Natural Products

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A Boron-Based Synthesis of the Natural Product (+)-*trans*-Dihydrolycoricidine**

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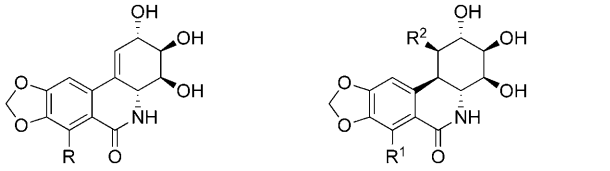
The members of the *Amaryllidaceae* family of natural products (Figure 1) have long been recognized for their medicinal properties.[1] In particular, many members of this small subgroup of isocarbostyrils exhibit unusually high levels of in vitro and in vivo antitumor and antiviral activity.[2]

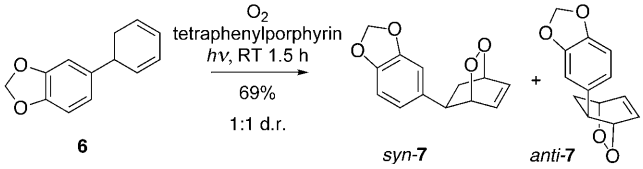


Narciclasine: R = OH (**1**) Pancratistatin: $R^1 = R^2 = OH$ (**3**)
Lycoricidine: R = H (**2**) *trans*-Dihydronarciclasine: $R^1 = OH$, $R^2 = H$ (**4**)
trans-Dihydrolycoricidine: R^1, $R^2 = H$ (**5**)

Figure 1. Representative *Amaryllidaceae* isocarbostyrils.

Despite their potential for clinical use many of these compounds are found in low natural abundance; whereas narciclasine (**1**) is available in practical quantities,[1a,3] the limited availability of lycoricidine (**2**), pancratistatin (**3**), and other derivatives poses one limitation to their development as viable therapeutic agents. Unsurprisingly, the limited availability of these isocarbostyrils, as well as their interesting frameworks, have made these attractive and relevant targets for organic synthesis, and many successful strategies for the construction of **1**, **2**, and **3** have been described.[4] In contrast, the syntheses of the natural products *trans*-dihydronarciclasine (**4**)[5] and *trans*-dihydrolycoricidine (**5**)[6] have not been explored as extensively even though they demonstrate potent cytotoxicities.[7] To date, three syntheses of (+)-**5** have been reported in the literature[8] and a third report describes the synthesis of the nonnatural enantiomer (−)-**5**.[9] Given their promising biological activity and their interesting structures, we have been attracted to the isocarbostyrils as synthetic targets and herein describe the preparation of **5** by a route that employs enantioselective conjugate allylation to control the absolute configuration. We also describe the first examples of diastereoselective diboration as a method to control the oxygenation pattern in the target molecule.

We envisioned an approach to the isocarbostyrils that centers on the diastereoselective 1,4-dioxygenation of cyclohexadiene **6** (Scheme 1), a compound that is readily available in enantiomerically pure form by a sequence employing an asymmetric conjugate allylation that was developed in our laboratory.[10] A preliminary attempt at the stereoselective dioxygenation of **6** employed a singlet oxygen cycloaddition as a method to establish the required functional group pattern.[11] While this transformation occurred in acceptable yield, the complete lack of stereocontrol in this reaction (1:1 diastereomer ratio) suggested that other methods for this dioxygenation would be required.[12]



Scheme 1. Singlet-oxygen cycloaddition of chiral cyclohexadiene **6**.

