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AN ENANTIO- AND DIASTEREOCONTROLLED SYNTHESIS OF (+)-7-DEOXY-*TRANS*-DIHYDRONARCICLASINE †

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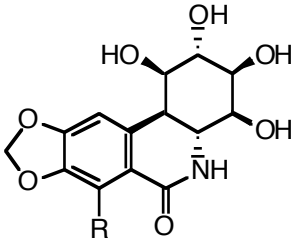
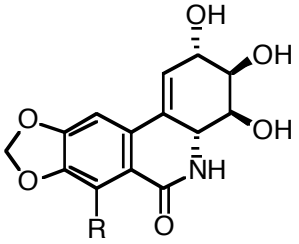
Abstract – An enantio- and diastereocontrolled synthesis of (+)-7-deoxy-*trans*-dihydronarciclasine, a potent antineoplastic phenanthridone alkaloid from the bulbs of *Hymenocallis carbaea* and *H. littoralis*, has been developed starting with the chiral cyclohexanoid building block.

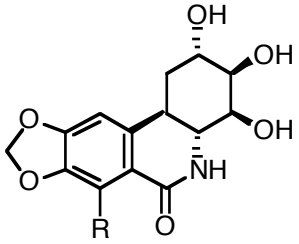
The polyhydroxylated phenanthridones of the Amaryllidacea group,[1] represented by pancratistatin (**1**),[2a] 7-deoxypancratistatin (**2**),[2b] narciclasine (**3**),[2c] lycoricidine (**4**),[2d] *trans*-dihydronarciclasine (**5**),[2e] and (+)-7-deoxy-*trans*-dihydronarciclasine (**6**),[2f] have attracted considerable attention due to their diverse range of pharmacological properties, including antineoplastic,[3] antiviral,[4] and antiparasite activity.[5] Their low natural abundance and unique structures encompassing up to six contiguous asymmetric centers on the cyclohexane ring have spurred synthetic researchers to develop an efficient route capable of assembling them in a stereocontrolled manner. [6,7]



Pancratistatin: R = OH (**1**)
7-Deoxypancratistatin: R = H (**2**)



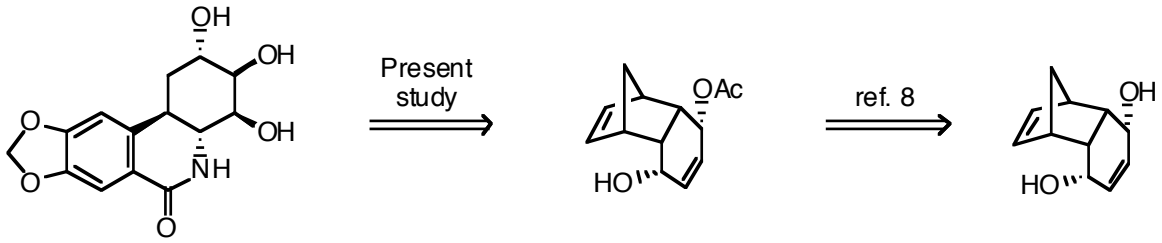
Narciclasine: R = OH (**3**)
Lycoricidine: R = H (**4**)



trans-Dihydronarciclasine: R = OH (**5**)
7-Deoxy-*trans*-dehydronarciclasine (**6**)

As part of our research interest directed toward exploiting the versatility of the chiral cyclohexanoid building block (**7**),[8,9] obtainable in both enantiomeric forms by the lipase-mediated asymmetric

desymmetrization of a *meso* precursor **8**, we examined a diastereo- and enantiocontrolled construction of (+)-7-deoxy-*trans*-dihydronarciclasine (**6**),[2f,10] isolated in 1993 by Pettit and coworkers as the principal substance responsible for the antitumor activity of the bulbs of *Hymenocallis carbaea* and *H. littoralis*. We report here an enantio- and diastereocontrolled synthesis of (+)-7-deoxy-*trans*-dihydronarciclasine (**6**) accomplished in a sequence of 21 steps from (+)-**7**.



