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A Diels−Alder Approach to the Stereoselective Synthesis of 2,3,5,6-Tetra- and 2,3,4,5,6-Pentasubstituted Piperidines

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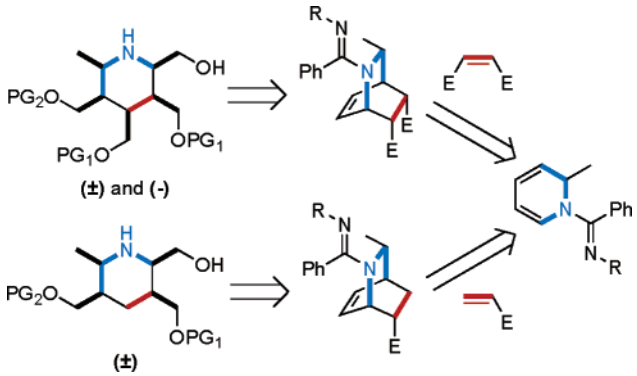
ABSTRACT



A stereoselective synthesis of 2,3,5,6-tetra- and 2,3,4,5,6-pentasubstituted piperidines was achieved from oxidative cleavage of 2-aza-bicyclo-[2.2.2]octene Diels−Alder adducts derived from *N*-protected 2-methyl-1,2-dihydropyridine. A chiral auxiliary mediated asymmetric synthesis of the pentasubstituted piperidine is also demonstrated. This methodology incorporates orthogonal protecting groups, thus providing a piperidine scaffold with easily modified points of diversity.

The pharmacological activity of natural products containing polysubstituted piperidine subunits has generated much interest toward their stereoselective synthesis.[1] The Diels−Alder reaction's ability to produce six-membered rings and potentially generate up to four contiguous stereogenic centers in a stereocontrolled fashion has made it a useful reaction in the synthesis of polysubstituted piperidines. In particular, aza-Diels−Alder reactions of imines[2] with dienes or dienophiles with azadienes[3] generate the piperidine backbone in one step. An alternate route is the Diels−Alder reactions of cyclic dienes such as *N*-carbamoyl-1,2-dihydropyridines with appropriate dienophiles to give azabicyclo[2.2.2]octene adducts, which are subsequently oxidatively cleaved to afford the piperidine backbone.[4] The readily available 1,2-dihydro-

(1) For recent reviews: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

(2) (a) Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C. *J. Org. Chem.* **2004**, *69*, 7114−7122. (b) Barluenga, J.; Mateos, C.; Aznar, F.; Valdes, C. *Org. Lett.* **2002**, *4*, 1971−1974. (c) Badorrey, R.; Cativiela, C.; Diaz-De-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1999**, *55*, 7601−7612. (d) Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C. *J. Org. Chem.* **1999**, *64*, 3736−3740. (e) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594−4599. (f) Waldmann, H. *Synthesis* **1994**, 535−551.

(3) (a) Toure, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429−8436. (b) Tietze, L. F.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1998**, 1629−1637. (c) Boger, D. L.; Hueter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839−11849. (d) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075−2080. (e) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999−3000. (f) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182−3189.

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pyridines (±)-**1** and (−)-**2** from cheap starting materials[5] and the possibility of rapid access to tetra- and pentasubstituted piperidines from mono- and disubstituted dienophiles prompted us to explore this route (Figure 1).

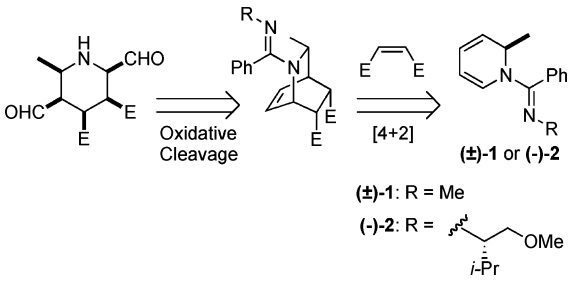


Figure 1. Retrosynthesis for pentasubstituted piperidines.

