# Antineoplastic Agents. 454. Synthesis of the Strong Cancer Cell Growth Inhibitors *trans*-Dihydronarciclasine and 7-Deoxy-*trans*-dihydronarciclasine[1a]

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To further pursue the antineoplastic leads offered by our isolation of *trans*-dihydronarciclasine (**1a**) and 7-deoxy-*trans*-dihydronarciclasine (**1c**) from two medicinal plant species of the Amaryllidaceae family, a practical palladium-catalyzed hydrogenation procedure was developed for the synthesis of these isocarbostyrils from narciclasine (**2a**) and 7-deoxynarciclasine (**2c**).

From a 1982 collection (bulbs) of the Chinese medicinal plant *Zephyranthes candida* (Amaryllidaceae)[1b] we isolated the strong ($ED_{50}$ 0.0032 $\mu$g/mL) P388 lymphocytic leukemia cell growth inhibitor *trans*-dihydronarciclasine (**1a**). The structure was established by detailed spectroscopic analyses of its peracetate derivative (**1b**)[1b] and confirmed by comparison with the minor product from catalytic hydrogenation of narciclasine (**2a**).[2] Hydrogenation afforded as the major product the expected *cis*-dihydronarciclasine (**3a**) accompanied by the *trans* isomer (**1a**) and iso-narciclasine (**4a**). Subsequently, *trans*-dihydronarciclasine (**1a**) was found to exhibit strong cancer cell growth inhibition (mean panel $GI_{50}$ 12.6 nM) against the U.S. National Cancer Institute (NCI) panel of cancer cell lines,[3a,b] whereas its *cis* isomer (**3a**)[3c] was only very weakly active (mean panel $GI_{50}$ 3800 nM). Importantly, the *trans* isomer **1a** gave an active Compare correlation coefficient of 0.92 with respect to (+)-pancratistatin (**5**).[3a] The *trans* isomer **1a** also showed strong activity against a range of RNA viruses, while the synthetic *cis* isomer (**3a**) was completely inactive.[4]

Because of the close structural and biological relationship of *trans*-dihydronarciclasine (**1a**) to (+)-pancratistatin (**5**), already in preclinical development, it became necessary to increase the availability of *trans* isomer **1a** and the closely related 7-deoxy-*trans*-dihydronarciclasine (**1c**) by synthesis. The latter was isolated from *Hymenocallis* sp. (P388 $ED_{50}$ 0.02 $\mu$g/mL) and gave an active Compare correlation coefficient of 0.89 with respect to (+)-pancratistatin (**5**).[3] The structural and biological relationships of **1a** and **1c** to (+)-pancratistatin (**5**) are of special importance owing to its well-known[5] in vitro and in vivo anticancer activity augmented by the rapidly increasing knowledge of the very promising activation of the mitochondrial route to cancer cell apoptosis.[6a] Importantly, pancratistatin has been shown to induce apoptosis routinely in various cancer cell lines at submicromolar concentrations while being nontoxic to normal human fibroblasts and endothelial cells at the same drug concentrations.[6b,c] As anticipated, narciclasine (**2a**) has recently been found to induce the mitochondrial and/or caspase-8/caspase-10 death receptor pathway in human MCF-7 breast and PC-3 prostate cancer cell lines.[5] Presumably, the strong cancer cell growth inhibitors **1a** and **1c** will also display related mechanisms of action, selectively targeting cancer cells.

Synthetic approaches to the multifunctional carbostyril structures of (+)-pancratistatin (**5**) and the narciclasines have presented significant challenges. Over the past 30 years, nine total syntheses of natural **5** have been reported, proceeding from those of Danishefsky[7a] in 1989 through Hudlicky[7b] and Trost[7c] in 1995, followed by Haseltine (1997),[7d] Magnus (1998),[7e] Rigby (2000),[7f] Pettit (2001),[7g] Kim (2002),[7h] and Li (2006),[7i] where the earliest was for (±)-**5**. Details of these syntheses have been examined in an important review by Kornienko,[7j] which also leads to narciclasine chemistry and syntheses.[7f] A substantial number of useful SAR studies have been completed based on **2a** and **5**. Those of Hudlicky[8a] and McNulty[8b] are two of the most recent and supplemented by a detailed review by Kornienko.[8c]

