Natural Products

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Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-*trans*-Dihydrolycoricidine**

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Abstract: *A total synthesis of the anticancer natural product (+)-trans-dihydrolycoricidine is reported from α-azidoacetone and cinnamaldehyde precursors. Key elements include an asymmetric organocatalytic sequence proceeding by a regiospecific secondary-amine-catalyzed syn Michael addition followed by an intramolecular aldol reaction. The sequence results in the formation of an advanced intermediate, containing three stereogenic centers, in one step which and was converted into the title compound in eight steps.*

Amaryllidaceae alkaloids[1,2] have occupied the attention of natural product and synthetic chemists[3] for many years in view of the biological activity displayed, including potent anticancer and antiviral activities, as well as the presence of synthetically challenging, densely functionalized aminocyclitol cores.[1,2] The lycorane isocarbostyrils **1**–**6** (Figure 1) including pancratistatin (**1**), narciclasine (**3**), and (+)-*trans*-dihydrolycoricidine (**6**), have attracted particular interest because of the potent and selective nanomolar anticancer activity demonstrated.[3] Several research groups described the systematic synthesis of deoxy analogues of the natural product **6**, including the 3-deoxy analogue **7**. Anticancer investigations of these analogues demonstrated that **6** constitutes the minimum anticancer pharmacophore in the series.[2l–p] Additionally, the 1-10b-styryl double bond in narciclasine (**3**) is associated with unwanted cytochrome P_{450} activity,[2q] thus highlighting the importance of **5** and **6** toward developing a potent and selective anticancer agent.

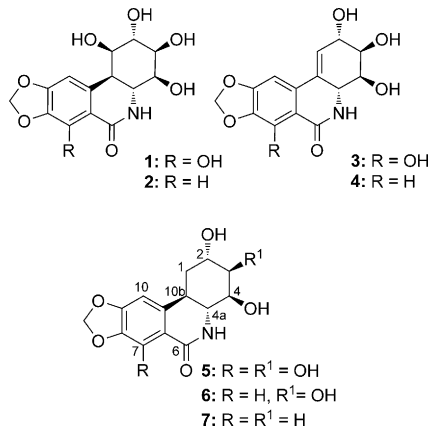
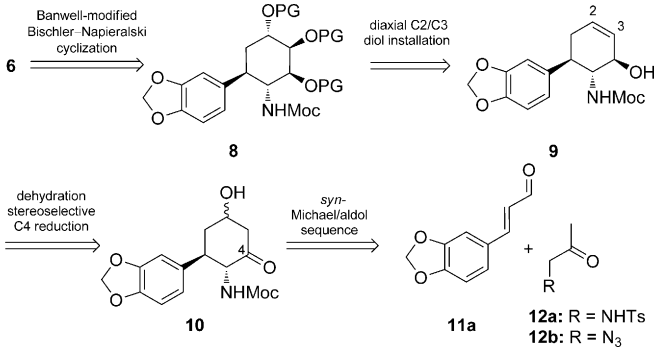


Figure 1. Structures of the bioactive amaryllidaceae alkaloids **1**–**6** and non-natural 3-deoxy derivative **7**.

Natural (+)-*trans*-dihydrolycoricidine (**6**) has been the subject of four previous total syntheses.[4] We were inspired by recent enantioselective organocatalytic approaches toward six-membered carbocycles[5a] to develop a stepwise [3+3]-type Michael/aldol sequence,[5b–g] involving an α-nitrogen-substituted acetone moiety reacting with an unsaturated aldehyde, as a possible rapid entry to the amaryllidaceae core. Such an approach would also open a valuable asymmetric entry to aminocyclitols, a large and expanding class of compounds with diverse biological activities.[6] In our retrosynthetic analysis (Scheme 1), we envisioned that **6** would be derived from the methoxycarbonyl-substituted aminocyclitol **8**, produced from the cyclohexene **9** by epoxidation and 2,3-diaxial diol formation. The critical synthesis of **9** via the aldol intermediate **10** would hinge upon the development of a successful regiocontrolled *syn*-stereoselective Michael addition of a suitable nitrogen-functionalized acetone (**12a**/**b**) with the cinnamaldehdye **11a**.



Scheme 1. Retrosynthetic analysis of (+)-*trans*-dihydrolycoricidine. The natural-product numbering system is employed. PG = protecting group, Moc = methoxycarbonylamino, Ts = *p*-toluenesulfonyl.

