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

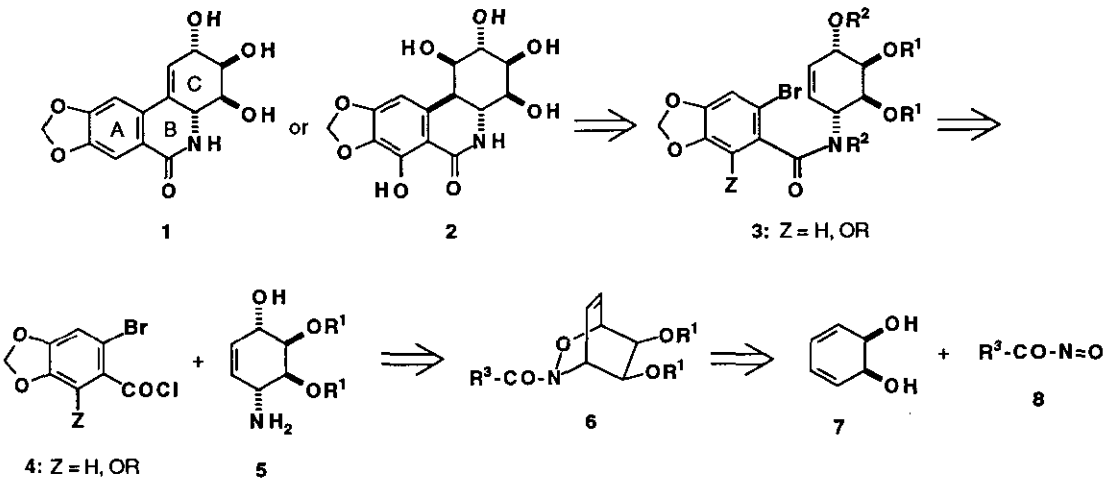
Stephen F. Martin*† and Hsi-Hwa Tso‡

†Department of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, USA. ‡Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan 11529, Republic of China

**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



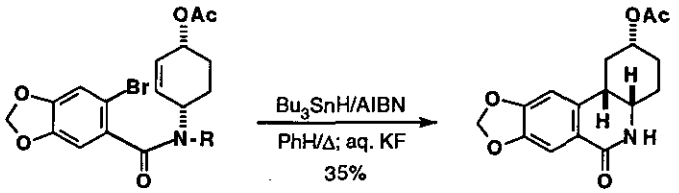

1 2 3: Z = H, OR

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

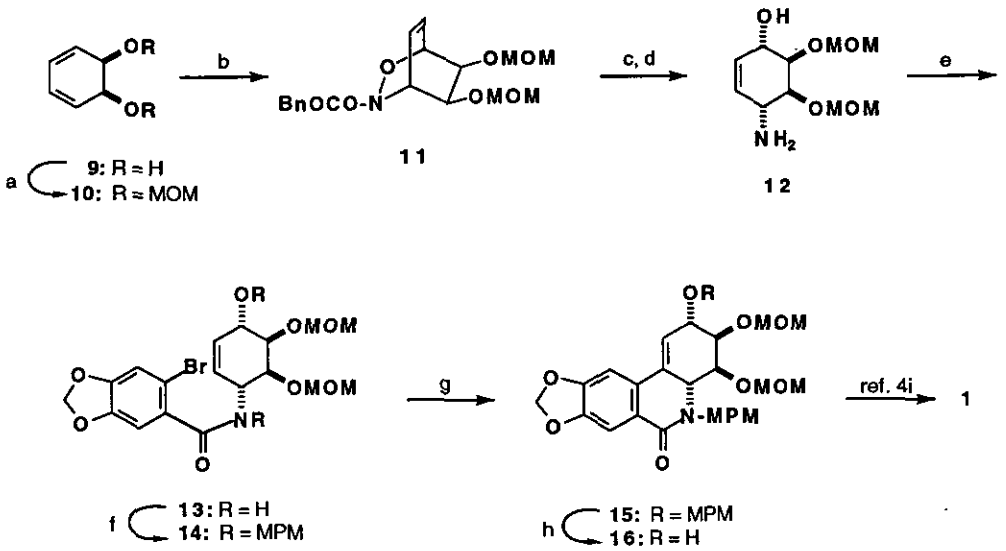



**17**: R = $COCF_3$
**19**: R = H

**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.

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