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A Diastereoselective Synthesis of 2,4-Disubstituted Piperidines: Scaffolds for Drug Discovery

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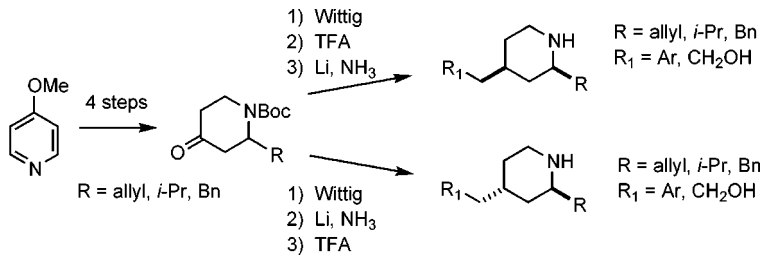
ABSTRACT



A method for the diastereoselective synthesis of 2,4-disubstituted piperidines has been developed which enables the complete control of reaction selectivity merely by changing the order of the reaction sequence. These targets provide convenient platforms for drug discovery which contain easily modified points of diversity.

The piperidine ring continues to be a common moiety in pharmaceutical research. A search of the chemical and patent literature reveals thousands of references to this simple ring system in clinical and preclinical research.[1] Not surprisingly, 1,4-disubstitution of the piperidine ring dominates the literature due to the ease of synthesis and the absence of complicating stereochemical issues. Since 1993 four new commercial products have appeared that possess this substitution pattern as the central component (Figure 1). Aricept (donepezil), an acetylcholinesterase inhibitor,[2] is currently being prescribed for the treatment of Alzheimer's disease. Naramig (naratriptan, **2**), an agonist of 5-HT_{1D} and 5-HT_{1B}, has shown promise in the treatment of migraine headaches.[3] Finally, Risperdal (risperidone, **3**) and Serdolect (sertindole, **4**), both nonselective 5-HT/D_2 antagonists, are currently being utilized in the treatment of schizophrenia.[4] Due to the established clinical value of these drugs, synthetic approaches to this simple ring system have drawn a great deal of attention.

A literature search of 2,4-disubstituted piperidines revealed a paucity of interest in both clinical and preclinical development. The added synthetic difficulties and potentially heightened development costs of this substitution pattern

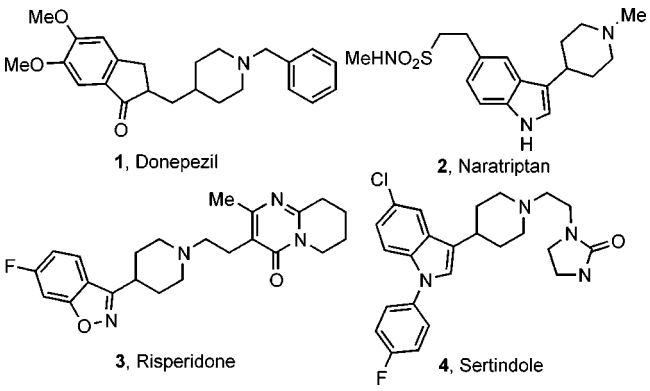


Figure 1. Recent product launches containing a 1,4-disubstituted piperidine ring as one of its major components.

(1) A substructure search of the piperidine ring using the electronic version of the Drug Data Report (MDL Drug Data Report) which includes data from July 1988 through December 1998 revealed over 12 000 discrete piperidine entities that have been mentioned in clinical or preclinical studies.

(2) Yamanishi, Y.; Ogura, H.; Kosasa, T. *Tanpakushitsu Kakusan Koso* **2000**, *45* (6), 1047−1051.

(3) Yevich, J. P.; Yocca, F. D. *Curr. Med. Chem.* **1997**, *4*, 295−312.

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could be the reason for the inactivity in this area of synthesis and drug discovery. Despite these perceived liabilities, it was our belief that the added structural information (available due to the different conformations produced with this alternate structural constitution) and the third site of diversity in this ring system would provide a powerful scaffold for further investigation (Figure 2).

