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Total Synthesis of (±)-Lennoxamine and (±)-Aphanorphine by Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins

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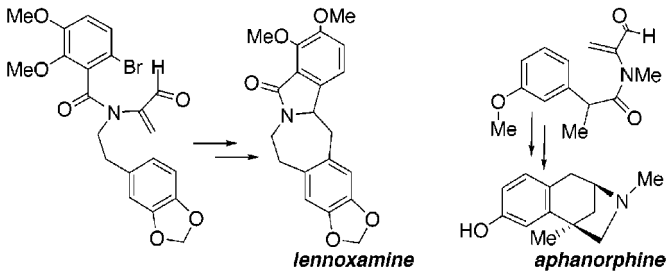
ABSTRACT

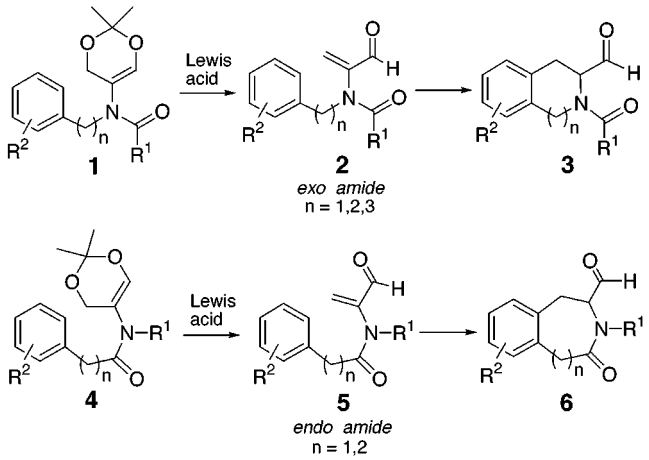


Intramolecular electrophilic aromatic substitution reactions of 2-amidoacroleins constitute the key steps in the total syntheses of lennoxamine and aphanorphine. The aldehyde moiety of one cyclization product was transformed to a double bond, which was then engaged in a radical cyclization to produce the complete ring system of lennoxamine. The aldehyde functionality of the other cyclization product was converted to the corresponding mesylate, which underwent intramolecular displacement by a lactam enolate to furnish the ring system of aphanorphine.

We recently reported on a new method for the preparation of a variety of heterocyclic ring systems that embody a β-phenethylamine substructure.[1] Thus, the 5-amido-4*H*-1,3-dioxins **1** and **4** (Scheme 1) were subjected to Lewis acids to effect catalyzed retrocycloadditions leading to the 2-amidoacroleins **2** and **5**, respectively, which underwent concomitant intramolecular electrophilic aromatic substitution reactions to afford the desired heterocyclic amides **3** or lactams **6**. We wished to test the utility of this methodology in the context of natural product synthesis. In particular, the aldehyde and amide moieties of the cyclization products **3** and **6** were expected to be useful for additional bond/ring forming reactions. While there exist numerous natural products of varying complexity that incorporate a β-phenethylamine subunit, we felt that the synthesis of the modest targets lennoxamine (**7**)[2] and aphanorphine (**10**)[3] would adequately showcase the versatility of this methodology. Recorded herein are relatively concise total syntheses of these natural products by application of this general strategy.

Our retrosynthetic analyses for the construction of lennoxamine and aphanorphine are outlined in Scheme 2. It was envisaged that the ring system of lennoxamine would become

Scheme 1



(1) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349.

