Natural Products

DOI: 10.1002/anie.200800488

Further Insight from Model Experiments into a Possible Scenario Concerning the Origin of Manzamine Alkaloids

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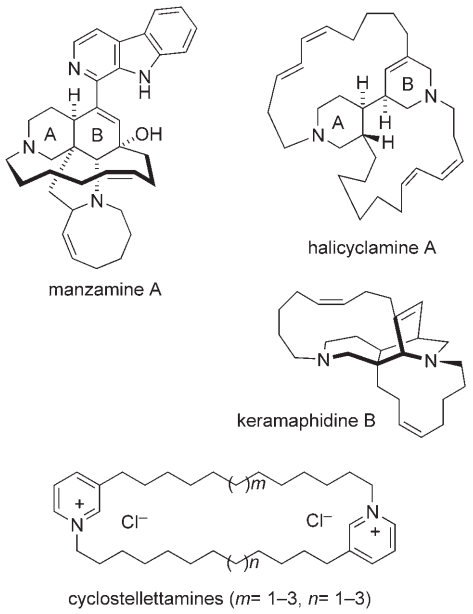
The story of the manzamine alkaloids, natural products extracted from sponges of the order Haplosclerida, began in 1986 with the discovery of manzamine A, followed by the identification of a number of related derivatives.[1,2] Halicyclamine A, keramaphidin B, and the cyclostellettamines are representative molecules of this series (Scheme 1).



Scheme 1. Some natural products representative of the manzamine family of alkaloids.

The common source of this new class of alkaloids and the structural similarities of these compounds suggest the existence of a unique biosynthetic pathway, in a particularly striking example of "nature diversity-oriented synthesis". The biosynthetic pathway is unknown to date; however, in 1992, Baldwin and Whitehead put forward the hypothesis that dihydropyridinium salts **1** formed through the condensation of aminoaldehydes with acrolein may serve as key intermediates(Scheme 2).[3] This hypothesis was tested experimentally and, remarkably, provided access to keramaphidin B.[4] However, the efficiency of this kind of strategy was limited as a result of a competing dihydropyridine redox process. Furthermore, the model proposed by Baldwin and Whitehead did not permit access to the manzamine skeleton. Studies towards the synthesis of cyclostellettamines led us to propose an alternate scenario based upon the chemistry of aminopentadienal species **2**, which could be formed from malonaldehyde instead of acrolein.[5] This modification of the initial proposal is summarized in Scheme 2. Experimental studies revealed that only regioisomers of aminopentadienals **2** were available (isomers **14**, see Scheme 5), but that these regioisomers do add to salts **1** to deliver the AB ring system of halicyclamine A (via analogues of **3**), whereas the condensation of aminopentadienoic esters enabled the synthesis of analogues of the AB ring system of manzamine A (via analogues of **4**).

Herein, we report further results related to the chemistry depicted in Scheme 2. We describe a new method based on the original proposal of Baldwin and Whitehead[3] for the preparation of salts **1**,[6] as well as a Chichibabin-like process for the formation of a common intermediate, which, depending on the reaction conditions, rearranges to give a ring system equivalent to the AB ring system of **3** or the AB ring system of **4**.

To our knowledge, the condensation of an unsaturated aldehyde, such as acrolein, with aldehydes and amines to give dihydropyridinium salts **1** has no equivalent in the literature. However, as acrolein can be viewed as the aldol-condensation product of acetaldehyde and formaldehyde, the reaction could be considered to be related to the Chichibabin synthesis of pyridines.[7] Indeed, this multicomponent procedure, known as early as the beginning of the 20th century, involves the condensation of three equivalents of an aldehyde with ammonia at high temperature to give 2,3,5-trisubstituted pyridines (Scheme 3, $R^1 = H$). If R^1 is an alkyl group, the reaction produces the corresponding pyridinium salts. In fact, the intermediates of this reaction are believed to be dihydropyridinium salts **7**, or even dihydropyridines **8**, which are oxidized spontaneously under the rather harsh and acidic reaction conditions. The initial main drawbacks of this process were the necessary use of the same aldehyde, which does not allow variation of the R groups,[8] and the difficulty in stopping the reaction at the dihydropyridinium stage.[9] The selective synthesis of salts **1** by the route proposed in Scheme 2 could thus be viewed as a useful modified Chichibabin synthesis of six-membered nitrogen heterocycles.