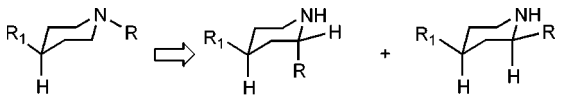


Figure 2. 2,4-Disubstituted piperidines can provide valuable structural information and an additional site of diversity.

Our strategy for the diastereoselective construction of 2,4-disubstituted piperidines relies on a well-known yet underutilized property of *N*-acylpiperidine (Figure 3).[5] Spectroscopic

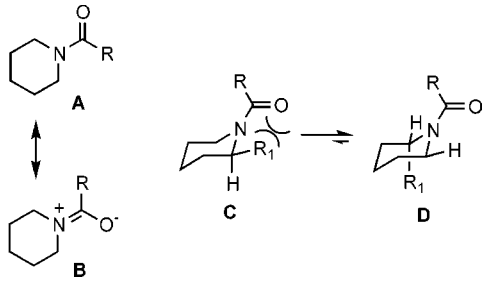
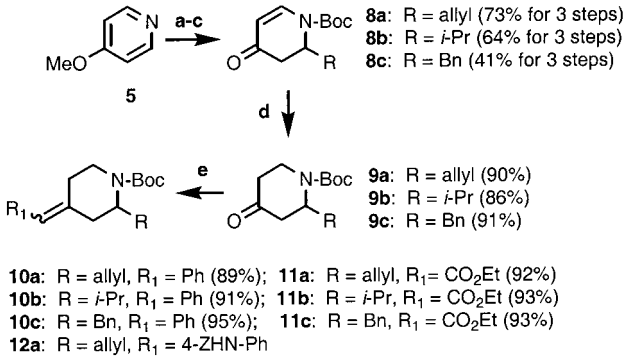


Figure 3. Pseudo $A^{1,3}$-strain in 2-substituted acylated heterocycles controls the ground state conformation (the Paulson effect).

evidence[6] suggests that resonance structure **B** contributes significantly to the ground state conformation of N-acylated piperidine. This electronic effect, coupled with a pendant 2-substituent on the ring, creates a scenario where pseudo allylic strain ($A^{1,3}$) governs the ground state conformation of the heterocycle. Thus, conformation **D**, which minimizes the pseudo allylic strain, is the lowest energy conformation and should dictate the stereochemical outcome of a thermodynamically controlled reaction pathway that generates an additional stereogenic center on the ring. Removal of this control element (nitrogen deprotection) should reverse the diastereochemical outcome of this transformation.

Our initial efforts in this area focused on the dissolving metal reduction of α,β-unsaturated esters and styrenes as a means of generating the thermodynamic reaction products. The synthesis of the required substrates was accomplished by utilizing methodology previously described (Scheme 1).[7]

Scheme 1. Synthesis of the Required Reduction Precursors[a]



[a] Reaction Conditions: (a) PhOC(O)Cl, THF, −20 °C; RMgCl, −78 °C; 10% HCl, 23 °C; (b) MeONa, MeOH, 23 °C; (c) Boc_2O, DMAP, MeCN, 23 °C; (d) Zn, HOAc, 50 °C; (e) *t*-BuOK, $PhCH_2P(Ph)_3Cl$, THF, 23 °C or $(Ph)_3P{=}CHCO_2Et$, toluene, reflux or 2 equiv of *t*-BuOK, 4-ZHN-$PhCH_2P(Ph)_3Cl$, THF, −78 to 23 °C.

Several commercially available Grignard reagents (allyl, *i*-Pr, and Bn) were added to the acylpyridinium salt of 4-methoxypyridine (**5**). We chose to execute this addition reaction via the intermediacy of the acylpyridinium ion generated from phenyl chloroformate. The synthetically more tractable *tert*-butylurethane could then be prepared by base hydrolysis and reprotection of the resulting amide. This sequence resulted in the production of vinylogous imides **8a**−**c** in good overall yields. Conjugate reduction of the olefin with zinc in acetic acid provided piperidones **9a**−**c**.[8] These conditions proved to be superior and more reliable on a large scale than previously published protocols.[9] Wittig olefination provided styrenes **10a**−**c** and α,β-unsaturated esters **11a**−**c** and **12a**[10] in good overall yields.