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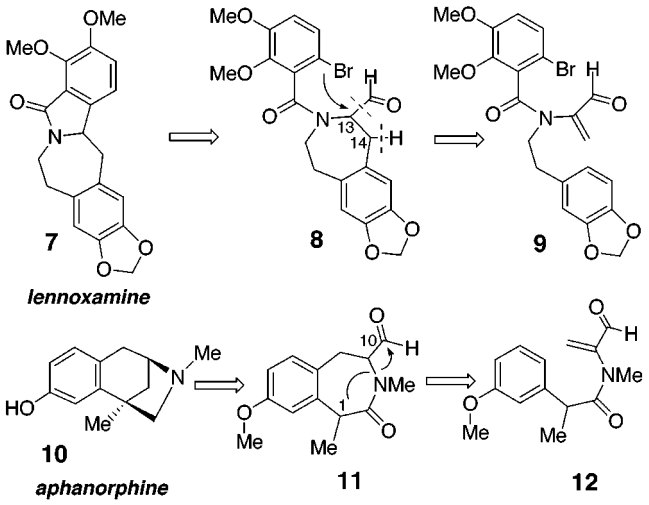
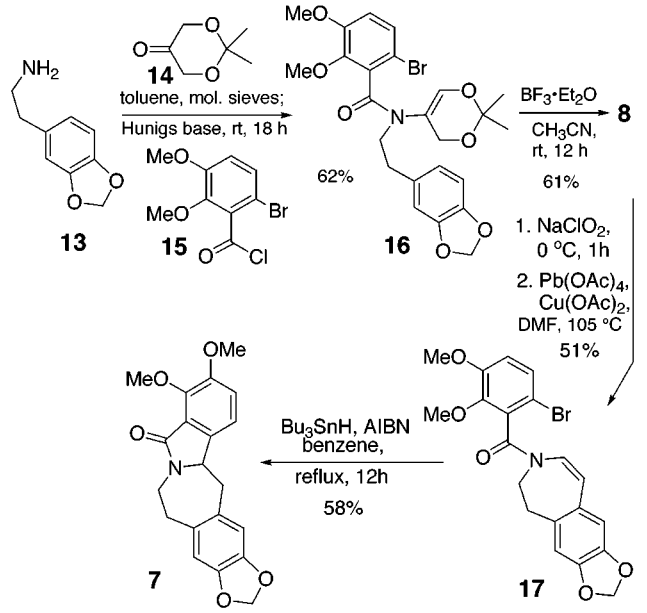
Scheme 2



available by a radical- or palladium-mediated cyclization of the bromoaryl ring with a C(13)−C(14) enamide. The enamide, in turn, could be derived from the aldehyde **8** by oxidative decarboxylation of an intermediate carboxylic acid. Finally, straightforward application of our cyclization protocol via 2-amidoacrolein **9** would furnish the tetrahydro-3-benzazepine **8**. The ring system of aphanorphine could be obtained by either an intramolecular aldol reaction of lactam aldehyde **11** or internal alkylation of a lactam enolate with a C(10) alkyl halide or sulfonate derivative. An intramolecular aromatic substitution reaction of 2-amidoacrolein **12** would afford the tetrahydro-3-benzazepine **11**. In short, these two projected syntheses feature the two types of cyclizations of 2-amidoacroleins (*exo* vs *endo* amide), as well as distinct ways of manipulating the aldehyde functionalities for additional ring formations.

We initially examined the total synthesis of lennoxamine. To that end, the amine **13** was condensed with 1,3-dioxin-5-one (**14**),[4] and the resultant imine was acylated in the same reaction flask with the acid chloride **15**[5] to afford the 5-amido-1,3-dioxin **16** (Scheme 3). As expected, the dioxin

Scheme 3



16 underwent a Lewis acid catalyzed retrocycloaddition to the 2-amidoacrolein **9** followed by an aromatic substitution reaction to afford the desired 3-benzazepine **8**. It is of interest to note that ^{1}H NMR analysis of the amide **8** was complicated not only by amide rotamers but also atropisomerism around the aryl-carbonyl single bond.[6] Indeed, the atropisomers could be partially separated by column chromatography but were found to interconvert upon standing at room temperature. The aldehyde functionality of 3-benzazepine **8** was converted to a C(13)−C(14) double bond by oxidation to the corresponding carboxylic acid followed by a Kochi reaction[7] to

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(4) Prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

(5) Prepared by treatment of the known 6-bromo-3,4-dimethoxybenzoic acid with thionyl chloride. Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931.

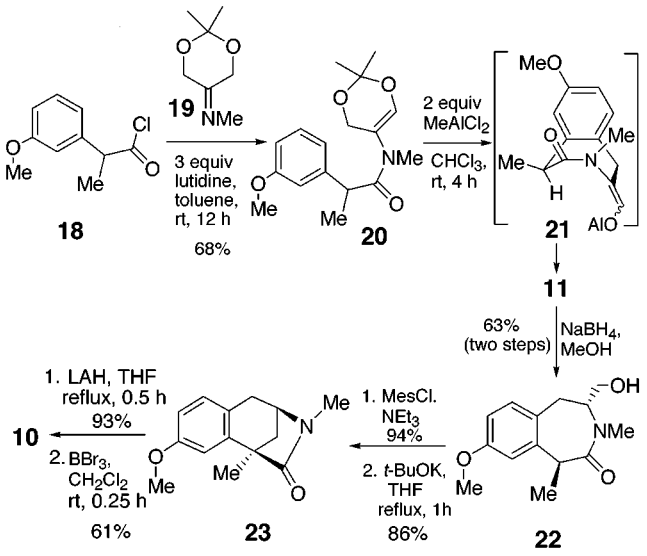
(6) For selected examples of this type of atropisomerism, see: (a) Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803. (b) Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatogr.* **1993**, *648*, 101. (c) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899. (d) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279.

