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Total Synthesis of (+)-*trans*-Dihydronarciclasine Utilizing Asymmetric Conjugate Addition

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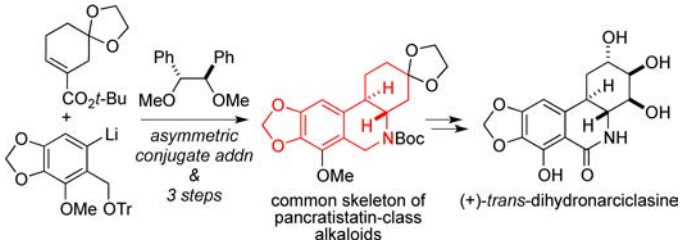
ABSTRACT



A highly efficient short-step construction of the common phenanthridine skeleton of pancratistatin-class alkaloids was accomplished in enantiomerically pure form using chiral ligand-controlled asymmetric conjugate addition. The utility of the intermediate was demonstrated by the total synthesis of (+)-*trans*-dihydronarciclasine with mild oxidation from an amine to an amide as a key step.

(+)-*trans*-Dihydronarciclasine (**1**), originally reported as a hydrogenation product of naturally occurring narciclasine,[1] was isolated from the Chinese medicinal plant *Zephyranthes candida* in 1990 by Pettit et al.[2] and is an important member of the *Amaryllidaceae* alkaloids (Figure 1). This alkaloid exhibits higher potency against selected human cancer cell lines than the intensively investigated (+)-pancratistatin (**2**).[3] Despite their moderate molecular size, **1** and **2** are challenging synthetic targets because of their structural complexity, which includes a highly oxygenated phenanthridinone core with successive stereogenic centers on the cyclohexane ring.[4] Although many total syntheses of **2** have been reported, only two asymmetric syntheses of **1** have been reported[5] since the first total synthesis of racemic *trans*-dihydronarciclasine in 2007.[6]

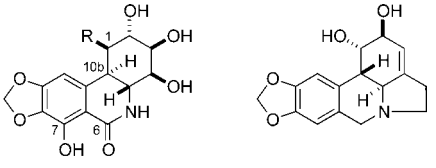


Figure 1. Some *Amaryllidaceae* alkaloids.

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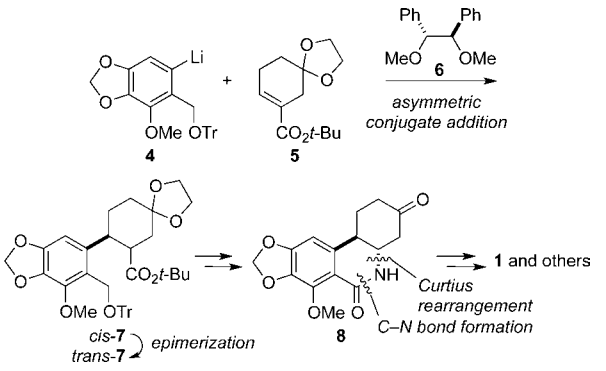
We previously reported the asymmetric total synthesis of another *Amaryllidaceae* alkaloid, (−)-lycorine (**3**), which has a different carbon skeleton, using an asymmetric conjugate addition−Michael cyclization cascade of linear α,ω-dialkenoate.[7] Herein, we describe the total synthesis of (+)-*trans*-dihydronarciclasine (**1**) using chiral ligand-controlled[8] asymmetric conjugate addition of cyclic enoate as a key step.

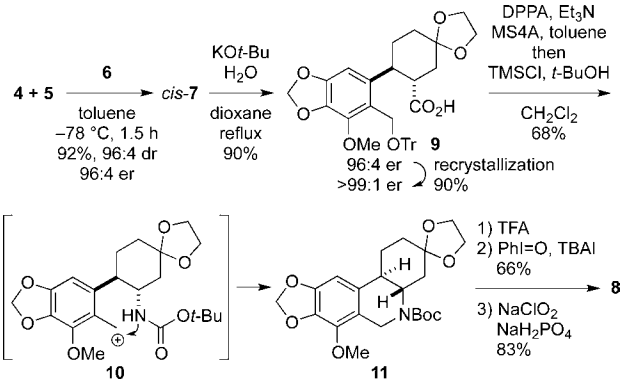
In our strategy, chiral ligand **6** mediates an asymmetric conjugate addition reaction[9] of aryllithium **4**, bearing a trityloxymethyl group at the *ortho* position,[10] with enoate **5** to give *cis*-**7** enantioselectively (Scheme 1). Epimerization followed by Curtius rearrangement and subsequent C−N bond formation leads to the construction of phenanthridindione **8**, a potential common intermediate of pancratistatin-class alkaloids like **1**.