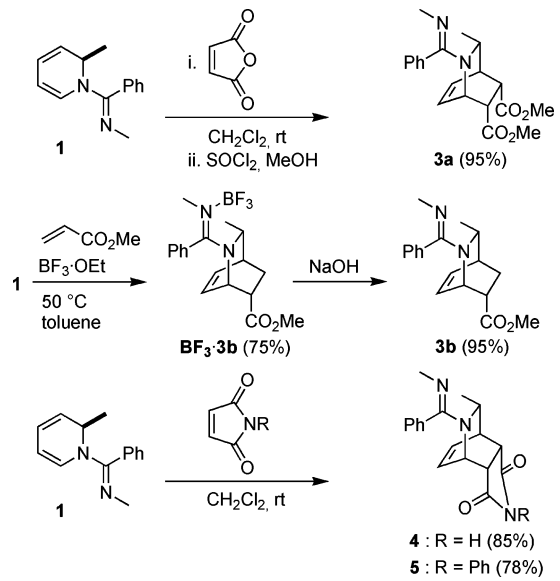
To the best of our knowledge, the Diels−Alder reactions of 1-*N*-amidine-1,3-dienes, whether acyclic or cyclic such as **1**, have not been reported. We herein communicate our progress in this area as well as methods employed to remove the amidine and oxidatively cleave the 2-aza-bicyclo[2.2.2]-octene adducts to afford tetra- and pentasubstituted piperidines.

The cycloaddition reaction of **1** with maleic anhydride in CH_2Cl_2 gave an adduct that was directly converted to the diester to afford **3a** (dr >95:5) (Scheme 1). The cycloadditions with other doubly activated dienophiles such as maleimide and phenyl maleimide proceeded with similar reactivity and selectivity to give **4** (dr >95:5) and **5** (dr >95:5), respectively. All three cycloadditions were facile, requiring 1 equiv of dienophile at room temperature for >95% conversion. The thermal cycloaddition reaction of **1** with methyl acrylate at 50 °C in toluene gave <30% conversion to **3b**. Fortunately, the corresponding Lewis acid promoted Diels−Alder reaction in the presence of $BF_3{\cdot}OEt_3$ at 50 °C afforded $BF_3{\cdot}$**3b** in 75% yield.[6] The free amidine **3b** could be obtained in 95% yield by treatment of $BF_3{\cdot}$**3b** with aqueous NaOH (Scheme 1).[7]

Our results show that these cycloaddition reactions are highly stereoselective, affording one diastereomer in each case (i.e., highly *endo*-selective and high diastereofacial selectivity of addition to diene).

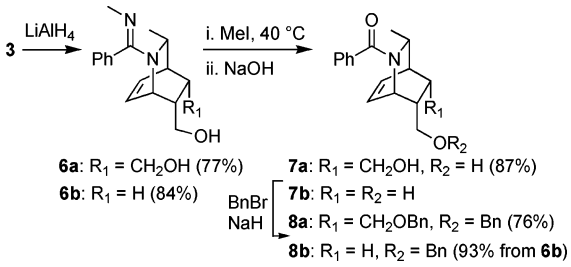
With the Diels−Alder adducts in hand, the focus was directed toward the reductive removal of the amidine moiety.

Scheme 1. Diels−Alder Reaction of **1** with Various Dienophiles



Reactions of **3b** with alane[8] or Birch conditions[9] both led to complex mixtures. We envisioned an alternate strategy that entailed changing the reactivity of the amidine moiety by reaction with MeI to form a dimethylated iminium salt, which could then undergo base hydrolysis to the corresponding amide.[10] Prior to alkylation with MeI, the esters **3a** and **3b** were reduced with $LiAlH_4$ to give **6a** and **6b** (Scheme 2).[11]

Scheme 2. Functional Group Interconversion of Amidine **6** to Benzamide **7**



Indeed, treatment of the iminium salts derived from **6a** and **6b** with aqueous NaOH afforded complete conversion to benzamides **7a** and **7b**, respectively (Scheme 2).