Considering the reactivity of α-nitrogen-functionalized carbonyl compounds in organocatalytic processes, Alexakis and co-workers reported the Michael addition of α-NH-tosylacetone derivatives to nitroalkenes, a reaction that was shown to proceed with *syn* stereoselectivity.[7a] Barbas and co-workers described the generation of enamines from α-azidoketones and trapping with imines as a route to chiral

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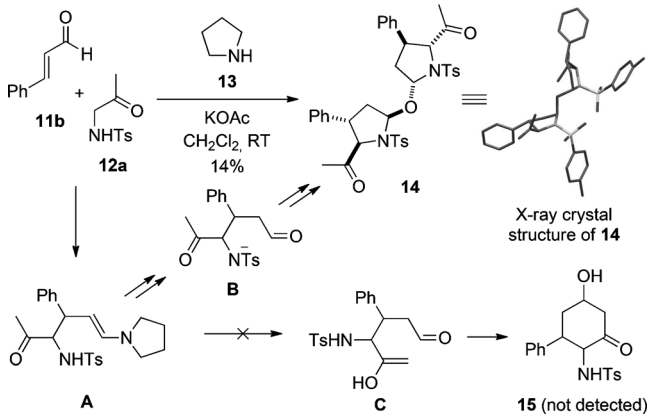
1,2- and 1,4-diamines.[7b] A few other examples of organocatalytic reactions involving α-nitrogen-containing carbonyl derivatives are known.[7c–f] A synthesis of six-membered carbocycles from a suitable α-nitrogen-functionalized carbonyl compound, involving a regiocontrolled Michael/aldol sequence as we envisioned (Scheme 1), has not been reported. Alonso and co-workers have recently reported a synthesis of pancratistatin (**1**) by employing the Michael addition of a symmetrical 1,3-dioxyketone to a doubly activated α-nitro-unsaturated aldehyde.[3o] Herein, we report our initial findings and success in developing this Michael/aldol sequence and an asymmetric synthesis of natural (+)-*trans*-dihydrolycoricidine (**6**).

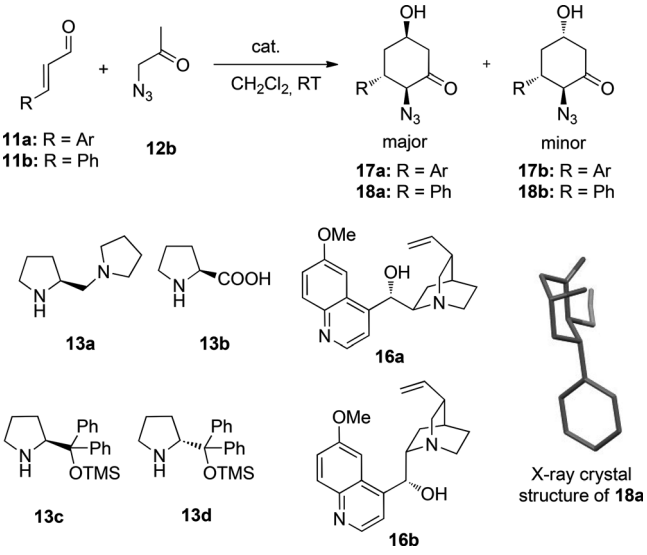
The study was initiated through investigation of a possible organocatalytic sequence using α-*N*-tosylacetone (**12a**) reacting with the model acceptor cinnamaldehyde (**11b**; Scheme 2)



Scheme 2. Possible reaction sequence leading to the dimeric adduct **14**.[11]

in dichloromethane with the catalyst **13**. While reaction was slow, a 1:1 adduct was indeed formed in low yield (14% upon isolated). This product proved to be the compound **14** (confirmed by X-ray analysis), the product of dimerization of the intermediate Michael addition adduct. No trace of the cyclohexane **15** was observed. We had envisioned a sequence in which the immediate Michael adduct **A** (Scheme 2) would undergo intramolecular proton transfer, thus leading to **C**, which would cyclize through the aldol process to yield **15**. We attributed formation of **14** to the presence of the acidic NH constituent in **A**, which leads to **B**, thus leading to **14** upon hydrolysis. These results immediately served to direct our attention to the corresponding possibility using the azidoacetone **12b**. The reaction of **11b** and **12b** was investigated using a variety of secondary-amine catalysts and reaction conditions. The use of L-proline (**13b**) or the prolinol silyl ether **13c** (Jørgensen's type) alone failed to generate the cyclohexane derivative in water or organic media (dichloromethane, toluene etc.; Table 1, entries 1 and 2). On the basis of the initial observations that led to **14**, we considered that a basic entity might be required to effect proton shuttling (e.g., azido analogue of **A** to **C** in Scheme 2), thus permitting the sequential Michael/aldol sequence. While use of a chiral tertiary amine alone proved ineffective (entry 3), to our