Scheme 1. Synthetic Strategy of **1**



A toluene solution of enoate **5** was added to a solution of aryllithium **4**, prepared from the corresponding aryl bromide (1.0 equiv) and butyllithium (1.0 equiv) in the presence of chiral ligand **6** (1.3 equiv) in toluene at −78 °C. After 26 h, a 95:5 mixture of *cis*- and *trans*-**7** was obtained in 70% combined yield, and 20% of **5** was recovered. The enantiomeric ratio of *cis*-**7** was 94:6 based on chiral stationary phase HPLC analysis. The relative and absolute configurations of *cis*-**7** were confirmed by epimerization to *trans*-**7** (see Supporting Information) and by conversion into **1**, respectively. With increased amounts of **4** and **6** (2.0 and 2.3 equiv, respectively), **5** was completely consumed, and the yield of *cis*-**7** was increased to 91% with slightly higher selectivity (95:5 er, 97:3 dr). Moreover, *cis*-**7** was produced in high yield and enantioselectivity (92%, 96:4 er) with comparable diastereoselectivity (96:4 dr) when 3.0 and 3.3 equiv of **4** and **6** were utilized, respectively (Scheme 2). It is noteworthy that chiral ligand **6** was quantitatively recovered without the loss of optical purity and was therefore reusable.

Scheme 2. Construction of Key Intermediate **11** Using Asymmetric Conjugate Addition of **4** and **5** and Curtius Rearrangement



Both epimerization at the α-position and hydrolysis of *tert*-butyl ester were simultaneously achieved by treatment with potassium hydroxide, generated *in situ* from potassium *tert*-butoxide and water,[11] in refluxing dioxane to afford *trans*-carboxylic acid **9** as a single diastereomer. Recrystallization of **9** from hexane/ethyl acetate (1:1) afforded enantiomerically pure **9** (> 99:1 er) in 90% yield.

Introduction of a nitrogen atom using diphenylphosphoryl azide (DPPA)[12] efficiently proceeded, forming the corresponding isocyanate. The isocyanate, however, had limited reactivity, probably due to steric hindrance, and only a trace amount of the corresponding *tert*-butyl carbamate was formed when heated with *tert*-butanol. To enhance the electrophilicity of the isocyanate by *in situ*-generated hydrogen chloride,[13] the isocyanate resulting from the Curtius rearrangement was treated with *tert*-butanol and chlorotrimethylsilane. Unexpectedly, the C−N bond forming cyclization took place along with the expected carbamate formation to give **11** in 68% yield in 2 steps. The production of **11** can be explained by a substitution reaction of the trityloxy group with the carbamate nitrogen atom *via* cationic intermediate **10** under acidic conditions. Thus, the phenanthridine core of pancratistatin-class alkaloids was constructed in optically pure form only in five steps, including the enantiomer enrichment by recrystallization. To demonstrate the utility of phenanthridine **11** as a synthetic intermediate, total synthesis of **1** was further explored.

First, oxidation of the benzylic methylene group in **11** was investigated to install the lactam moiety. Although various reaction conditions, such as *tert*-butylperoxyiodane,[14] ruthenium trichloride with sodium perchlorate,[15]

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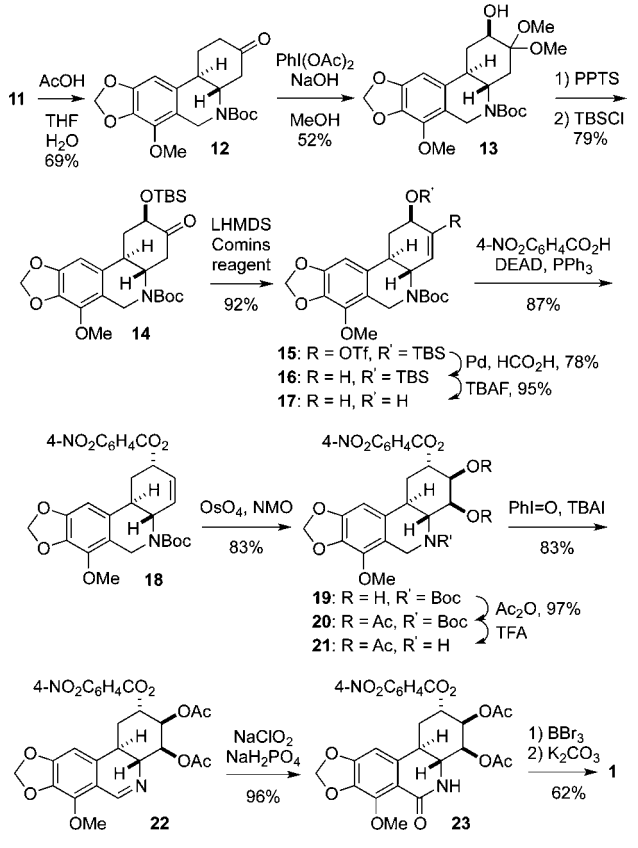
or *N*-bromosuccinimide with benzoyl peroxide[16] were attempted, **11** and its Boc- and/or acetal-deprotected analogs were labile under these oxidation conditions, giving complex mixtures, probably due to the electron rich aromatic ring. Finally, as shown in Scheme 2, the desired oxidation was accomplished in a stepwise manner: Treatment of **11** with TFA to hydrolyze the acetal and remove the Boc group, followed by oxidation of the resulting amine with iodosobenzene in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI),[17] gave the corresponding imine in 66% yield in 2 steps.[18] The desired lactam **8** was obtained in 83% yield by our mild oxidation of the imine with sodium chlorite.[19] Unfortunately, **8** was insoluble in most solvents, which caused difficulty in further transformations. We therefore performed this benzylic amine oxidation at a later stage in the synthesis.