After some unsuccessful attempts, we have now found a sequence that mimics this process (Scheme 4). The Strecker

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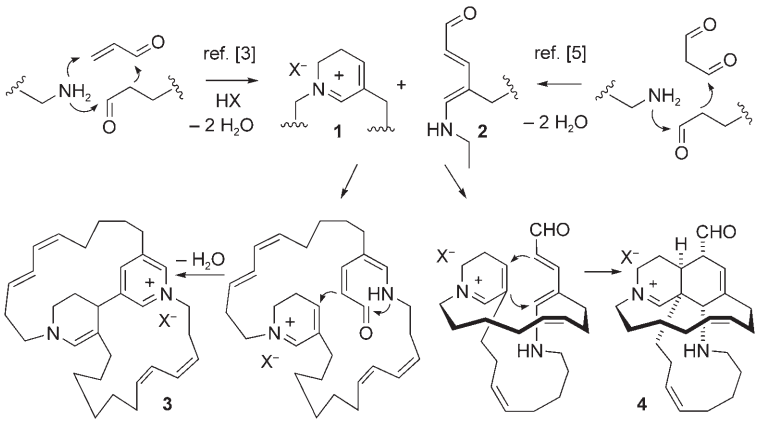
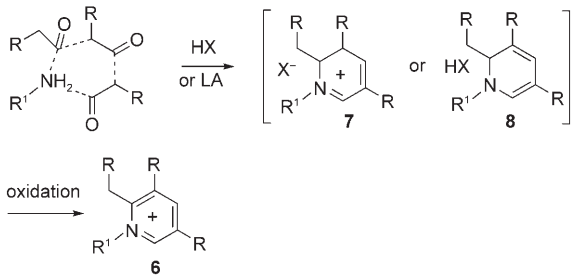


Scheme 2. Proposed biosynthetic route (modified from the original hypothesis of Baldwin and Whitehead[3]).

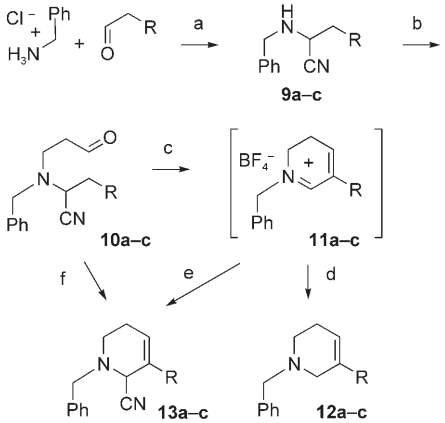


Scheme 3. The Chichibabin synthesis of pyridines and pyridinium salts. LA = Lewis acid.

adducts **9a–c** were obtained in quantitative yield from the corresponding aldehydes and benzylamine hydrochloride, and condensed with excess acrolein to give the crude aldehydes **10a–c**, again in quantitative yield. These aldehydes are very sensitive to acids and bases (retro-Michael process), but were found to undergo smooth cyclization at ambient temperature in the presence of $AgBF_4$ (1 equiv) to give salts **11a–c**.[10] Compounds **11a–c** were not isolated, but were observed in the ^{1}H NMR spectra of the crude reaction mixture. Their reduction with $NaBH_4$ afforded tetrahydropyridines **12a–c** in 45–65% overall yield, whereas the trapping of **11a–c** with KCN afforded aminonitriles **13a–c** in 37–52% overall yield (in four steps from the starting aldehydes). Interestingly, the treatment of **10a** with a catalytic amount of $Zn(OTf)_2$ resulted in the direct formation of aminonitrile **13a** in 33% overall yield (in three steps from the starting aldehyde). This new synthesis of aminonitrile derivatives **13**, which complements the traditional synthetic route (the Polonovski–Potier oxidation of tetrahydropyridines),[6,11] was thus carried out without the isolation of any intermediates.

The treatment of aldehyde **10a** with $ZnBr_2$ in the presence of aminopentadienal **14a**[12] resulted in the formation of **15a** (Scheme 5),[13] which was recovered after flash chromatography on alumina in 22% overall yield (in three steps from propionaldehyde). This result demonstrated that it was possible to couple cyclization to the dihydropyridinium salt **11a** with the nucleophilic addition of an aminopentadienal in a one-pot procedure. Moreover, the use of $Zn(OTf)_2$ as a Lewis acid delivered the pyridinium salt **16a** or **16b** directly in 25% overall yield (in three steps from propionaldehyde). Finally, we confirmed that the reduction of salt **16b** afforded the previously reported halicyclamine model compounds **17b** and **18b**. Thus, the new procedure is shorter than our previous approach and enables rapid access to pyridinium derivatives **16**,[14] which are of interest for the total synthesis of the halicyclamine class of natural products, as well as sarains 1–3 (if one considers the aminonitrile functionality as a masked iminium cation).[15]

The treatment of the pure adduct **15a** with acetic anhydride, followed by reduction with excess $NaBH(OAc)_3$, afforded a new rearrangement