Recent studies in our laboratory have focused on the development of a platinum-catalyzed enantioselective 1,4-diboration of 1,3-dienes as a method for 1,4-dioxygenation of these substrates.[13] In a related vein, we considered that a diastereoselective version of this reaction might be useful for the elaboration of complex diene substrates and enable the synthesis of the highly hydroxylated core of the isocarbostyrils such as **1**–**5**. Initially, the diboration of 5-phenyl-1,3-cyclohexadiene using bis(pinacolato)diboron ($B_2(pin)_2$) and catalytic amounts of [$Pt(dba)_3$] and PCy_3 was examined (Table 1, entry 1). The reaction proceeded for 14 hours at 60 °C and was then subjected to an oxidative work-up with NaOH and H_2O_2. This 1,4-dihydroxylation occurred with excellent yield and greater than 20:1 diastereoselectivity (Table 1, entry 1). Examination of other substrates revealed that high levels of stereocontrol and good reaction yields are a general feature of these reactions. Similar to examples with aryl-substituted substrates, alkyl substituents also provide high levels of stereocontrol. X-ray analysis of both aryl- and alkyl-substituted reaction products indicated that the diboration occurs with *anti* stereoselection as might be anticipated from the steric influence of the aryl and alkyl groups on the substrate.[14] Lastly, the diboration of α-phellandrene (entry 5) was examined. The [4+2] singlet-oxygen cycloaddition with this substrate has been the subject of numerous studies and is notoriously nonselective.[15] However, diene diboration

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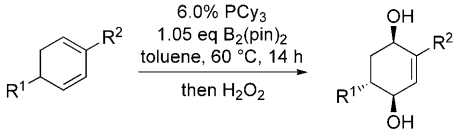
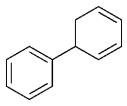
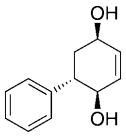
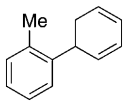
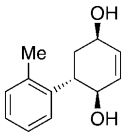
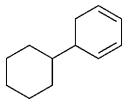
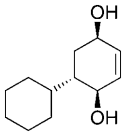
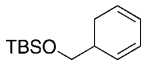
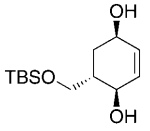
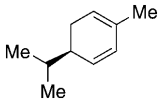
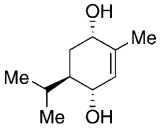
Table 1: Dioxygenation of 1,3-dienes through diboration/oxidation.[a]

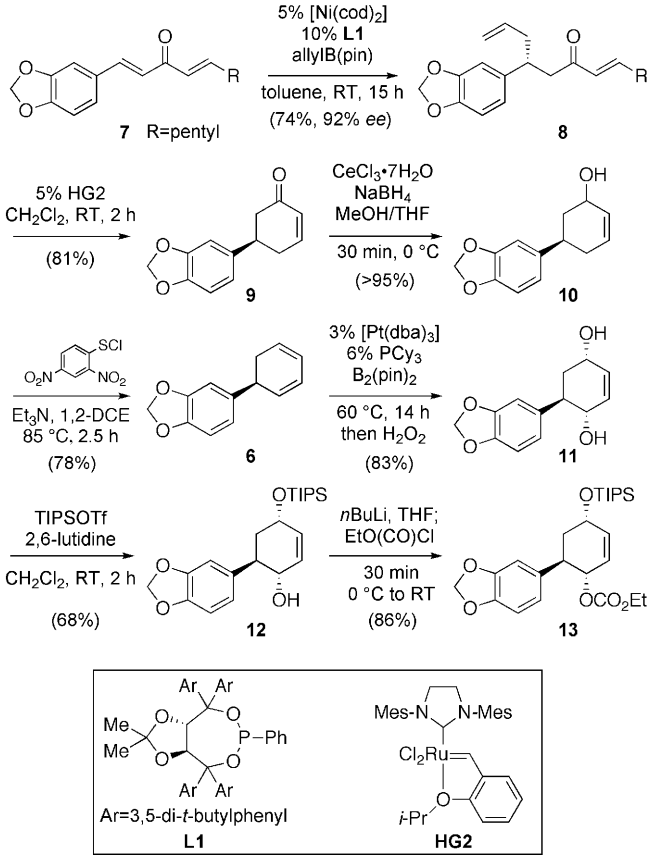


Entry	Substrate	Product	Yield [%][b]	d.r.[c]
1			86	>20:1
2			71	>20:1
3			93	>20:1
4			69	>20:1
5[d]			87	>20:1