The need to begin more detailed preclinical development of **1a** and **1c** led to our syntheses of the potentially useful phosphate prodrugs *trans*-dihydronarcistatin (**6a**) and 7-deoxy-*trans*-dihydronarcistatin (**6b**).[9] In concert with the increased requirements for both precursors, it became important to uncover a selective hydrogenation reaction for conversion of the obvious precursors narciclasine (**2a**) and 7-deoxynarciclasine (**2c**) readily available from certain *Narcissus* (Amaryllidaceae) species[3a,9] to the required dihydro derivatives. That approach appeared to be of more immediate practicality than multistep total syntheses.[8c,10]

## Results and Discussion

Functional groups such as hydroxyl, ester, and amide often direct the stereochemistry of hydrogenation.[11a,b] Homogenous hydrogenation of allylic alcohols usually occurs with high stereoselectivity. Catalysts used in such hydroxy-directed hydrogenation often include Wilkinson's catalyst (**7**) [$RhCl(PPh_3)_3$] and Crabtree's catalyst (**8**) [$Ir(COD)(Pcy_3)(py)$]PF.[11c] Consequently, narciclasine, protected as its acetonide (**2d**),[2] was treated with Crabtree's catalyst (**8**) in dichloromethane, but failed to yield any product of hydrogenation. The reaction was also attempted with Wilkinson's catalyst (**7**) in toluene, and again narciclasine acetonide (**2d**) resisted hydrogenation. With a related trisubstituted styrene that proved unreactive toward hydrogenation with Wilkinson's catalyst even under forcing conditions, it was successfully hydrogenated when first converted to its alkoxide, but that led exclusively to the *cis* isomer.[12] This approach was again unsuccessful when using narciclasine acetonide (**2d**). Since a hydrogenation reaction is believed to be associated with the olefin's ability to donate unshared electron pairs to unfilled surface orbitals of the catalyst metal,[13] the double bond in narciclasine was considered too hindered to allow this type of hydroxyl group-directed reduction. Attention was therefore directed to ionic hydrogenation.

The ionic hydrogenation ($CF_3CO_2H$, $Et_3SiH$) of a $\Delta^{8(9)}$-D-homosteroid is known to proceed stereospecifically to give a D-homosteroid with the *trans-antitrans* configuration.[14] Such sterically hindered olefins have been hydrogenated at low temperature in dichloromethane with trifluoroacetic acid as a proton donor and triethylsilane as a hydride donor.[15] Interestingly, in our experiments narciclasine (**2a**) and derivatives **2b** and **2d** resisted hydrogenation with triethylsilane−trifluoroacetic acid in dichloromethane at both −75 and 25 °C. Consequently, it seemed best to study the

