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Total Synthesis of (+)-*trans*-Dihydronarciclasine by a Catalytic Enantioselective Regiodivergent Nitroso Diels–Alder Reaction

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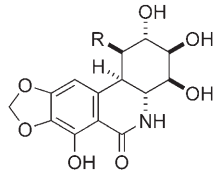
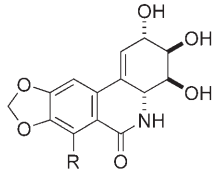
Isocarbostryls are hydroxylated phenanthridones that belong to an interesting class of biologically active natural products of the *Amaryllidaceae* group.[1] *trans*-Dihydronarciclasine (**1**), pancratistatin (**2**), lycoricidine (**3**), and narciclasine (**4**) are some members of this family. These compounds



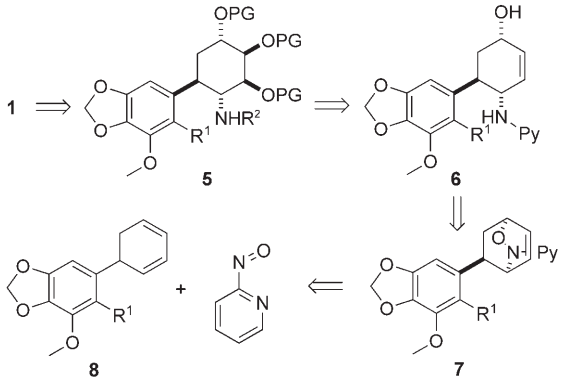
1 (R = H, (+)-*trans*-dihydronarciclasine)
2 (R = OH, pancratistatin)



3 (R = H, lycoricidine)
4 (R = OH, narciclasine)

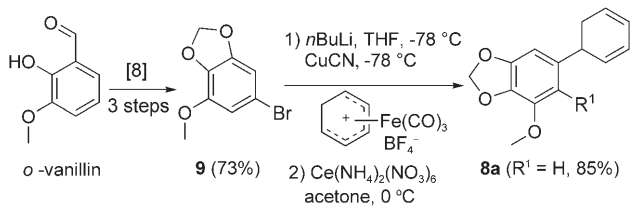
show potent antitumor and antiviral activity.[1] Owing to their biological activity and their stereochemical complexity, the isocarbostryls and their derivatives have become interesting and challenging targets for natural product synthesis.[2] *trans*-Dihydronarciclasine (**1**) has been shown to have a far higher activity against selected human cancer cell lines than the intensively investigated pancratistatin (**2**).[3] Herein we report the first total synthesis of enantiomerically pure (+)-*trans*-dihydronarciclasine (**1**).[4–6]

The retrosynthetic analysis is presented in Scheme 1. As a key step we planned to use our recently developed enantioselective nitroso Diels–Alder reaction for the transformation of racemic dienes **8** to the adducts **7**.[7] Reductive N–O bond cleavage should provide **6**. Subsequent diastereoselective dihydroxylation, O-protection, N-carbamoylation, and pyridyl group cleavage would lead to compounds **5** in which all the stereogenic centers are installed. Ring closure can either occur by a Bischler–Napieralski reaction (R^1 = H, R^2 = CO_2Me)[6] or by lactamization (R^1 = COX, R^2 = H). Removal of the protecting groups should finally afford **1**.



Scheme 1. Retrosynthesis of (+)-*trans*-dihydronarciclasine **1** (PG = protecting group).

Bromide **9** was readily prepared on a large scale starting from *o*-vanillin (Scheme 2).[8] Br–Li exchange and transmetalation to copper followed by reaction with a Fe-complexed cyclohexadienyl cation and subsequent oxidative decomplexation provided diene **8a** in 85% overall yield.[9] The syntheses of dienes **8b–e** are described in the Supporting Information.



Scheme 2. Synthesis of racemic diene **8a**.

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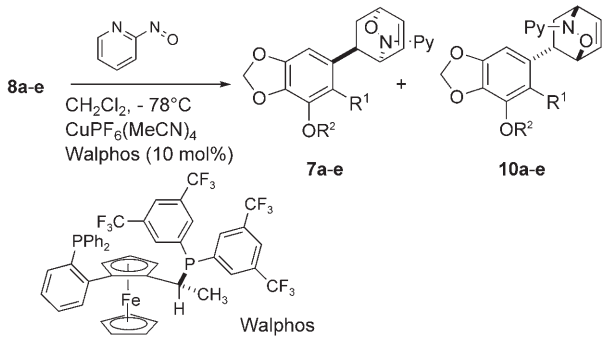
The enantioselective regiodivergent Diels–Alder reaction was studied with dienes **8a–e** and 2-nitrosopyridine under the previously reported conditions to afford **7a–e** and **10a–e**, respectively (Scheme 3).[7,10] Pleasingly, reaction of diene



Scheme 3. Catalytic regiodivergent nitroso Diels–Alder reaction.

