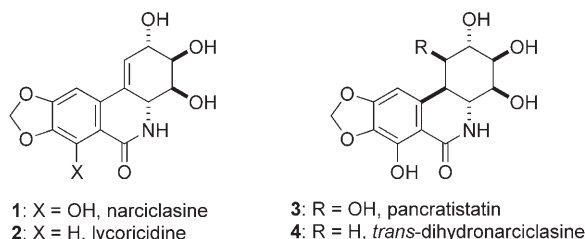


Total Synthesis of ($\pm$)-*trans*-Dihydronarciclasine through a Highly *endo*-Selective Diels–Alder Cycloaddition of 3,5-Dibromo-2-pyrone**

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Over the past several decades, there has been tremendous interest in the synthesis of narciclasine (**1**), lycoricidine (**2**), and pancratistatin (**3**; Scheme 1). These naturally occurring

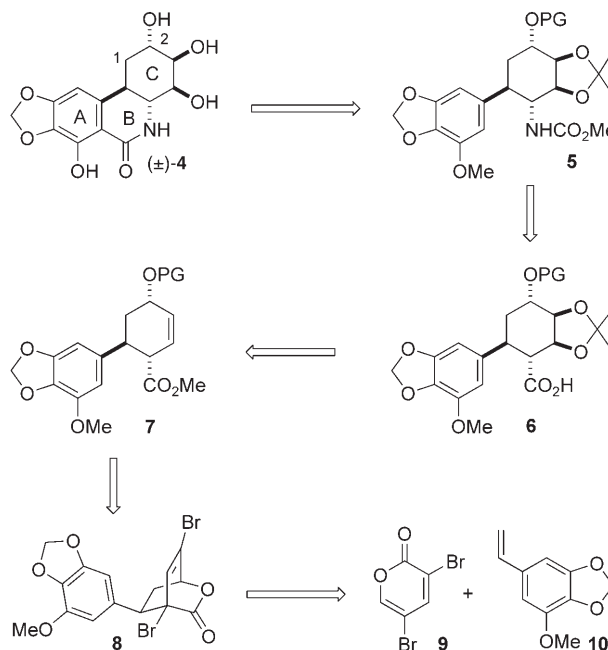
in preparation for the *trans* junction with the lactam subunit of ($\pm$)-**4** (Scheme 2). In this strategy, the B ring of the phenanthridone framework would be constructed from



Scheme 1. Selected examples of naturally occurring isocarbostryls.

isocarbostryls have been isolated primarily from plants of the genus *Amaryllidaceae* and are known to have potent anti-tumor and antiviral activities.^[1] The molecular basis of their anticarcinogenesis has been attributed to their inhibition of protein synthesis at the peptide-bond-forming step, except in the case of pancratistatin (**3**).^[2] Stimulated by the need for more potent antitumor agents with better therapeutic profiles, considerable effort has been devoted to the isolation and creation of structural congeners and analogues of these compounds.^[3] *trans*-Dihydronarciclasine (**4**), isolated by Pettit et al. from the Chinese medicinal plant *Zephyranthes candida* in 1990,^[4] is of particular interest as it exhibits even higher potency (two- to tenfold higher) than pancratistatin against selected human cancer cell lines.^[5]

As part of our ongoing research program to explore the synthetic utility of 3,5-dibromo-2-pyrone (**9**) as an ambident enophile,^[6] we envisaged that the Diels–Alder cycloaddition of **9** with the styrene **10** would provide the cycloadduct **8**, which could be converted into compound **6** with all the essential substituents in the correct relative configuration, including suitable substitution at C2 (numbering for **4**) and a *trans* relationship of the aryl and carboxylic acid substituents



Scheme 2. Retrosynthesis of *trans*-dihydronarciclasine (**4**). PG = protecting group.

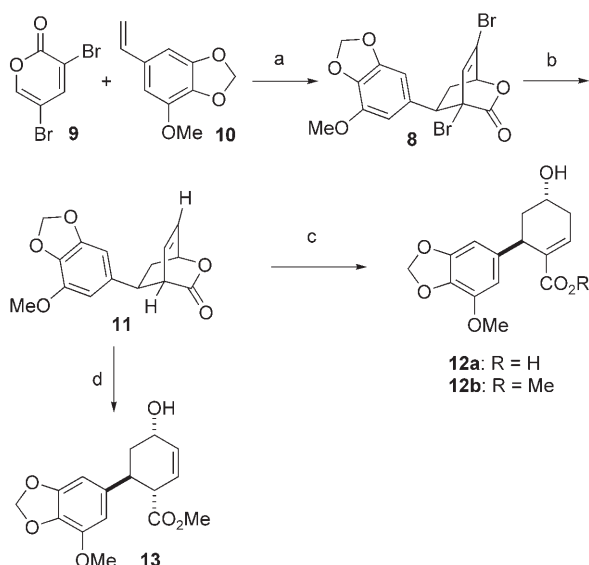
carbamate **5** by employing a Bischler–Napieralski reaction. The requisite carbamate **5** could be accessed from **6** by a Curtius rearrangement and methanolysis of the resulting isocyanate.