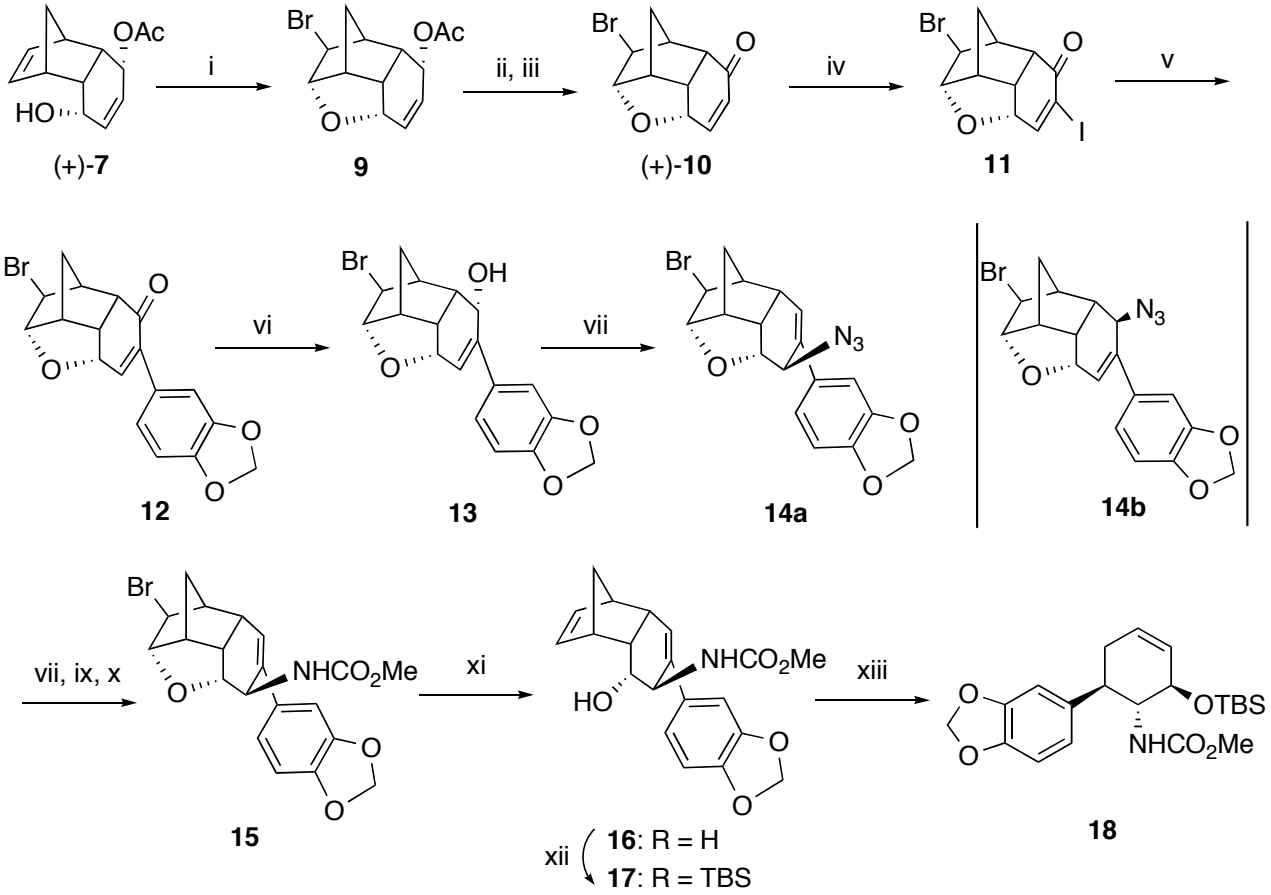
(+)-7-Deoxy-*trans*-dehydronarciclasine (**6**) (+)-**7** *meso*-**8**

Scheme 1.