Table 1: Selected studies on optimization of the reaction parameters.[a]



Entry	Catalyst	Substrate	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	**13b**	**11b**	n.r.	n.d	n.d.
2	**13c**	**11b**	n.r.	n.d.	n.d.
3	**16a**	**11b**	n.r.	n.d.	n.d.
4	**13a**	**11b**	64	29	4:1
5	**13c**/DIPEA	**11b**	29	90	5:1
6	**13b/16a**	**11b**	60	6	17:1
7	**13c/16a**	**11b**	48	93	>20:1
8	**13c/16b**	**11b**	50	91	>20:1
9	**13d/16a**	**11b**	52	92[e]	>20:1
10	**13d/16a**	**11a**	56	>98[f]	>20:1
11[g]	**13d/16a**	**11a**	65	>98[f]	>20:1

[a] Unless noted, the reaction was conducted with **11a**/**11b** (0.50 mmol), **12b** (0.75 mmol, 1.5 equiv), cat. (10 mol%) for 32 h at RT. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC, and the absolute configuration was assigned based on the X-ray crystal structure of **20**.[11] [d] The d.r. values of **18a**/**18b** were determined by ^{1}H NMR spectroscopy and HPLC. [e] *ent*-**18a** was obtained. [f] *ent*-**17a** was obtained. [g] **11a** (4.7 mmol) and **12b** (4.5 mmol) 24 h at RT. Ar = (2,3-methylenedioxy)phenyl, DIPEA = *N*,*N*-diisopropylethylamine, TMS = trimethylsilyl.

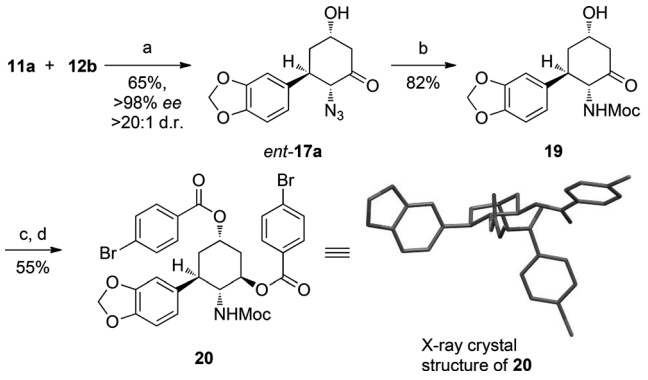
delight, it was determined that the catalyst **13a**, containing a basic pyrrolidyl side chain, provided the necessary turnover and reasonable yields of the cyclohexane derivatives **18a** and **18b**, which were isolated as a 4:1 ratio of diastereomers (entry 4). The diastereomers **18a** and **18b** were readily separated on silica gel and a single-crystal X-ray structural determination on *rac*-**18a** confirmed the regiospecificity and *syn* stereoselectivity of the Michael addition and the overall relative stereochemistry on the cyclohexane ring (Table 1). Resolution of *rac*-**18a** was also readily accomplished using HPLC (see the Supporting Information). The use of the prolinol catalyst **13c** in the presence of an external, nonchiral base (DIPEA) also gave the desired cyclohexanone in moderate yield and high *ee* value, but with a low d.r. value on the aldol step (entry 5). We next determined that the use of **13b** and an added chiral tertiary base such as the quinidine **16a** allowed conversion with a much higher d.r. value (entry 6), but low *ee* value. While the use of **13b** and **16a**

(entry 6) had a marked effect on the d.r. value of the reaction, the *ee* value (6%) was unacceptable.

