SYNTHETIC STUDIES ON THE NARCICLASINE ALKALOIDS. A SYNTHESIS OF (±)-LYCORICIDINE

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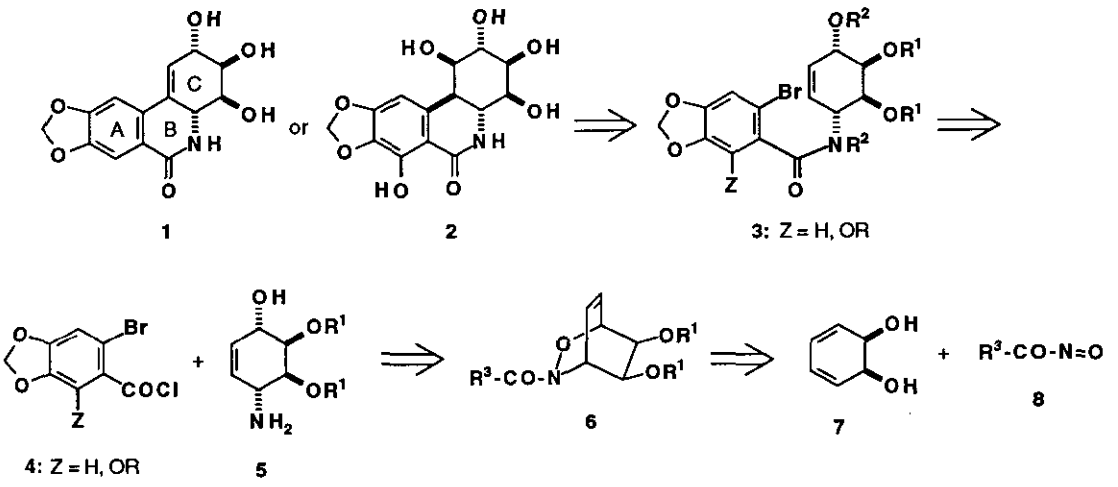
Abstract- The hetero Diels-Alder reaction of benzyl nitrosocarbamate with the diene (**10**) and the Heck cyclization of the derived amide (**14**) served as the key steps in a concise synthesis of (±)-lycoricidine (**1**).

In the context of a general program directed toward developing new concise entries to members of the narciclasine family of the *Amaryllidaceae* alkaloids,[1] we selected lycoricidine (**1**)[2] and pancratistatin (**2**)[3] as suitable targets of opportunity.[4] Although we have explored several different strategies for the synthesis of such alkaloids, that outlined in Scheme I has emerged as one practical solution to the problem. However, prior to the successful implementation of this plan, it was necessary to answer a number of questions. For example, in order to address

Scheme I



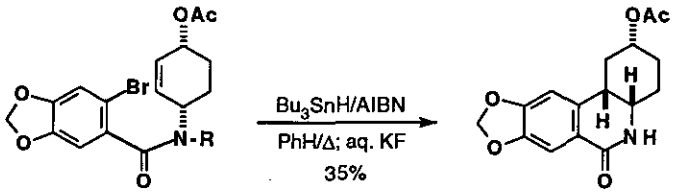
1 2 3: Z = H, OR

4: Z = H, OR 5 6 7

one of the challenges in this area, we recently invented a novel protocol for effecting the enantioselective synthesis of aminocyclitols such as **5** employing highly diastereoselective [4+2] cycloadditions of chiral nitroso dienophiles with a number of different dienes.[5] Another obstacle to be surmounted before reducing this strategy to practice, required the development of efficient methods to effect closure of the B ring, and toward this end we surveyed the feasibility of inducing radical and Heck cyclizations of substances related to **3**. We now report the successful application of the principal elements of this approach to a facile total synthesis of racemic lycoricidine (**1**).

The first stage of the synthesis required assemblage of amides such as **13** or **14** to test various tactics for effecting closure of the B ring. Toward this end, readily available *cis*-1,2-dihydrocatechol (**9**) was protected, and the resulting diene (**10**) was subjected to a bimolecular hetero Diels-Alder reaction[5,6] with benzyl nitrosocarbamate to give the adduct (**11**)[7] (Scheme II). Dismantling the protected cycloadduct (**11**) proceeded in a straightforward fashion and involved the dissolving-metal reduction of the N-O bond followed by alkaline hydrolysis of the carbamate moiety. Selective *N*-acylation of **12** with the acid chloride (**4**), which was prepared from the corresponding known acid[8] by reaction with thionyl chloride in the presence of a catalytic amount of DMF, then gave the key intermediate (**13**).