With our intent on employing the Banwell-Bischler-Napieralski reaction[11] for the B-ring construction and our interest in verifying the stereoelectronic bias of the tricyclic system as the diastereocontrolling element, we selected a route that involves Pd-catalyzed coupling for installing the 3,4-methylenedioxyphenyl moiety onto the cyclohexane frame. Thus, we first transformed (+)-**7** into the α-iodo enone (**11**). On treatment with NBS in dichloromethane at -20 °C, the cyclopentene olefin and the hydroxy group of **7** was simultaneously protected by the formation of a bromo ether to give **9** in 62% yield. **9** was converted into the enone (**10**), through sequential deacetylation and oxidation. The exposure of (+)-**10** to iodine in pyridine and CCl_4[12] gave the desired α-iodo enone (**11**), which was immediately subjected to the Pd-catalyzed cross-coupling reaction employing suitable aryl donors. After considerable experimentation, we found that the addition of CuCl[13] and Ph_3As[14] markedly enhances the catalytic efficiency of $PdCl_2(PPh_3)_2$ for Stille coupling using 3,4-methylenedioxyphenyltributylstannane[15] at an ambient temperature to furnish **12**, mp 194-195 °C, $[\alpha]_D^{32}$ –715° (c 0.58, $CHCl_3$), in 65% yield in two steps. In our hands, the attempted Suzuki coupling required harsh conditions, leading to a considerable decomposition of **11**.

To introduce a carbamate functionality which is destined to constitute the B-ring, **12** was reacted with a mixture of DIBAH and 2,6-di-*tert*-butyl-4-methylphenol,[16] prepared *in situ* in CH_2Cl_2 at -78 °C, to give *endo*-**13**, mp 232-233 °C, $[\alpha]_D^{24}$ +102° (c 0.68, $CHCl_3$), exclusively *via* a chemo- and diastereoselective delivery of a hydride from a convex face. On Mitsunobu reaction using $(PhO)_2PON_3$, DIPT and PPh_3,[17] the allylic alcohol (**13**) furnished the azide (**14a**), $[\alpha]_D^{31}$ –10.9° (c 0.73, $CHCl_3$), as a single isomer, presumably *via* the S_N2' pathway.[18, 19] No trace amount of the normal S_N2 product (**14b**) was detected in this particular case. **14a** was then reduced, carbamoylated, and hydrogenated to furnish **15**, mp

131-132 °C, $[\alpha]_D^{29}$ +66.7° (c 0.78, $CHCl_3$), as a sole product in 98% yield, confirming again the excellent diastereocontrolling potency of the tricyclic system. Having secured the three requisite contiguous stereogenic centers, the bromo ether moiety of **15** was reductively disarmed to give rise to **16**, mp 152-153 °C, $[\alpha]_D^{27}$ +43.1° (c 0.52, $CHCl_3$), on Zn-mediated reduction in the presence of acetic acid,[20] with the regeneration of a cyclopentene olefin and the hydroxy functionalities. After the protection of the hydroxy group by the TBS group, the resulting **17** was heated at reflux in Ph_2O in the presence of $NaHCO_3$[21] to give cyclohexene (**18**), $[\alpha]_D^{28}$ –36.0° (c 0.45, $CHCl_3$), by retro Diels-Alder reaction. Without the TBS protection or in the absence of $NaHCO_3$, the yield of **18** was reduced considerably.