[a] Reactions were conducted with exclusion of moisture and under a nitrogen atmosphere. [b] The yield is of the isolated product and is an average of at least two experiments. [c] Diastereoselectivity was determined by ^{1}H NMR analysis (400 MHz); for >20:1, the minor diastereomer was not detected. [d] To achieve optimal yield with this substrate, the [Pt(dba)$_3$] and PCy$_3$ were premixed at RT for 1 h. Cy = cyclohexyl, dba = dibenzylideneacetone, pin = pinacol, TBS = *tert*-butyldimethylsilyl.

occurs with excellent regio- and diastereoselectivity, cleanly delivering the 1,4-dihydroxylation product in excellent yield. The outcome with this substrate suggests that substituents on the diene do not necessarily interfere with the reaction and can provide products with enhanced substitution.

With an effective strategy for the diastereoselective dihydroxylation of cyclohexadiene substrates in place, efforts toward the construction of *trans*-dihydrolycoricidine were initiated. As depicted in Scheme 2, enantioselective conjugate allylation of dialkylidene ketone **7** (derived from the corresponding cinnamic acid in two steps) furnished allylated product **8** in 74% yield and 92% *ee*, as previously described for the enantiomer of **8**.[10a] Ring-closing metathesis employing the second-generation Hoveyda–Grubbs catalyst[16] provided enone **9** (81% yield), which was subjected to a Luche reduction to afford allylic alcohol **10** in 98% yield. Treatment of **10** with 2,4-dinitrobenzenesulfenyl chloride effected an allylic transposition and a subsequent sulfoxide elimination to provide enantioenriched diene **6**.[17] As anticipated, the diboration/oxidation of **6** occurred with excellent levels of

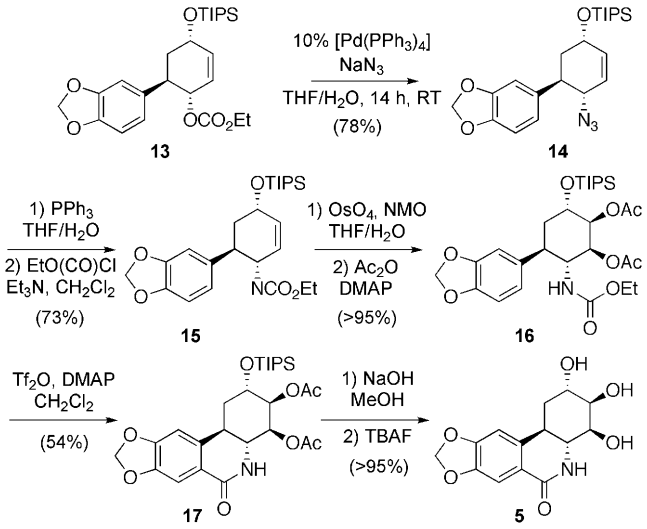


Scheme 2. Synthesis of **13**. cod = 1,5-cyclooctadiene, DCE = dichloroethane, Mes = 2,4,6-trimethylphenyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl.

diastereoselection to provide diol **11** in 83% yield. Notably, in comparison to the simple phenyl-derived substrate (entry 1, Table 1), this example shows that diene **6** is processed efficiently and without interference from the Lewis basic functionality in the substrate.

Substitution at position C4a of **11** with retention of configuration was required to transform the existing hydroxy group into an amine. We anticipated that the steric hindrance provided by the aryl group should enable the selective protection of the C2-hydroxy group, and leave the C4a-hydroxy group free for subsequent activation in preparation for allylic substitution. After surveying reaction conditions, it was found that this protection was best accomplished by the treatment of **11** with TIPSOTf (1.1 equiv) at room temperature, to provide **12** in 68% yield (Scheme 2). The remaining allylic alcohol at position C4a was then derivatized as the ethyl carbonate, to give **13**.

