Synthesis of Tricyclic Nitrogen Compounds *via* a Tandem Cyclization–Cycloaddition–Cationic Cyclization Sequence

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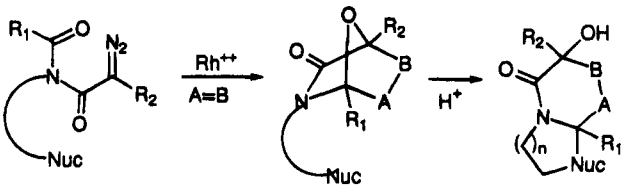
Summary: The intramolecular cycloaddition of isomünchnone dipoles containing alkenyl π-bonds produces oxabicyclic amides. These cycloadducts were employed as masked *N*-acyliminium ions for cationic π-cyclizations as an approach to B-ring homologues of erythrinane alkaloids.

A major challenge in organic synthesis today is to devise reactions that can form several carbon–carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control.[1-3] Carbon–carbon bond-forming reactions involving *N*-acyliminium ions play an extremely important role in the synthesis of nitrogen heterocycles.[4] Speckamp[5] and Hart,[6] in particular, were the pioneers in this area showing that *N*-acyliminium ions are valuable intermediates in the synthesis of a broad range of alkaloids. The versatility of *N*-acyliminium ions for the synthesis of a wide variety of nitrogenous materials underscores the continuing need to find new methods for their preparation.[7] *N*-Acyliminium ions are traditionally generated from the N-acylation of imines,[8] N-protonation[9] and oxidation[10] of amides, electrophilic additions to enamides,[11] and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[4] These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall α-amidoalkylation. Our earlier studies dealing with the 1,3-dipolar cycloaddition of isomünchnones[12] derived from α-diazoimides **1** provided us with a uniquely functionalized cycloadduct **2** containing a "*masked*" *N*-acyliminium ion. By incorporating an internal nucleophile on the tether, annulation of the original dipolar cycloadduct **2** would allow the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids.[13] By starting from simple acyclic diazoimides **1**, we have established a tandem *cyclization–cycloaddition–cationic π-cyclization* protocol as a method for the construction of complex nitrogen polyheterocycles of type **3**. The present paper documents the results of our studies in this area.



1 **2** **3**

Construction of the prerequisite diazoimides necessary for dipole generation was accomplished by transformation of the corresponding carboxylic acids to their respective amides. Conversion to the diazoimides was straightforward using established malonylacylation[14] and diazotization[15] procedures. Treatment of diazoimides **4**, **5**, and **6** with a catalytic quantity of rhodium(II) perfluorobutyrate (pfb) in CH_2Cl_2 at 25 °C provided cycloadducts **7** (98%), **8** (95%), and **9** (90%). Assignment of the stereochemistry of the cycloadducts was based (NMR) on related substrates previously synthesized in these laboratories.[12] Formation of the *endo*-cycloadduct with respect to the carbonyl ylide dipole in these cycloadditions is in full accord with molecular mechanics calculations which show a large energy difference between the two diastereomers. When the individual cycloadducts were exposed to $BF_3{\cdot}OEt_2$ (2 equiv) in CH_2Cl_2 at 0 °C, the cyclized products **10** (97%), **11** (95%), and **12** (85%) were isolated as single diastereomers. The structural assignments were based, in part, on the appearance of two

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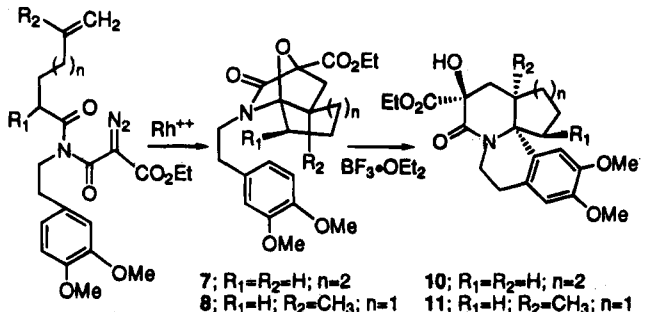
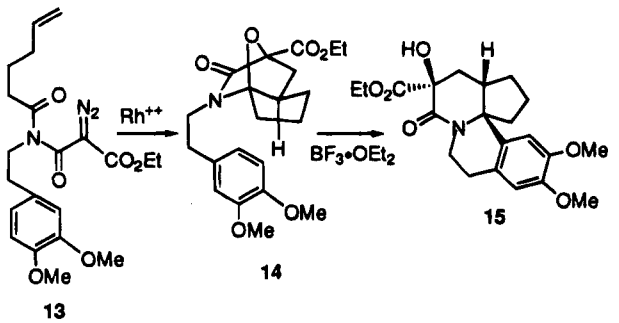
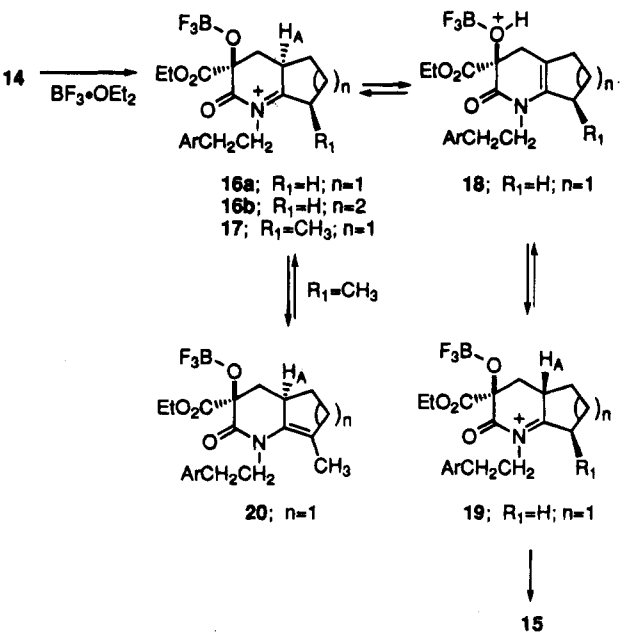


aromatic CH protons which were observed as two individual singlets, each integrating for one proton. The proposed *cis* stereochemistry of the A/B ring junction for **10-12** was assigned by analogy to similar erythrinane products obtained *via a Mondon-enamide-type* cyclization.[16-18] This was unequivocally established by an X-ray crystal analysis of all three cycloadducts.[19] Note that in all three cases the *anti* stereochemical relationship is still maintained between the hydroxyl stereocenter (from the oxygen bridge) and the bridgehead proton (R_2 = H) or methyl (R_2 = CH_3) group.