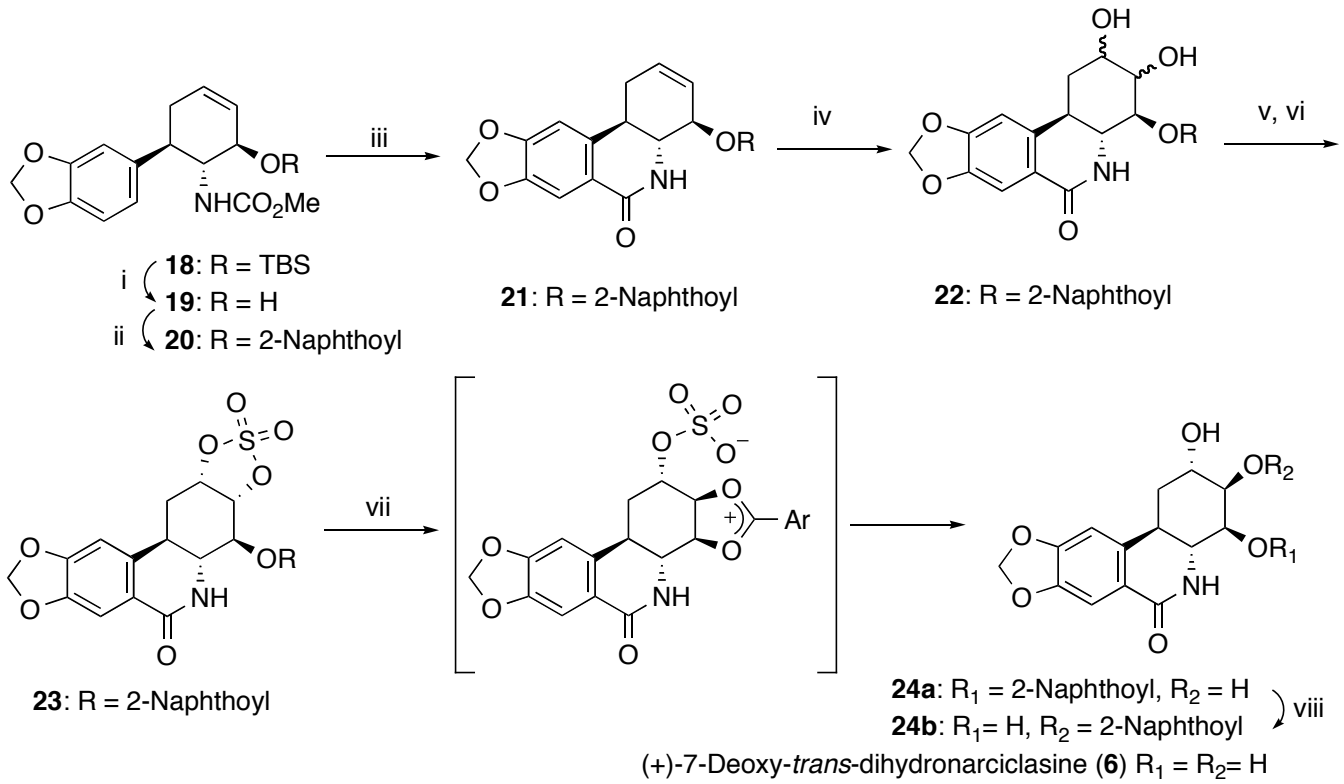


Scheme 2. *Reagents and conditions*: (i) NBS (4 equiv.), CH_2Cl_2, -30 °C, 2.5 h, 62%; (ii) K_2CO_3, MeOH, rt, 1 h, 99%; (iii) PDC (2.2 equiv.), CH_2Cl_2, rt, 2 h, 96%; (iv) I_2 (2 equiv.), pyridine-CCl_4 (1 : 5), rt, 2 h; (v) 3,4-methylenedioxy- phenyltributylstannane (1.5 equiv.), $PdCl_2(PPh_3)_2$ (0.1 equiv.), Ph_3As (0.2 equiv.), CuCl (2 equiv.), THF, rt, 18 h, 63% (2 steps); (vi) DIBAH (5 equiv.), 2,6-di-*tert*-butyl-4-methylphenol (7.5 equiv.), CH_2Cl_2, -78 ºC, 1.5 h, 86%; (vii) DPPA (2.5 equiv.), PPh_3 (2.5 equiv.), DIAD (2.5 equiv.), rt, 2 h, 76%; (viii) H_2, 10% Pd/C, AcOEt, rt, 10 h, 95%; (ix) $ClCO_2Me$, 1N NaOH, THF, rt, 1.5 h, 95% (2 steps); (x) H_2, 50% $Pd(OH)_2$/C, MeOH, rt, 92%; (xi) Zn (20 equiv.), MeOH-AcOH-THF (60 : 6 : 10), reflux, 2.5 h, 94%; (xii) TBSOTf, Et_3N, CH_2Cl_2, -78 ºC, 2 h, 95%; (xiii) $NaHCO_3$ (5.6 equiv.), Ph_2O, reflux, 12 min, 87%.