(4) (a) Maison, W.; Grohs, D. C.; Prenzel, A. H. G. P. *Eur. J. Org. Chem.* **2004**, 1527−1543. (b) Arakawa, Y.; Murakami, T.; Ozawa, F.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron* **2003**, *59*, 7555−7563. (c) Maison, W.; Adiwidjaja, G. *Tetrahedron Lett.* **2002**, *43*, 5957−5960. (d) Maison, W.; Kuntzer, D.; Grohs, D. *Synlett* **2002**, 1795−1798.

(5) Prepared from diastereoselective 1,2-nucleophilic additions of organometallic reagents to triflic anhydride activated pyridinium salts: Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.

(6) For a recent example of an isolation of a BF_3−imine complex, see: Ma, Y.; Lobkovsky, E.; Collum, D. B. *J. Org. Chem.* **2005**, *70*, 2335−2337

(7) The yield was calculated on the basis of mass recovery of **3b** from a 1:1 complex of BF_3:**3b**.

(8) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368−2371.

(9) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747−2750.

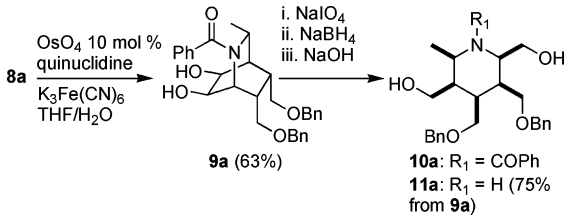
(10) For hydrolysis of dimethyliminium salts, see: (a) Manh, G. T.; Purseigle, F.; Dubreuil, D.; Pradere, J. P.; Guingant, A.; Danion-Bougot, R.; Danion, D.; Toupet, L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2821−2828. (b) Nakayama, J.; Otani, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* **1997**, *38*, 5013−5016. (c) Alonso, M. A.; Ubeda, J. I.; Avendano, C.; Menendez, J. C.; Villacampa, M. *Tetrahedron* **1993**, *49*, 10997−11008. (d) Kantlehner, W.; Greiner, U. *Synthesis* **1979**, 339−342. (e) Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 917−918.

(11) Compound **6a** crystallized as monohydrate; see Supporting Information for crystal structure.

The newly acquired benzoyl moeity served as *N*-protecting group to be removed at a later stage. To prevent acetal formation from aldehydes formed during an oxidative cleavage of alkenes **7a** and **7b**, the hydroxyl groups were benzylated to give **8a** and **8b**, respectively (Scheme 2).

Dihydroxylation of **8a** using a modification of the racemic Sharpless procedure, known to dihydroxylate sterically hindered alkenes, gave poor conversions to **9a** (<40%).[12] We later found that the use of quinuclidine as an additive gave reproducible and improved yields of **9a** (63%, dr >95:5) (Scheme 3). As expected, the sterically less hindered face

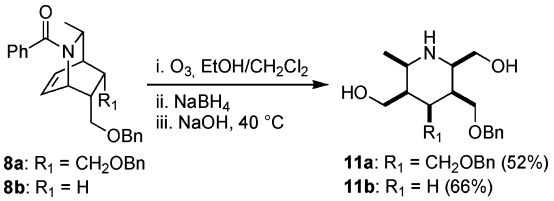
Scheme 3. Two-Step Oxidation−Reduction−Hydrolysis



was dihydroxylated.[4a,12b,13] Diol **9a** was cleaved using silica-supported sodium periodate.[14] A reductive workup with $NaBH_4$ was used to avoid epimerization of the dialdehyde.[15] Upon NaOH quench, it was observed that the benzamide moiety of **10a** was prone to a neighboring hydroxyl facilitated base hydrolysis and **9a** gave **11a** (75%) in one step (Scheme 3).