A palladium-catalyzed allylic substitution of **13** was used for the amination of C4a. The choice of the nucleophile was critical with basic nucleophiles resulting in elimination of the intermediate π-allyl compound. The use of an azide anion, however, was found to provide an optimal solution and allowed conversion of the methyl carbonate into the allylic azide **14**. Azide **14** was converted into the corresponding carbamate **15** in 73% yield by using a Staudinger reaction with subsequent addition of ethyl chloroformate (Scheme 3).



Scheme 3. Completion of the synthesis of (+)-*trans*-dihydrolycoricidine. DMAP = 4-dimethylaminopyridine, NMO = *N*-methylmorpholine *N*-oxide, TBAF = tetra-*n*-butylammonium fluoride.

In an effort to convert **15** into a derived cyclic lactam, the substrate was subjected to the Banwell-modified Bischler–Napieralski reaction conditions,[18] however, only decomposition products were observed. This problem was remedied by using a strategy similar to that used by Kadas and coworkers;[7b] first **15** was subjected to an OsO_4-catalyzed dihydroxylation to afford a single diastereomer of the diol, which was acylated with Ac_2O. This alternative substrate for the ring closure (**16**) was treated with Tf_2O and DMAP (5:3) to afford the desired lactam **17** in 54% yield. Removal of the acetate and TIPS protecting groups with methanolic NaOH and TBAF, respectively, provided (+)-*trans*-dihydrolycoricidine (**5**). By NMR analysis, the synthetic material was found to be identical to the natural product. Moreover, HPLC analysis of the enantiomerically enriched material, in comparison to the racemic material, showed the synthetic material to have retained the 92% *ee* from the initial conjugate allylation step.

In conclusion, we have completed the synthesis of the natural product (+)-*trans*-dihydrolycoricidine (**5**) by a route that relies on enantioselective conjugate allylation and diastereoselective diboration to establish the absolute and relative stereochemistry. This represents the first reported application of both of these methodologies in natural product synthesis. Modification of the dialkylidine ketone substrate in the conjugate allylation should allow for a similar synthesis of *trans*-dihydronarciclasine (**4**). Furthermore, the diastereoselective diboration described in this paper promises convenient access to highly versatile 1,4-diols for a variety of other applications and examination of this reaction in the synthesis of other natural products will be the subject of future studies.

Experimental Section

Diastereoselective diene diboration: In the dry box, an oven-dried 6-dram scintillation vial equipped with a magnetic stir bar was charged with $[Pt(dba)_3]$ (11.2 mg, 0.013 mmol, 0.03 equiv), tricyclohexylphosphine (6.9 mg, 0.025 mmol, 0.06 equiv), and toluene (4.1 mL). After stirring the reaction mixture in the dry box for 5 min, diene **6** (82.2 mg, 0.41 mmol, 1 equiv) and $B_2(pin)_2$ (109.5 mg, 0.43 mmol, 1.05 equiv) were added. The vial was sealed with a polypropylene cap, removed from the dry box, and the reaction mixture was stirred at 60 °C for 14 h. The reaction mixture was cooled to 0 °C and then THF (4.5 mL), 3 M aqueous sodium hydroxide (3.0 mL), and 30% aqueous hydrogen peroxide (1.5 mL) were added. The reaction mixture was stirred under ambient atmosphere while slowly warming to RT over 4 h. The reaction mixture was cooled to 0 °C and saturated aqueous sodium thiosulfate (10 mL) was added. The reaction mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (50–70% EtOAc in hexanes) to afford (1*S*,4*S*,5*R*)-5-(benzo[*d*][1,3]dioxol-5-yl)cyclohex-2-ene-1,4-diol as a white solid (80.0 mg, 83%).

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