(7) For a review, see: (a) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279. For oxidative decarboxylation of α-amido acids with lead tetraacetate, see: (b) Lohmar, R.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 450. (c) Wegmann, H.; Steglich, W. *Chem. Ber.* **1981**, *114*, 2580. (d) Lipinski, C. A.; Aldinger, C. E.; Beyer, T. A.; Bordner, J.; Burdi, D. F.; Bussolotti, D. L.; Inskeep, P. B.; Siegel, T. W. *J. Med. Chem.* **1992**, *35*, 2169. (e) Urban, F. J.; Moore, B. S. *J. Heterocycl. Chem.* **1992**, 29, 431. (e) Osada, S.; Fumoto, T.; Kodama, H.; Kondo, M. *Chem. Lett.* **1998**, *7*, 675. For decarbonylation of α-amino or α-amido activated carboxylic acid derivatives, see: (f) Hernández, A. S.; Thaler, A.; Castell, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314 and references therein. (g) Martín-López, M.

afford the desired enamide **17** (51%, two steps). Finally, subjection of the aryl bromide **17** to standard free radical cyclization conditions gave (±)-lennoxamine (58%) accompanied by debromo **17** in 26% yield, which could not be attenuated by alternative reducing agents [$(Me_3Si)_3SiH$] and/or syringe pump addition techniques. The spectral properties of synthetic **7** were identical to those previously reported.[2]

The total synthesis of aphanorphine was initiated by treatment of the acid chloride **18**[8] with the *N*-methylimine **19** to afford the 5-amido-1,3-dioxin **20** (Scheme 4). The

Scheme 4



retrocycloaddition, cyclization of amido dioxin **20** proceeded smoothly upon treatment with $MeAlCl_2$ in chloroform (rt, 4 h) to afford the aldehyde **11** as a single (*trans*) diastereomer. Aldehyde **11** was not stable at room temperature for extended periods of time. Not surprisingly, all attempts to effect a base- or acid-catalyzed epimerization at C(10) for the purpose of determining whether the *trans* stereoisomer is the result of thermodynamic control vis-à-vis kinetic, equatorial protonation of the presumed exocyclic aluminum enolate intermediate **21** were unsuccessful. In addition, none of the desired aldol adduct derived from intramolecular addition of the lactam enolate of **11** to the aldehyde functionality could be detected in these experiments. Accordingly, aldehyde **11** was directly reduced without purification to afford the chromatographically stable alcohol **22** in 63% yield for the two steps. Moreover, subjection of alcohol **22** to KO-*t*-Bu in *t*-BuOH (60 °C, 2 h) gave rise to the epimeric *cis* diastereomer of **22** (26:74, *cis*:*trans*), suggesting that the stereoselective production of *trans* aldehyde **11** is kinetically controlled. To our delight, the mesylate derivative of alcohol **11** underwent a smooth displacement by the lactam enolate generated with KO-*t*-Bu in THF to afford the bridged bicyclic lactam **23**. Straightforward reduction of the lactam moiety of **23** followed by demethylation of the aryl ether using established conditions (BBr_3, CH_2Cl_2) then delivered (±)-aphanorphine, whose spectral data were identical to those reported previously.[3]

In summary, we have shown that the products derived from intramolecular electrophilic aromatic substitution reactions of 2-amidoacroleins facilitate the rapid construction of two dissimilar natural product ring systems by further transformation of the post-cyclization aldehyde and amide functionalities. We expect that the total syntheses of other β-phenethylamine-bearing natural products will also benefit from this general strategy. These investigations are underway.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Prepared by treatment of the known acid with thionyl chloride. Kubler, W.; Petrov, O.; Winterfeld, E.; Ernst, L.; Schomburg, D. *Tetrahedron* **1988**, *44*, 4388.