Reduction of the styryl derivatives **10a**−**c** (as 1:1 mixtures of *E*- and *Z*-olefins, Table 1) using typical conditions for dissolving metal reductions (50 equiv of Li, NH_3, THF, −78 to −28 °C) followed by removal of the nitrogen protecting group provided the *trans*-piperidines (**13a**−**c**) with excellent diastereoselectivity and overall yields.[11] Transformation of the α,β-unsaturated esters **11a**−**c** using the same protocol provided the corresponding amino alcohols (**13d**−**f**) with comparable selectivities and slightly reduced yields.[12] Amino alcohol **13d**, containing three chemically orthogonal moieties, can be used to prepare highly diverse and unique derivatives.

(4) For sertindole, see: Targum S.; Zborowski, J.; Henry, M.; Schmitz, P.; Sebree, T.; Wallin B. *Eur. Neuropsychopharmacol.* **1995**, *5*, 4−71. For resperidone, see: Schotte, A.; Janssen, P. F. M.; Gommeren, W.; Luyten, W. H. M. L.; Van Gompel, P.; Lesage, A. S.; De Loore, K.; Leysen, J. E. *Psychopharmacology* **1996**, *124*, 57−73.

(5) For two examples that use this control element in an intermolecular fashion, see: (a) Krow, G. R.; Alston, P. V.; Szczepanski, S. W.; Raghavachari, R.; Cannon, K. C.; Carey, J. T. *Synth. Comm.* **1990**, *20(13)*, 1949−1958. (b) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103−4110.

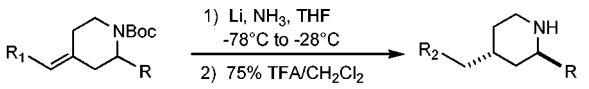
(6) Paulson, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1966**, *5* (10), 899−900.

(7) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27* (38), 4549−4552. An auxiliary-mediated process has also been developed to provide these substrates in optically pure form. See: Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574−2576.

(8) We wish to thank Professor Daniel Comins for making us aware of this reaction.

(9) (a) Comins, D. L.; Dehgani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302. (b) Waldman, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 444.

Table 1. Reduction of the N-Acylated Piperidines



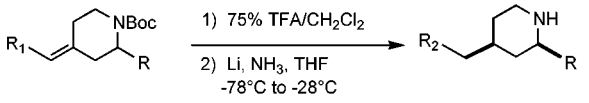
mixture of olefins	R	R_1	R_2	selectivity (*trans*:*cis*)	yield (%)	product
10a	allyl	Ph	Ph	88:1[a]	97	**13a**
10b	*i*-Pr	Ph	Ph	4:1[a]	100	**13b**
10c	Bn	Ph	Ph	18:1[a]	100	**13c**
11a	allyl	CO_2Et	CH_2OH	>20:1[b]	44	**13d**
11b	*i*-Pr	CO_2Et	CH_2OH	8:1[b]	76	**13e**
11c	Bn	CO_2Et	CH_2OH	>20:1[b]	92	**13f**
12a	allyl	4-ZHN-Ph	4-NH_2-Ph	9:1[b]	90	**13g**

[a] HPLC (see supplemental data for details) [b] ^{1}H NMR

Reduction of olefin **12a** conveniently removes the aniline protecting group, unveiling an additional site of chemical diversity.