Interestingly, when the dipolar cycloadduct **14** derived from the unsubstituted alkenyl diazoimide **13** was exposed to BF_3•OEt_2, the resulting cyclized product **15** (90%) was identified as the all *syn* tetracyclic lactam **15** by an X-ray crystal analysis.[19] Thus, in contrast to the other three systems, the bridgehead proton of **15** lies *syn* to the hydroxyl stereo center of the original cycloadduct.



We assume that the intermediate *N*-acyliminium ions formed from the Lewis acid-assisted ring opening of the isomünchnone cycloadducts undergo rapid proton loss to produce tetrasubstituted enamides.[20] In the case of **14**, this process is clearly evident as witnessed by the stereochemical outcome observed in product **15**. Loss of the bridgehead proton H_A in **16** (dihedral angle 90° with respect to the *N*-acyliminium ion π-bond) is fast relative to π-cyclization. Intramolecular axial reprotonation of enamide **18** from the β-face generates the diastereomeric iminium ion **19** which then undergoes intramolecular



cationic π-cyclization from the least sterically congested face to give the observed all *syn* isomer **15**. Molecular mechanics calculations show that the *cis* A/B ring fusion in **15** is 4.6 kcal favored over the *trans* diastereomer, and presumably some of this thermodynamic energy difference is reflected in the transition state for cyclization. The additional methyl group present in the related 6/5 cycloadduct **9** (*i.e.*, **17**) promotes loss of the proton adjacent to it, and this results in the formation of enamide **20**. Stereoselective reprotonation from the least congested α-face regenerates **17** which is trapped intramolecularly by the aromatic nucleus. Cyclization always occurs from the least hindered side as has already been established by Mondon and coworkers.[16] Cationic cyclizations of this type are known to be governed by steric control.[21] In the case of cycloadduct **8**, the bridgehead proton does not exist, and thus deprotonation can only occur in one direction. We believe that the initially formed iminium ion derived from **7** (*i.e.*, **16b**; n = 2) undergoes fast π-cyclization prior to proton loss. In this case, the deprotonation step is significantly slower than in the 6/5 system due to the larger dihedral angle (113°) between proton H_a and the π-system of the *N*-acyliminium ion. Once again the stereochemical outcome in **10** is the result of a stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion from the least hindered side.

Two additional systems which illustrate the scope and variety of π-systems which can be employed in this tandem process are outlined below. The Rh(II)-catalyzed reaction of diazoimide **21** gave rise to a transient bicyclic adduct that was not isolable, as it underwent rapid ring opening to give the conjugated indenyl enamide **22** (85%). Exposure of **22** to BF_3•OEt_2 in CH_2Cl_2 at 40 °C resulted in a 3:1 mixture of diastereomeric tetracyclic lactams **23** in 88% yield, thereby demonstrating that tethered alkenes can also be utilized in the third step of these cascade reactions. Another substitution variation that was also investigated corresponded to the placement of an indolyl tether on the amide nitrogen. Thus, treatment of diazoimide **24** with $Rh_2(pfb)_4$ gave cycloadduct **25** (98%) which was readily converted into **26** in 60% isolated yield as a

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(20) In the related *N*-benzyl system, it was possible to isolate the analogous enamide (CH_2Ph; R_1 = H) in 75% yield since cyclization onto the aromatic ring does not occur.

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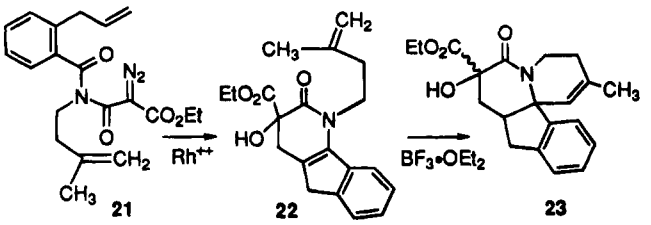

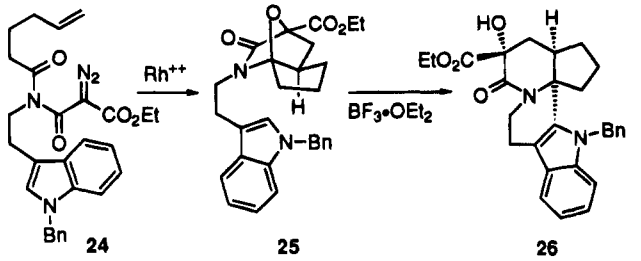

single diastereomer. The stereochemical assignment is based on analogy to the tetracyclic system **15**.

In conclusion, the results presented herein demonstrate the potential of using the tandem cyclization–cycloaddition–cyclization reaction of diazoimides for the construction of polyheterocyclic ring systems. Further work on the chemistry of these versatile cycloadducts and their application to alkaloid synthesis will be reported in due course.

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Supplementary Material Available: Experimental details for the preparation of as well as spectroscopic data for all new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.