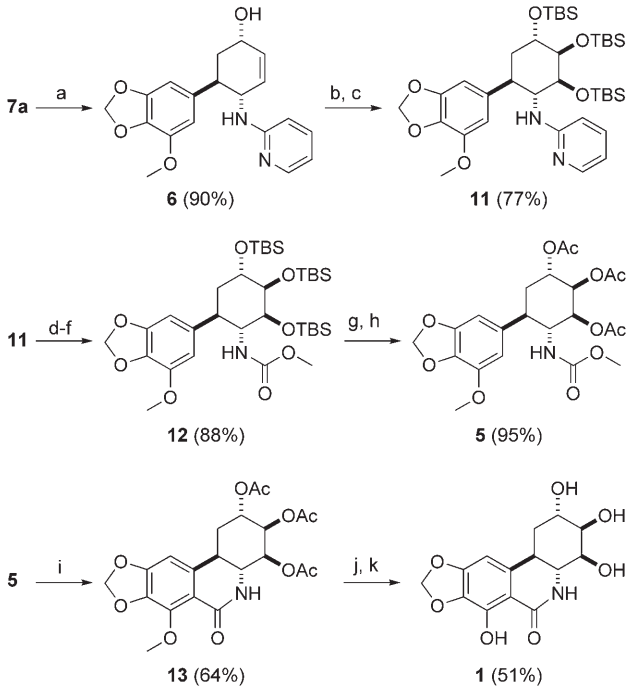
8a afforded the desired regioisomer **7a** in 48% yield with excellent enantioselectivity (>99% *ee*, Table 1, entry 1). The relative configuration was assigned by NMR spectroscopy. It turned out that lower selectivities for the required isomer were obtained for dienes **8b–e** ($R^1 \neq H$, Table 1, entries 2–5). Therefore, the synthesis was continued with **7a**, and the lactamization approach for the final ring closure (see Scheme 1) was abandoned.

Table 1. Enantioselective regiodivergent nitroso Diels–Alder reaction.

Entry	R^1	R^2	Yield [%][a] (*ee*, **7a–e**)[b]	Yield [%][a] (*ee*, **10a–e**)[b]
1	H	Me	48 (>99%, **7a**)	51 (92%, **10a**)
2	CO_2Me	Me	53 (86%, **7b**)	38 (97%, **10b**)
3	CH_2OH	Me	55 (92%, **7c**)	45 (95%, **10c**)
4	CH_2OTBS	Me	53 (70%, **7d**)	33 (98%, **10d**)
5	$CONMe_2$	TBS	54 (73%, **7e**)	32 (95%, **10e**)

[a] Yield of isolated product. [b] Determined by HPLC.

Reductive N–O bond cleavage was achieved by treatment of **7a** with $[Mo(CO)_6]$ and $NaBH_4$ in aqueous MeOH to give **6** (90%; Scheme 4).[11] Diastereoselective dihydroxylation and persilylation provided **11**. Carbamoylation of the amino group occurred smoothly using the corresponding Mg amide (97%). The pyridyl group was cleaved by quarternizing the pyridyl moiety with methyl triflate and consequent base hydrolysis of the pyridinium salt to give **12** (one pot, 91%).[12] Subsequent desilylation and O-acetylation afforded triacetate derivative **5** (95%). A Bischler–Napieralski reaction according to a literature procedure[6a] occurred with good regioselectivity to afford the protected *trans*-dihydronarciclasine **13** (64%).[13] Removal of the protecting groups finally provided enantiomerically pure (+)-*trans*-dihydronarciclasine **1** ($[\alpha]^{25}_D = +4.1\ deg\,cm^3\,g^{-1}\,dm^{-1}$, $c = 4.5\ mg\,cm^{-3}$, THF; $[\alpha]^{25}_D = +4.7\ deg\,cm^3\,g^{-1}\,dm^{-1}$, $c = 5.4\ mg\,cm^{-3}$, THF[5]).



Scheme 4. Completion of the total synthesis. a) $[Mo(CO)_6]$, $NaBH_4$, $MeOH/H_2O$; b) $K_2OsO_2(OH)_4$, NMO, acetone/H_2O; c) TBSCl, imidazole, DMF, 75°C; d) MeMgCl, MeOCOCl, THF; e) MeOTf, CH_2Cl_2, 0°C; f) NaOH, $MeOH/H_2O$, 50°C; g) TBAF, THF; h) Ac_2O, pyridine; i) Tf_2O, DMAP, CH_2Cl_2; j) BBr_3, CH_2Cl_2; k) NaOMe, MeOH. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TBAF = tetrabutylammonium fluoride, DMAP = 4-dimethylaminopyridine.

In conclusion, we have presented an efficient 17-step synthesis to enantiomerically pure **1** in 5.6% overall yield starting from commercially available *o*-vanillin. The key step was a Cu-catalyzed highly stereoselective divergent nitroso Diels–Alder reaction on racemic diene **8a**. The biologically active natural product is available in larger quantities by this novel route (up to 50 mg were readily prepared).

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Keywords: biologically active compounds · copper · cycloaddition · natural products · stereoselective synthesis

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[13] The other regioisomer was formed in 18% yield.

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