To install the remaining two hydroxy groups at a suitable diastereoselectivity, the TBS group in **18** was replaced with the 2-naphthoyl group to give **20**, mp 161-162 °C, $[\alpha]_D^{27}$ –255° (c 1.32, $CHCl_3$), *via* **19**.

The projected ring B formation was carried out at this point by treating **20** with Tf_2O and DMAP in cold CH_2Cl_2[12] to predominantly afford the desired product (**21**) in 84 % yield.

Although all the attempted diastereoselective epoxidations were unsuccessful, the catalytic osmylation of **21** gave the diol (**22**) in 92% yield as an inseparable 11 : 1 mixture,[22] in which the stereochemistry of the major diastereomer was tentatively assigned as α-diol, on the basis of steric considerations. On treatment with thionyl chloride followed by oxidation with $RuCl_3/NaIO_4$,[23] the diol (**22**) provided two diasteromeric cyclic sulfates, from which **23**, mp 222-223 °C, $[\alpha]_D^{27}$ +134° (c 0.22, $CHCl_3$), was obtained in 52% yield. The cyclic sulfate **23** was cleaved through the participation of the naphthoate functionality to give a mixture of **24a** and **24b**, by heating in pyridine at reflux and the following hydrolysis with 2 N aq. H_2SO_4 in acetonitrile. Finally, the mixture was subjected to methanolysis to furnish (+)-7-deoxy-*trans*-dihydronarciclasine (**6**), mp 299-303 °C, $[\alpha]_D^{27}$ +124° (c 0.1, DMSO), [lit.,[2f] mp 303-304 °C, $[\alpha]_D^{25}$ +138° (c 0.96, DMSO)], in 84% yield. The overall yield of (+)-7-deoxy-*trans*-dihydronarciclasine (**6**) from the chiral building block (+)-**7** was 3.2 % in 21 steps.



Scheme 3. *Reagents and conditions*: (i) TBAF, THF, rt, 5.5 h, 97%; (ii) 2-naphthoyl chloride (1.5 equiv.), pyridine (15 equiv.), DMAP (0.2 equiv.), rt, 1.5 h, 97%; (iii) Tf_2O (6 equiv.), DMAP (6 equiv.), CH_2Cl_2, 0 °C, 4 h, 84%; (iv) OsO_4 (0.5 equiv.), NMO (1.5 equiv.), THF-H_2O (10 : 1), 10 h, 92%; (v) $SOCl_2$ (1.4 equiv.), pyridine, –30 °C to –20 °C, 1.5 h; (vi) $RuCl_3 \cdot 3H_2O$ (0.2 equiv.), $NaIO_4$ (4 equiv.), CCl_4-MeCN (1 : 1), rt, 1.5 h, 52% (2 steps); (vii) pyridine, reflux, 1.5 h then 2N H_2SO_4-$CHCl_3$ (1 : 4), 70 °C, 12 h, 64%; (viii) NaOMe (10 equiv.), MeOH, rt, 2 h, 84%.

In conclusion, we have demonstrated an alternative utilization of the cyclohexanoid chiral building block [(+)-**7**] in the total synthesis of (+)-7-deoxy-*trans*-dihydronarciclasine.

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† Dedicated to the late Dr. Kenji Koga, Emeritus Professor of Tokyo University.

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