In some preliminary experiments, we assessed the viability of constructing the B ring of the narciclasine alkaloids by radical cyclizations,[9,10] and we found that the model substrate (**17**) did undergo such cyclization to give **18**, albeit in modest yield. On the other hand, the secondary amide (**19**) failed to cyclize under any of the conditions

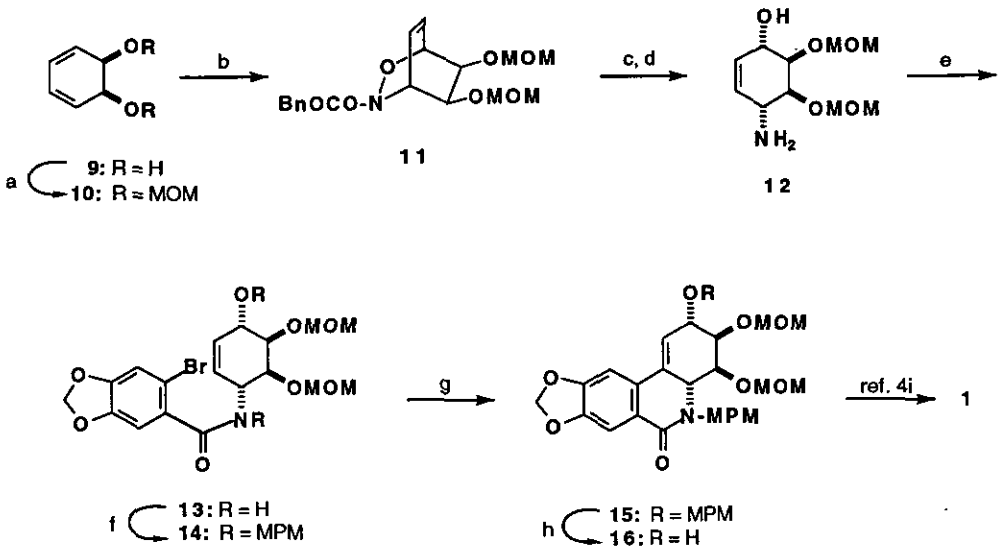


17: R = $COCF_3$
19: R = H

18

that were examined.[10] Based upon these findings, we examined the feasibility of forming the B ring from the tertiary amide (**14**) by radical cyclization; unfortunately, all such efforts were unavailing. We turned therefore to the alternate tactic of using the Heck reaction[11,12] to solve this problem. After considerable experimentation, we discovered that the critical cyclization of **14** to give **15** proceeded smoothly and in good yield under conditions originally reported by Grigg[12b] and later employed by Ogawa;[4i] the use of thallium (I) acetate as a base was crucial to the success of this reaction. The structure of **15** was verified by its conversion into the allyl alcohol (**16**) by oxidative removal of the MPM protecting group.[13] The ^1H nmr spectrum of **16** thus obtained was identical to a ^1H nmr spectrum of an authentic sample.[14] Since optically pure **16** has been previously converted

Scheme II



(a) MOMCl, Et_2NPr, CH_2Cl_2; 92%. (b) BnOCONHOH, n-Bu_4NIO_4, CH_2Cl_2, -15 °C; 69%. (c) 5% Na(Hg), Na_2HPO_4, aq. EtOH, 0 → 25 °C; 86%. (d) aq. EtOH, NaOH, Δ; 98%. (e) **4** (Z = H), Et_3N, CH_2Cl_2, 25 °C; 90%. (f) NaH, MPMCl, DMF, 25 °C; 71%. (g) $Pd(OAc)_2$, DIPHOS,TlOAc, DMF, 145 °C; 51%. (h) DDQ, CH_2Cl_2/H_2O (20:1), 25 °C; 81%.

into (+)-lycoricidine (**1**) in three steps,[4i] the present preparation of racemic **16** constitutes in a *formal sense* the total synthesis of racemic **1**.

This synthesis of racemic lycoricidine requires a total of only eleven steps from the commercially available diol (**9**) and substantiates the *viability of our concise entry to the narciclasine family* of alkaloids. The application of this general strategy to the asymmetric syntheses of pancratistatin (**2**) and related alkaloids is the subject of current investigations, the results of which will be reported in due course.

ACKNOWLEDGMENT

We thank the National Institutes of Health, the Robert A. Welch Foundation, and the National Science Council of the Republic of China for support of this research. We also thank Dr. Andrew B. Herbert (ICI Biological Products) for a generous gift of *cis*-1,2-dihydrocatechol and Mr. Terrance L. Clayton for conducting a number of exploratory experiments in attempts to form the B ring by radical cyclizations of **14** and various derivatives of **13**.

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Received, 9th November, 1992