Taking this facilitated hydrolysis into account, we performed the ozonolysis of **8a** and **8b** followed by $NaBH_4$ reduction and treatment with NaOH at 40 °C to afford **11a** (52%) and **11b** (66%) in one pot (Scheme 4). NMR data

Scheme 4. One-Pot Oxidation−Reduction−Hydrolysis



supports the all-*cis* relative configuration of substituents for **11a** and **11b**.[16] Crystal structure confirmed the all-*cis* configuration of **11a** (Figure 2).

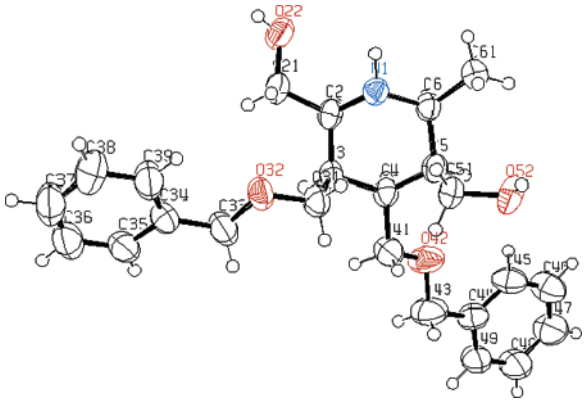
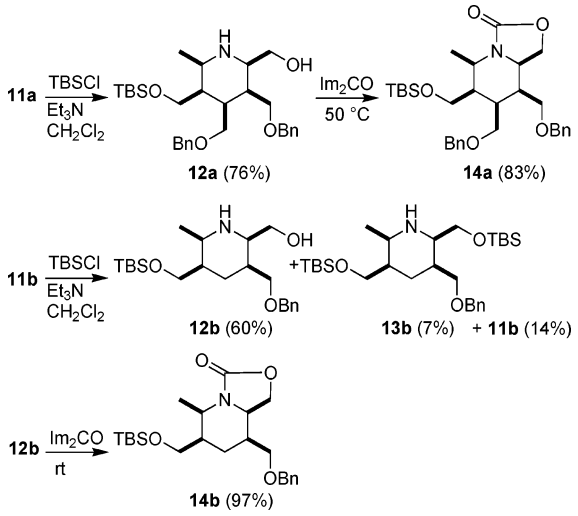


Figure 2. Crystal structure of **11a**.

The pharmacological importance of β-hydroxylamines and the potential use of substrates such as **11a** and **11b** in natural product synthesis provided the impetus to differentiate the primary alcohols.[17] The silylation of **11a** and **11b** was highly regioselective for γ-hydroxyl (γ:β 15:1 for both) and afforded **12a** (76%) and **12b** (60%) (Scheme 5).[18] The regioselectivity

Scheme 5. Regioselective Silylation of Diols **11a** and **11b** and Ensuing Carbamate Formation



may be explained due to the reduced nucleophilicity of the β-hydroxyl group as a result of hydrogen bonding to the neighboring amine. The derivatization to carbamates **14a** and **14b** provided confirmation of silylation at the γ-hydroxyl

(12) DABCO and $MeSO_2NH_2$ as additives: (a) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120−14125. (b) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189−3191. (c) Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095−1104.

(13) Koenigsberger, K.; Faber, K.; Marschner, C.; Penn, G.; Baumgartner, P.; Griengl, H. *Tetrahedron* **1989**, *45*, 673−680.

(14) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.

(15) The dialdehyde readily epimerizes overnight at room temperature.

(16) See Supporting Information for NMR analysis (NOE and ^3J) of related **12a** and **12b**.