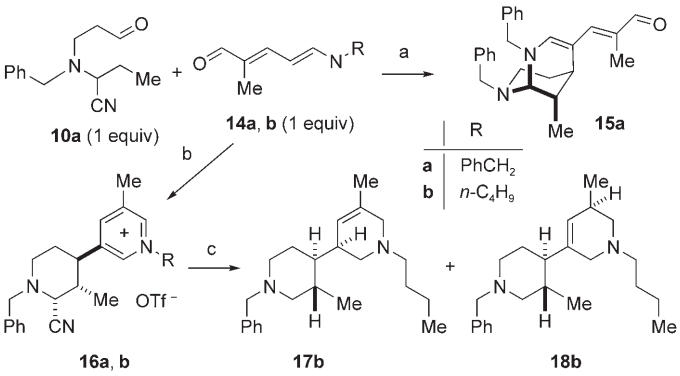


	R	Yield of **12** [%; steps a–d]	Yield of **13** [%]
a	Me	45	40 (steps a–c,e) 33 (steps a–b,f)
b	Ph	65	52 (steps a–c,e)
c	$(CH_2)_3$OTBDMS	49	37 (steps a–c,e)

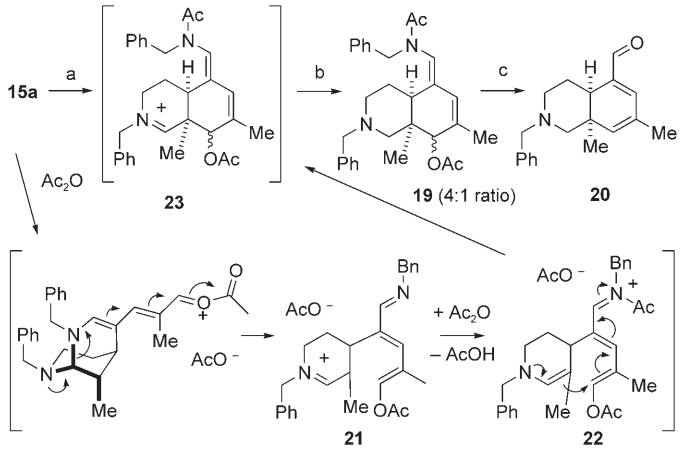
Scheme 4. A new "Chichibabin-like" three-component route to tetrahydropyridines **12** and dihydropyridinium salts **11** or their cyano-substituted analogues **13**: a) KCN, H_2O/MeOH, room temperature, quantitative; b) acrolein, neat or in CH_2Cl_2, room temperature, quantitative; c) $AgBF_4$, CH_2Cl_2/THF, room temperature; d) $NaBH_4$, MeOH (see table for yields of **12**); e) KCN, H^+ (see table for yields of **13**); f) $Zn(OTf)_2$, THF, 75 °C, 24 h, 33% for **13a**. TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

product, the bicyclic derivative **19**, as a mixture of diastereoisomers in a 4:1 ratio (the orientation of the OAc group in the two diastereoisomers is not known) and in 44% yield.[16] This derivative possesses an AB ring motif related to that of the manzamines. The treatment of **19** under acidic conditions afforded the known dienal **20**.[5a]

A plausible mechanism for the rearrangement to give the intermediate iminium salt **23** is depicted in Scheme 6. Regioselective acylation at the oxygen atom of the aminopentadienal functionality of **15a** would result in ring opening to give iminium salt **21**. Further acylation at the nitrogen atom



Scheme 5. One-pot access to adduct **15a** and halicyclamine model compounds **16a**,**b**: a) $ZnBr_2$ (0.5 equiv), DCE, 75 °C, 15 h, 22%; b) $Zn(OTf)_2$, 25% for **16a**, 25% for **16b**; c) $NaBH_4$, MeOH, 40% (**17b**+**18b**). DCE = 1,2-dichloroethane.



Scheme 6. Rearrangement of adduct **15a** in the presence of acetic anhydride: a) $(CH_3CO)_2O$ (3 equiv), DCE, 60 °C, overnight; b) $NaBH(OAc)_3$, THF, 44% from **15a**; c) aqueous HCl (pH 1), EtOH, reflux, overnight, 55%. Bn = benzyl.

in the side chain, followed by cyclization of the resulting activated 1,3-diene **22**, would then afford the bicyclic intermediate **23**.

In conclusion, these results with simplified models fully demonstrate the feasibility of the chemistry depicted in Scheme 2. A particularly interesting feature of this approach is the selective formation of either the halicyclamine or the manzamine skeleton through the condensation of five different species in a consecutive manner.[17] The synthetic sequence generates diversity, as the variation of four different substituents is possible. The extension of this procedure to the synthesis of macrocyclic derivatives is now under investigation. These new results further illustrate the synthetic interest of aminopentadienal derivatives, introduced previously by us to the arena of natural product synthesis.[5c,18] In particular, the formation of derivative **19** revealed that these species can be activated selectively by treatment with acid anhydrides. The use of these activated species in Pictet–Spengler reactions will be reported in the near future.

Received: January 30, 2008
Published online: June 11, 2008

Keywords: aldehydes · biomimetic synthesis · cycloaddition · natural products · nitrogen heterocycles

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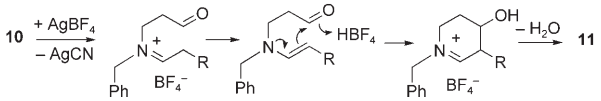

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