Congruent with our original goals, changing the order of the synthetic operations is predicted to reverse the selectivity of these reductions. Thus, acid-catalyzed removal of the *tert*-butylurethane from **10a** (Table 2) followed by dissolving

Table 2. Reduction of the Free Amines



mixture of olefins	R	R_1	R_2	selectivity (*trans*:*cis*)	yield (%)	product
10a	allyl	Ph	Ph	1:29[a]	95	**14a**
10b	*i*-Pr	Ph	Ph	1:>30[a]	77	**14b**
10c	Bn	Ph	Ph	1:28[a]	63	**14c**
11a	allyl	CO_2Et	CH_2OH	1:10[b]	55	**14d**
11b	*i*-Pr	CO_2Et	CH_2OH	1:13[b]	94	**14e**
11c	Bn	CO_2Et	CH_2OH	1:>30[b]	60	**14f**
12a	allyl	4-ZHN-Ph	4-NH_2-Ph	1:>10[b]	88	**14g**

[a] HPLC (see supplemental data for details) [b] ^{1}H NMR

metal reduction afforded the *cis*-diastereomer with excellent diastereoselectivity and excellent overall yield. Further examination of Table 2 reveals that comparable selectivities and yields were obtained with the remaining examples studied (**10b**−**c**, **11a**−**c**, **12a**). Merely by changing the order of the synthetic operations one can dictate which stereochemical outcome the reaction will afford. This protocol provides for simple access to all four stereoisomers and should be applicable to other similar ring systems.

The conformational flexibility imparted to these substrates after the removal of the nitrogen protecting group complicated the assignment of the relative stereochemistry. However, this problem was addressed by rigidifying the entire system by conversion to the quinolizinone ring system. Thus, acylation of allyl derivatives **13a** and **14a** followed by ring-closing metathesis (Figure 4) provided quinolizinones **15** and

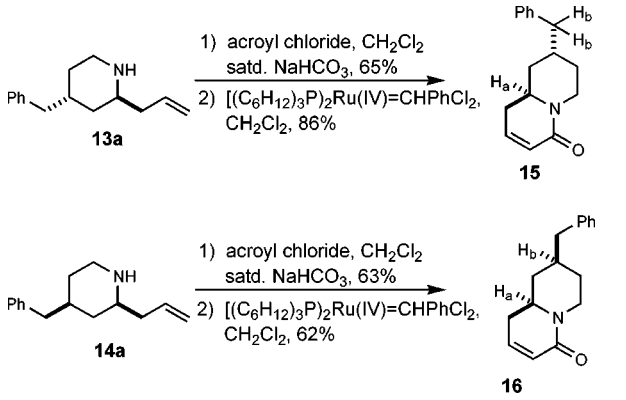


Figure 4. Structural assignment of each diastereomer.

16, respectively. This represents a novel approach to the quinolizidine ring system.[13] These bicycles now possessed predictable and definitive spectroscopic properties necessary for an unambiguous assignment of the relative stereochemistry.[14]

In conclusion, a highly diastereoselective synthesis of 2,4-disubstituted piperidines has been developed which provides access to both diastereomers simply by changing the order of the reaction sequence. These substrates are easily accessible in optically enriched form and should be useful intermediates for the assembly of novel diverse piperidine scaffolds. Further application of this methodology is underway and will be reported in due course.

Acknowledgment. We thank Dr. Paul Anderson, Dr. George Trainor, and Dr. Soo Ko for their support of this research. We thank Greg Nemeth for his help in the assignment of the relative stereochemistry of these compounds. We thank Mike Haas for his valuable help with providing mass spectral data for these compounds.

Supporting Information Available: Representative experimentals and spectral data (^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectra) for all new compounds and the structural assignments for compounds **15** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The synthesis and use of this Wittig reagent will be described elsewhere.

(11) Catalytic hydrogenation (H_2, 10% Pd/C, EtOAc) provided a slight preference (2:1) for the *cis*-diastereomer as measured by ^{1}H NMR spectroscopy.

(12) The chemical yields of these substrates tended to be lower due to side reactions (amide formation and incomplete ester reduction) associated with the ester functionality.

(13) Our work in this area will be disclosed in a separate Letter. For a similar approach to α,β-unsaturated-2-piperidinones, see: Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677−680.

(14) For **15**: An NOE between the proton adjacent to the nitrogen (H_a) and the benzylic protons (H_b) confirmed the *trans* relationship between the substituents. For **16**: An NOE between the proton adjacent to the nitrogen (H_a) and the proton adjacent to the 4-substituent (H_b) confirmed the *cis* relationship between the substituents.