The construction of ($\pm$)-*trans*-dihydronarciclasine (**4**) began with the multigram-scale preparation of dienophile **10** from 5-bromovanillin according to methods described in the literature (Scheme 3).^[7] The Diels–Alder cycloaddition reaction was performed by heating a mixture of **10** and 3,5-dibromo-2-pyrone (**9**) in toluene at 80 °C. A readily separable *endo/exo* mixture of cycloadducts was produced in a combined yield of 99 % (*endo/exo* 98:2). The isolated *endo* adduct **8** was then treated with excess Bu₃SnH to remove both bromine atoms and provide **11**. Ring opening of the lactone under basic conditions proved problematic, as both hydrolysis and methanolysis were accompanied by alkene isomerization to produce the α,β -unsaturated carboxylic acid **12a** and ester **12b**, respectively. Fortunately, acidic methanolysis of **11** afforded cleanly the methanolysis product **13** in good yield, with only a trace of the isomerization product **12b** formed.

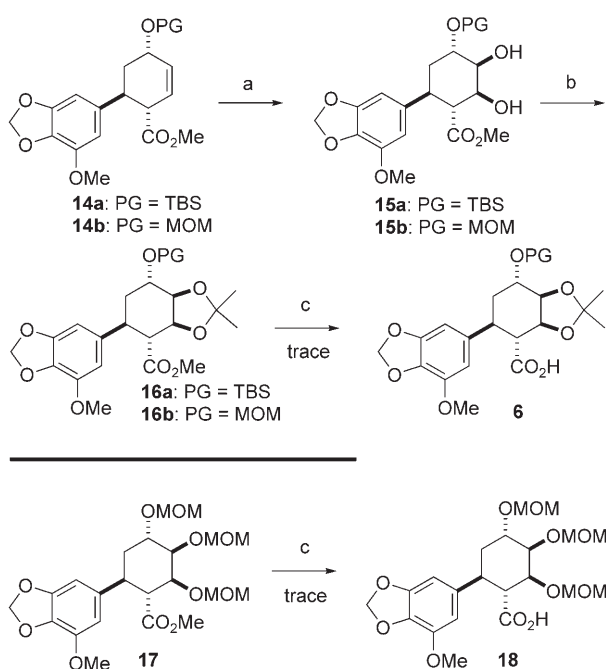
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[**] Financial support was provided by the Korean Science and Engineering Foundation through the Center for Bioactive Molecular Hybrids (CBMH), Yonsei University. I.J.S. is grateful for a BK21 fellowship. E.S.C. acknowledges the Undergraduate Research Program at Hanyang University.

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Scheme 3. Synthesis of intermediate **13**: a) toluene, 80 °C, 99% (*endo/exo* 98:2); b) Bu_3SnH (2.5 equiv), AIBN, benzene, reflux, 98%; c) LiOH or NaOMe , RT, **12a**: 85%, **12b**: 97%; d) MeOH , TsOH , 0 °C $\rightarrow$ RT, overnight, 82%. AIBN = azobisisobutyronitrile, Ts = *p*-toluenesulfonyl.