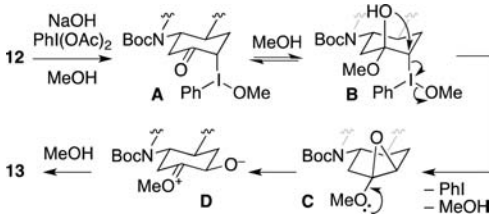
Thus, the oxygen functionalities were stereoselectively introduced on the cyclohexane ring as follows (Scheme 3). Hydrolysis of the acetal moiety of **11** with acetic acid in aqueous THF at 80 °C gave ketone **12**, which was then stereo- and regioselectively oxidized to dimethyl acetal **13** by iodobenzene diacetate in the presence of sodium hydroxide in methanol.[20] Other methods for α-oxidation of ketone utilizing *m*-CPBA,[21] oxaziridine,[22] palladium(II),[23] 2-iodoxybenzoic acid,[24] or oxodiperoxymolybdenum·pyridine·HMPA,[25] resulted in low yield or a complex mixture.

Scheme 3. Total Synthesis of (+)-*trans*-Dihydronarciclasine (**1**)



Stereoselective formation of **13** was rationalized by the reaction pathway shown in Scheme 4. First, the α-position of ketone **12** was oxidized by iodine(III) species through the corresponding enolate stereoselectively from the axial side to give intermediate **A**. Then, the stereospecific formation of epoxide **C** via reversively generated hemiacetal **B** was followed by ring-opening and the addition of methanol to the resulting intermediate **D** to produce **13**.

Scheme 4. Rationale for the Stereoselective Formation of **13**



The dimethyl acetal moiety of **13** was hydrolyzed with PPTS in wet acetone, and subsequent protection of the hydroxy group with a TBS group afforded α-siloxy ketone **14**, which was then regioselectively converted into vinyl triflate **15** in 92% yield by successive treatment with LHMDS and Comins reagent.[26] The triflyloxy group was removed in 78% yield by catalytic hydrogenolysis using formic acid as a hydride source,[27] and allylic alcohol **17** was obtained in 95% yield after removal of the TBS group of **16** by TBAF. Stereochemical inversion of the secondary alcohol **17** was accomplished by modified Mitsunobu conditions[28] to give 4-nitrobenzoate **18** in 87% yield. Dihydroxylation of **18** with osmium tetroxide and NMO diastereoselectively gave diol **19** in 83% yield along with its diastereomer in 16% yield, and amine **21** was obtained in 97% yield after acetylation of **19** and removal of the Boc group of **20**.

The amine was then oxidized to lactam under the aforementioned conditions. Despite the highly functionalized

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structure of **21**, two-step oxidation via imine **22** successfully provided **23** in 80% yield. This result clealy demonstrated the excellent functional group tolerance of our oxidation method.[19]

Finally, removal of the methyl and acyl groups afforded (+)-*trans*-dihydronarciclasine (**1**), whose specific rotation, ^{1}H and ^{13}C NMR, MS, and IR data were consistent with those previously reported.[1,5,6]

In summary, we developed four-step construction of the common skeleton of the pancratistatin-class alkaloids using our chiral diether-controlled asymmetric conjugate addition methodology and achieved total synthesis of (+)-*trans*-dihydronarciclasine. This synthetic strategy is versatile and potentially applicable to the synthesis of other known members of this class of alkaloids, such as 6- and/or 7-deoxy, and/or 1,10b-dehydro analogs.[4] This synthesis highlights the utility of our protocol for oxidation of an amine to an amide.

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Supporting Information Available. Experimental details, characterization data and NMR spectra of new compounds, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.