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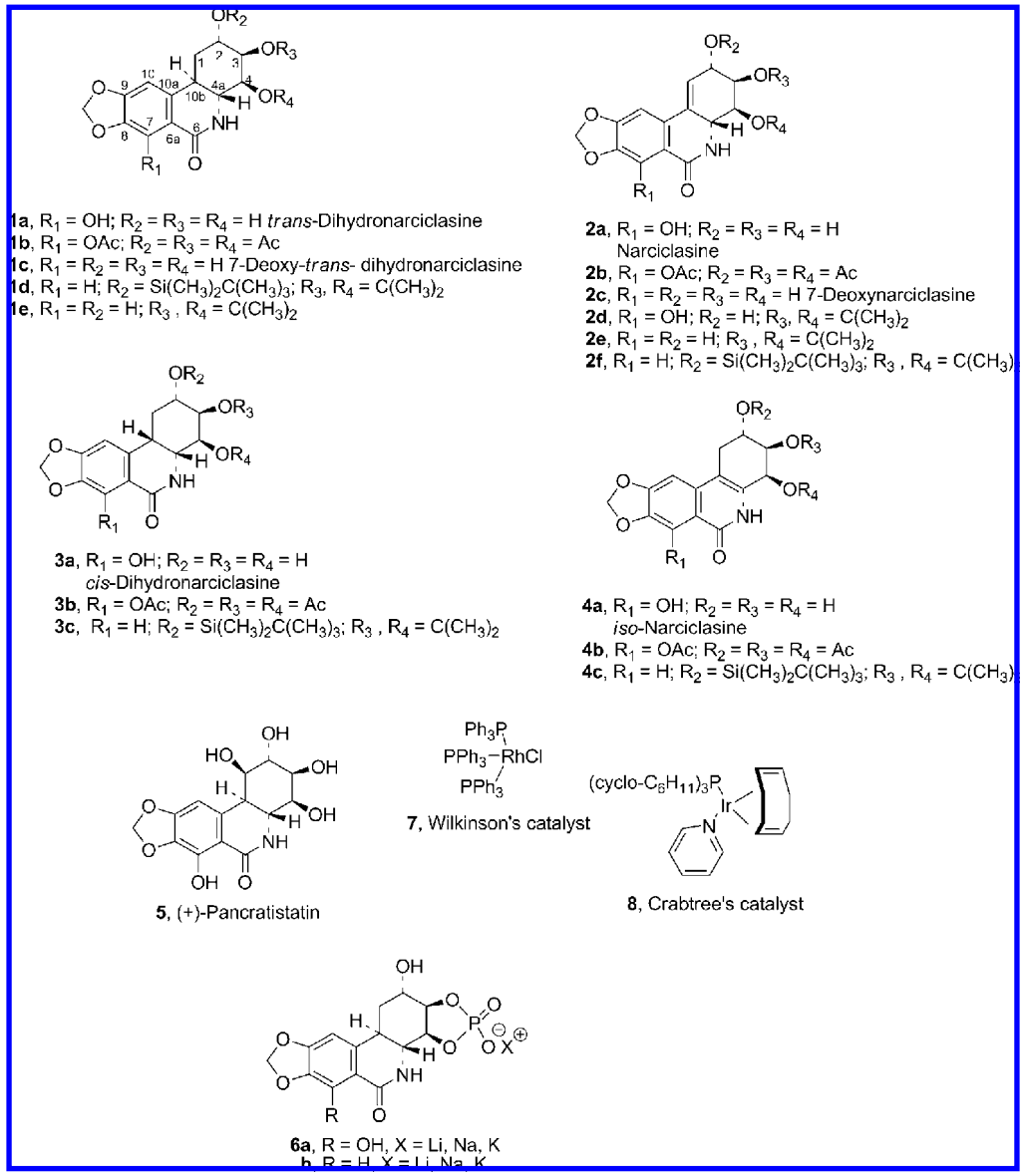
**Chart 1**




palladium-catalyzed hydrogenation of narciclasine (**2a**) in detail with the prospect of uncovering a technique that would favor the *trans* isomer **1a**.

While we and others[2] have hydrogenated narciclasine (**2a**) using Adam's catalyst ($PtO_2$) in ethanol, 28% of the *trans* isomer **1a** was usually obtained, along with 58% of the *cis* isomer **3a** and 13% of iso-narciclasine (**4a**). Since a related styrene-type olefin has also been shown to afford different ratios of *cis:trans* isomers by simply using various solvents for the reduction,[16] the hydrogenation of narciclasine peracetate (**2b**)[17−19] was conducted in the presence of 5% Pd/C (20 mol %) at 1 atm using a variety of solvents: ethyl acetate, ethanol, acetic acid, hexane, tetrahydrofuran, pyridine, and *N*,*N*-dimethylformamide. The results are shown in Table I. The *trans*:*cis*:*iso* ratios were determined by $^1$H NMR and were based on a 100% conversion of starting material to product. The best ratio observed (51:47:2, respectively) was with acetic acid as solvent on a small scale (approximately 0.020 g of narciclasine peracetate). Scaleup with this solvent gave a wide variation in results. When 5 g of narciclasine was hydrogenated in acetic acid in the presence of 5% Pd/C (8 mol %) for 20 h, only starting material was recovered. Repeating the hydrogenation with narciclasine peracetate employing 1 g and using 10% Pd/C (25.8 mol %) the *trans* and *cis* products were isolated in 30% and 62% yield, respectively, following chromatography on silica gel. The eluent solvent system