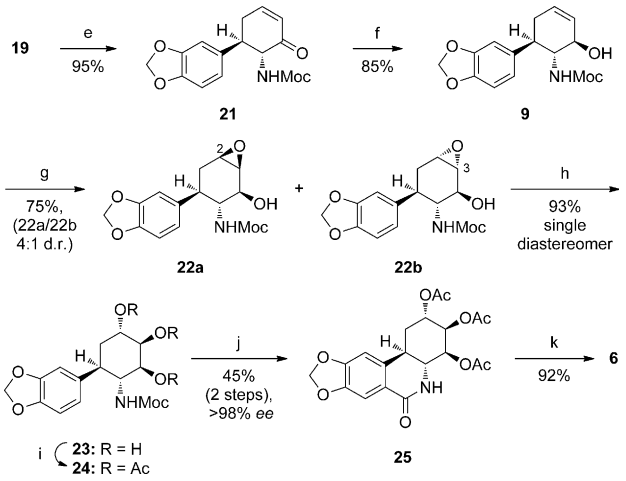
From these results (Table 1, entries 1–6) we hypothesized that to achieve high *ee* and d.r. values, the use of **13c** in conjunction with a bulky chiral cinchona base might be required. We therefore investigated a series of combinations of chiral secondary amines in the presence of a bulky basic tertiary amine cocatalysts with stunning results. While neither the prolinol catalyst **13c**/**13d** nor the quinidine **16a** or quinine **16b** alone provided significant turnover, we were delighted to find that dual catalysis provided **18a** in 48–50% yield upon isolation, and also now with high d.r. values (>20:1) and greater than 90% *ee* (entries 7 and 8). The absolute stereochemistry of the product (see below) proved to be governed only by **13c**, with either enantiomer of the quinine increasing the selectivity on the aldol reaction alone (d.r.). Switching to the secondary amine antipode **13d** yielded *ent*-**18a** (compare entries 7 and 9) in similar yield and stereoselectivity as before. Finally, the same process conducted on the methylenedioxy-substituted cinnamaldehyde **11a**, available in one step from piperonal,[8] proved even more stereoselective and the desired cyclohexane *ent*-**17a** (entry 10) was isolated in 56% yield and with greater than 98% *ee*. The reaction also proved highly effective on scale up (65% yield upon isolation), thus providing reliable access to greater than 500 mg quantities of the desired stereoisomer *ent*-**17a** (entry 11).

The absolute configuration of *ent*-**17a** was determined as depicted in Scheme 3. The azido group was reduced and the resulting cyclohexylamine protected in situ with DMDC as the methoxycarbonylamino (Moc) derivative **19**. Reduction of the 4-oxo group to the C4 equatorial alcohol and bis(benzoylation) of the resulting 2,4-diol with 4-bromobenzoylchloride gave the derivative **20**. A single-crystal X-ray diffraction analysis confirmed the relative and absolute stereochemistry as depicted (Scheme 3). Thus it was definitively shown that use of the (*R*)-(+)-stereoisomer of prolinol silyl ether catalyst **13d** provided the Michael/aldol cycloadduct having the correct absolute configuration as found in the natural anticancer agent (+)-*trans*-dihydrolycoricidine (**6**).

We finally turned our attention to completion of the synthesis of **6**, as outlined in Scheme 4. The adduct *ent*-**17a**, obtained as described (Table 1, entry 11), was converted into the methoxycarbamate **19** as before. Treatment with methanesulfonyl chloride in the presence of Hünig's base effected dehydration to give the cyclohexanone **21** in 95% yield. Chemoselective reduction of the carbonyl group in **21** using lithium tri-*tert*-butoxyaluminium hydride gave the equatorial alcohol **9** (85%). Epoxidation of **9** was accomplished using *m*CPBA, thus yielding a mixture of the β-epoxide **22a** and α-epoxide **22b** in a 4:1 ratio.[9] The epoxides could be easily separated on silica gel and were isolated in 59% (**22a**) and 16% (**22b**) yields and independently characterized. Stereoselective opening of the epoxides was achieved as expected,[2m] through either axial attack at C2 (**22a**) or C3 (**22b**), thus giving the same 2,3,4-triol **23** in 96% yield (from **22a**). The triol derivative was protected as the triacetate **24** without incident, and **24** cyclized following the Banwell[10] modification of the Bischler–Napieralski reaction to give **25** in 52% yield and greater than 98% *ee* (see Table S1 in the Supporting Information). Finally, removal of the acetate protecting groups yielded natural **6** in 92% yield from **25**. Overall, **6** was obtained in nine chemical steps from **12b** and **11a**, with an overall yield of 12% and greater than 98% *ee*. While the absolute configuration was determined as described in Scheme 3, optical rotation and all other spectroscopic characterization data for (+)-*trans*-dihydrolycoricidine (**6**) were in accord with published values (see Tables S2 and S3 in the Supporting Information).[4]



