, and the resulting 3-benzazepine product was found to possess a very low ee (6%). Taken together, these results suggest that the C(4) center is unaffected by the cyclization conditions. Consequently, if the C(4) substituent could be introduced stereoselectively in amino alcohol **8**, then the resulting *cis* and *trans* 3-benzazepines would be expected to be enantiomerically pure.[11]

We next turned our attention to the synthesis of C(7)-unsubstituted 3-benzazepines via oxazolidine **13**. As outlined in Scheme 4, addition of methylmagnesium bromide to **13** afforded the corresponding amino alcohol **15a**. Treatment of **15a** with neat methanesulfonic acid at 0 °C provided two products in a 1.8:1 ratio: the desired *cis*-1,4-disubstituted-3-benzazepine (*cis*-**16a**) and an unanticipated minor product which, after extensive spectroscopic analysis, was determined

Scheme 4



to be the [6,6]-spiropiperidine dienone *trans*-**17a**. *Neither the* trans *diastereomer of* ***16a*** *nor the* cis *diastereomer of* ***17a*** *could be detected by* ^{1}*H NMR of the crude cyclization product.* Entries 15−18 of Table 1 summarize the 3-benzazepines synthesized via the opening of oxazolidine **13**.

The synthesis of a spiropiperidine dienone similar to *trans*-**17a** has been reported,[12] and it is noteworthy that although the cyclization precursor is very similar to amino alcohol **15a**, the formation of a 3-benzazepine product was not observed. Moreover, the product spiropiperidine dienone was reported to be unstable in strong acid or base and rapidly reverted to starting material upon exposure to 0.1 N aqueous HCl. We did not observe *trans*-**17a** to be unstable.

In summary, we have developed two general and efficient methods for the synthesis of 1,4-disubstituted-3-benzazepines. The reductive amination route (Scheme 1) allows the rapid analoging of the N(3) position of **3**, while the oxazolidine route (Scheme 3) offers rapid entry into C(4) analogues of **3**. Depending upon the substitution pattern of the aryl ring of the Weinreb amide precursor (**5** or **12**), one of two possible minor products is formed in addition to the major *cis*-1,4-disubstituted-3-benzazepine: starting from **5**, the corresponding *trans*-1,4-disubstituted-3-benzazepine is provided in ∼10% yield; starting from **12**, the corresponding *trans*-1,4-disubstituted spiropiperidine dienone is afforded in ∼20% yield. While side products are generally undesirable in organic synthesis, the unusual divergence in reaction pathways reflected by the formation of either *trans*-1,4-disubstituted-3-benzazepines or *trans*-1,4-disubstituted spiropiperidine dienones merits further investigation.

Acknowledgment. The authors thank Judd Berman, Darryl McDougald, Michael Rabinowitz, Ron Sherrill, and Jim Veal for helpful discussions and Randy Rutkowske for 2-D NMR experiments. J.S.S. was supported by a Glaxo Wellcome summer internship (1995).

Supporting Information Available: Synthetic procedures for the preparation of **9a** from **4a** and **16a** from **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(11) Our asymmetric synthesis of 1,4-disubstituted-3-benzazepines will be disclosed in a subsequent publication.

(12) Sill, A. D.; Housmyer, C. L.; Gibboney, K. *Tetrahedron* **1987**, *43*, 1177.