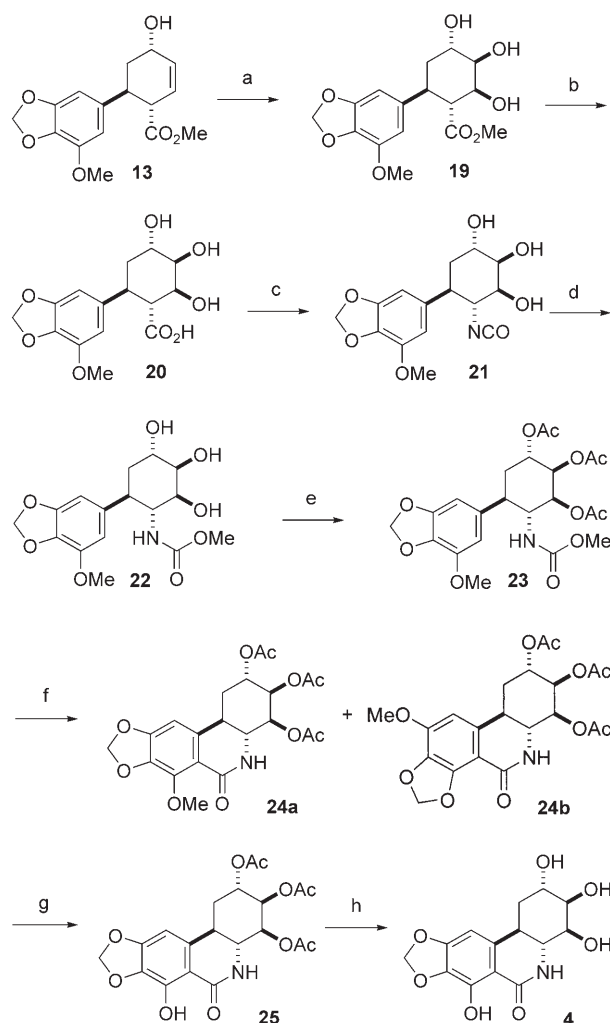


Scheme 4. Attempted hydrolysis: a) OsO_4 , NMO, THF, RT, overnight, 95%; b) acetone, TsOH , 96%; c) LiOH , THF, H_2O , RT $\rightarrow$ reflux. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

The installation of the *cis* vicinal diol preceded hydrolysis of the ester to prevent alkene isomerization. Our initial route involved protection of the allylic hydroxy group, as we foresaw the possible formation of a cyclic carbamate after the Curtius rearrangement.^[8] Dihydroxylation of the protected allylic alcohols **14a** and **14b** proceeded exclusively at the less hindered β face to give **15a** and **15b** upon treatment with

catalytic OsO_4 in the presence of 4-methylmorpholine *N*-oxide (NMO; Scheme 4).^[9] Compounds **15a** and **15b** were transformed successively into acetonides **16a** and **16b**, respectively. The hydrolysis of both **16a** and **16b** required forcing reaction conditions and provided only a trace amount of the desired product as a result of the steric hindrance around the ester group. As similar failure was observed with the MOM-protected compound **17**, we concluded that a less sterically demanding protecting group was required.

With few appropriate protecting groups left to test, we decided to carry out the sequence without protection of the hydroxy groups. Thus, the unprotected allylic alcohol **13** was dihydroxylated to give triol **19** by treatment with catalytic OsO_4 in the presence of NMO (Scheme 5). The hydrolysis of the methyl ester now proceeded smoothly at ambient temper-



Scheme 5. Synthesis of *trans*-dihydronarciclasine (**4**): a) OsO_4 , NMO, THF, RT, overnight, 98%; b) LiOH , THF, H_2O , RT, overnight, 92%; c) DPPA, Et_3N , toluene, reflux, 2 h; d) NaOMe , MeOH , reflux, 0.5 h, 78% over two steps from **20**; e) acetic anhydride, DMAP, pyridine, CH_2Cl_2 , RT, 20 min, 90%; f) trifluoromethanesulfonic anhydride, DMAP, CH_2Cl_2 , 0 $\rightarrow$ 5 °C, 12 h, combined yield of 81% (**24a/24b** 3:1); g) BBR_3 , CH_2Cl_2 , $-78 \rightarrow 0$ °C, 0.5 h, 40% (32% overall yield from **23**); h) NaOMe , MeOH , RT, 0.5 h, 99%. DMAP = 4-dimethylaminopyridine, DPPA = diphenylphosphoryl azide.

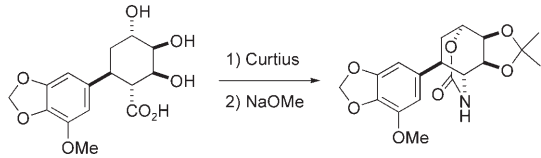
ature to provide the corresponding carboxylic acid **20** in 92 % yield. Subsequent Curtius rearrangement with DPPA produced the isocyanate **21**, which was then directly treated with NaOMe to give methyl carbamate **22** in 78 % yield over two steps. Acetylation of the hydroxy groups to give **23** set the stage for the ensuing Bischler–Napieralski reaction. In analogy with the literature precedent, the ring-closing reaction provided an inseparable mixture of the two regioisomers **24a** and **24b** in a ratio of 3:1.^[10,11] Deprotection of the phenolic methyl ether with BBr₃ furnished **25** in 40 % yield (32 % overall yield from **23**; **24b** remained intact). Removal of the acetyl protecting groups afforded (±)-*trans*-dihydronarciclasine (**4**) in 99 % yield. Both ¹H and ¹³C NMR spectroscopic data matched the reported data.^[4a]

In summary, we have completed the first total synthesis of (±)-*trans*-dihydronarciclasine in 11 steps and 15.8 % overall yield by utilizing a highly *endo* selective Diels–Alder cycloaddition of 3,5-dibromo-2-pyrone.

Received: November 13, 2006

Published online: February 15, 2007

Keywords: antitumor agents · cycloaddition · lactones · natural products · total synthesis

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