Scheme 3. Reagents and conditions: Yields of isolated products are indicated.[11] a) **13d** (10 mol%) and **16a** (10 mol%), CH_2Cl_2, RT, 24 h, 65%. b) DMDC (3.0 equiv), H_2, 10% Pd/C (0.075 equiv), 50 psi, MeOH, RT, 16 h, 82%. c) $Me_4NHB(OAc)_3$ (4.0 equiv), acetonitrile/AcOH (96:4), RT, 12 h, 77%. d) *p*-BrBzCl (3.0 equiv), DMAP (0.10 equiv), py, 0°C, 8 h, 71%. Bz = benzoyl, DMAP = 4-dimethylaminopyridine, DMDC = dimethyl dicarbonate.



Scheme 4. Reagents and conditions: Yields of isolated products are indicated. e) MsCl (1.30 equiv), DIPEA (3.0 equiv), CH_2Cl_2, 0°C→RT, 10 h, 95%. f) $LiHAl(OtBu)_3$ (3.0 equiv), THF, 0°C→RT, 7 h, 85%. g) *m*CPBA (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, RT, 24 h, **22a** 59%, **22b** 16%. h) NaOBz (0.06 equiv), H_2O, 95°C, 16 h, 93%. i) Ac_2O (6.0 equiv), py, RT, 16 h, 87%. j) Tf_2O (5.0 equiv), DMAP (3.0 equiv), CH_2Cl_2, 0°C→RT, 16 h, 52%. k) K_2CO_3 (0.10 equiv), $MeOH/H_2O$ (1:9), RT, 16 h, 92%. MsCl = methanesulfonyl chloride, *m*CPBA = *meta*-chloroperbenzoic acid, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

In conclusion, we have developed a nine-step total synthesis of the anticancer natural product (+)-*trans*-dihydrolycoricidine (**6**) from readily available starting materials. Key features of the synthesis involve the regiospecific organocatalytic addition of α-azidoacetone (**12b**) onto Michael acceptors such as 3,4-methylenedioxycinnanmaldehyde (**11a**), by a *syn*-stereoselective process and subsequent intramolecular aldol reaction, thus yielding highly functionalized cyclohexanones such as **17a**/**18a** (or enantiomers). The process occurs with high enantioselectivity when employing chiral prolinol silyl ether secondary amine catalysts, and high d.r. values were achieved by use of a base as a cocatalyst. The sequence may proceed through either enamine or iminum ion activation. Further exploration of the scope and mechanism of this sequence and application toward the synthesis of other amaryllidaceae constituents and aminocyclitols is being actively pursued in our laboratory. Demonstration of this asymmetric Michael/aldol sequence from α-azocarbonyl compounds and unsaturated aldehydes opens many possibilities for the synthesis of related alkaloids. Perhaps, more importantly, this methodology provides a rapid asymmetric entry to the larger class of aminocyclitols, which display therapeutic activities toward a wide range of targets.[6]

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[11] CCDC 987917 (**14**), CCDC 985658 (**18a**), and CCDC 984484 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Natural Products

J. McNulty,*
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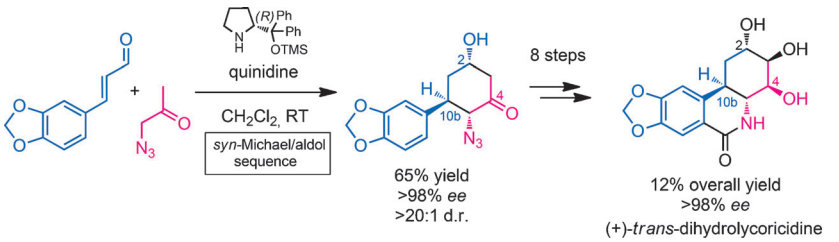
Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-*trans*-Dihydrolycoricidine



Taking steps: A stepwise organocatalytic Michael addition/aldol sequence is described involving secondary-amine-catalyzed regioselective addition of azidoacetone to cinnamaldehyde derivatives followed by intramolecular aldolization. Application of this route to aminocyclitols is demonstrated by a short, asymmetric synthesis of the anticancer natural product (+)-*trans*-dihydrolycoricidine.