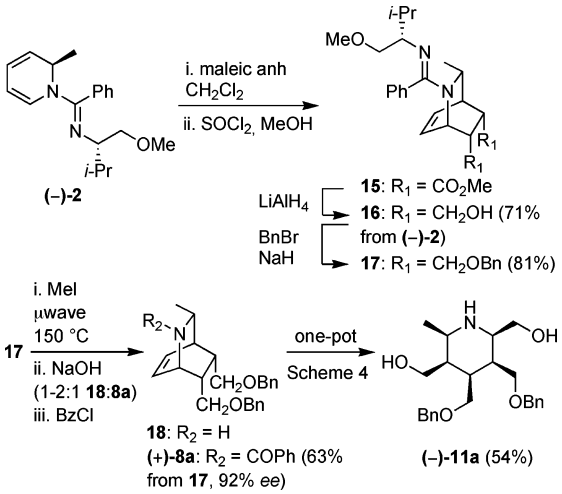
(17) For bioactive amino alcohols, see: (a) Wu, X.; Dubois, K.; Rogiers, J.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 3043−3051. (b) Harrison, T.; Williams, B. J.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2733−2734. (c) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545−2550. For related tetrasubstituted natural product **223A**, see: (d) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715−1717.

(18) The silylation of **11b** gave an easily separable mixture of **12b** (60%), **13b** (7%) and recovered **11b** (14%).

(Scheme 5). An analysis of NMR data showed that the piperidine ring of **14a** favors a chair conformation. However, the piperidine ring of **14b** adopted a twist-boat so as to avoid unfavorable 1,3-diaxial interactions between the CH_2OTBS and CH_2OBn substituents.[19] This avoidance of 1,3-diaxial interactions may explain the relatively facile formation of **14b** at room temperature compared to **14a** at 50 °C (Scheme 5).

To apply our methodology to the synthesis of enantioenriched piperidines, we investigated a chiral auxiliary approach to **11a** from (−)-**2**. The facile reaction of (−)-**2** with maleic anhydride (1 equiv, rt) followed by diester formation to **15** and $LiAlH_4$ reduction gave **16** (71% over three steps, *dr* >95:5) (Scheme 6). As was the case with

Scheme 6. Chiral Auxiliary Approach to (−)-**11a**



diene **1**, the cycloaddition of (−)-**2** with maleic anhydride was highly diastereoselective. Dibenzylation of **16** gave **17** (81%). The alkylation−hydrolysis protocol previously used to convert **6** to **7** was ineffective to convert **17** to benzamide (+)-**8a**. This was a consequence of a slow rate of alkylation of **17** with MeI at 40 °C. The rate of alkylation was dramatically increased with μwave at 150 °C. The ensuing hydrolysis of iminium salt gave varying mixtures of (+)-**8a** and **18**. The "free" amine **18** was conveniently converted in situ to (+)-**8a** by addition of benzoyl chloride. Finally, (+)-**8a** was isolated in 63% from **17** (Scheme 6). The enantiopurity of (+)-**8a** (92% ee) was established by SFC on chiral stationary phase.[20] The one-pot oxidation−reduction−hydrolysis protocol was used to convert (+)-**8a** to (−)-**11a** in 54%.

In conclusion, we have developed an expedient and stereoselective synthesis of tetra- and pentasubstituted piperidines. In particular, starting from 1-*N*-amidine-1,3-dienes **1** or (−)-**2**, the polysubstituted piperidines (±)-**11a**, (±)-**11b**, and (−)-**11a** were conveniently obtained in six steps in 25%, 37%, and 20% overall yields. The key reactions of this methodology were the diastereoselective [4 + 2] cycloadditions of **1** and (−)-**2**, the facile functional group conversion of amidines **6** to benzamides **7**, and the one-pot oxidation−reduction−hydrolysis of **8** to **11**. In addition, it was demonstrated that **11** could undergo regioselective silylation to provide versatile building blocks **12**.

Acknowledgment. This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), Merck Frosst Canada & Co., Boehringer Ingelheim (Canada) Ltd., and the Université de Montréal. We would like to thank Charles Banville for his preliminary work on potential routes and Francine Bélanger-Gariépy for X-ray analysis. M.S. would like to thank Alexandre Lemire and Dr. Thilo Focken for useful conversations.

Supporting Information Available: General information, experimental procedures, and characterization data for **3**−**9** and **11**−**17**, crystal structures of **6a** and **11a** in CIF format, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See Supporting Information for NMR analysis of **14a** and **14b**.

(20) See Supporting Information for SFC traces.