**Table I.** Effect of Solvent on Hydrogenation of Narciclasine Acetate (**2b**) with 5% Pd/C (20 mol %) at 1 atm, 25 °C for 2 h

| | | products | | | |
|---|---|---|---|---|---|
| solvent | wt, g (**2b**) | % **2b**[a] | % *trans*[a] (**1b**) | % *cis*[a] (**3b**) | % *iso*[a] (**4b**) |
| hexane | 0.026 | 100 | | | |
| pyridine | 0.022 | 100 | | | |
| dimethylformamide | 0.019 | | 38 | 42 | 20 |
| tetrahydrofuran | 0.025 | 70 | 15 | 15 | |
| ethyl acetate | 0.025 | | 47 | 40 | 13 |
| ethanol | 0.219 | | 36 | 54 | 10 |
| ethanol−$CH_2Cl_2$ (1:1) | 0.025 | 22 | 25 | 53 | |
| ethanol−$CH_2Cl_2$ (1:1)[b] | 0.200 | | 65 | 25 | |
| acetic acid | 0.024 | | 51[c] | 47 | 2 |

[a] Values determined by $^1$H NMR. [b] Isolated yield from reaction with 10% Pd/C (10% mol). [c] Increased to 57% with 55 mol % of Pd/C, but dropped to 49% with 100 mol % of Pd/C.

1:1 $CH_2Cl_2$−$CH_3CH_2OH$ gave good results (65% *trans* following chromatography) when narciclasine tetraacetate (200 mg) was hydrogenated in the presence of 10% Pd/C (10 mol %). The peracetylated isomers **1b**, **3b**, and **4b** were separated by column chromatography on silica gel. The structure of the synthetic *trans*

isomer **1b** was established by detailed spectral data comparison with an authentic sample.[1b,3]

Once a method for the hydrogenation of **2b** to **1b** was developed, a similar procedure was employed for the conversion of 7-deoxy-narciclasine (**2c**) to 7-deoxy-*trans*-dihydronarciclasine (**1c**). The *cis* diol was first protected as the acetonide **2e** in good yield (92%). The phenol group was next protected as its silyl ether (**2f**) to avoid the potential problems that had already been encountered when proceeding with hydrogenation of narciclasine acetonide (**2d**). Hydrogenation of the olefin was then attempted using the conditions most successful in the reduction of peracetate **2b** to the *trans*-dihydroperacetate **1b**. Hydrogenation of **2f** (0.05 g) with 10% Pd/C (10 mol %) at 1 atm in 1:1 $CH_2Cl_2-CH_3CH_2OH$ gave a reasonably separable mixture of the *trans*:*cis*:*iso* product in 56:26:10% yields, respectively. However, yields suffered upon scaleup, and for example the *trans* was reduced to 27% when a 2 g scale was used. The natural *trans* isomer **1d** was obtained by cleavage of the acetonide group using formic acid (60%) followed by silyl ether deprotection with TBAF to yield **1c**, which was identical with an authentic sample of 7-deoxy-*trans*-dihydronarciclasine.[3a]

The scaleup preparation of *trans*-dihydronarciclasines **1a** and **1c** utilizing the preceding hydrogenation improvements increased the availability of both cancer cell growth inhibitors for conversion to the respective phosphate prodrugs[9] and further preclinical development.

## Experimental Section

**General Experimental Procedures.** Narciclasine (**2a**) was isolated from the bulbs of *Narcissus imcomparabilus* as previously described[20] and 7-deoxynarciclasine (**2c**) from the bulbs of *Hymenocallis littoralis*.[3a] All solvents were redistilled; 5% and 10% Pd/C as well as 4-dimethylaminopyridine were purchased from Sigma-Aldrich Co., while acetic anhydride, pyridine, *tert*-butyldimethylsilyl chloride, and imidazole were purchased from Lancaster Chemical Company. Reaction progress was ascertained by thin-layer chromatography using Analtech silica gel GHLF Uniplates visualized under long- and short-wave UV irradiation and developed using an ethanolic solution of phosphomolybdic acid reagent (Sigma-Aldrich Co.). Column chromatography was performed with silica gel 60 (230−400 mesh) from E. Merck. All reaction products were colorless solids unless otherwise noted. All solvent extracts of aqueous phases were dried over anhydrous magnesium sulfate.

All melting points were determined with an Electrothermal digital melting point apparatus model IA9200 and are uncorrected. Optical rotation values were recorded using a Perkin-Elmer 241 polarimeter. High- and low-resolution FAB spectra were obtained from a Kratos MS-50 mass spectrometer (Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE) using a glycerol−triglycerol matrix with a JEOL LCMate magnetic sector instrument either in the FAB mode, with a glycol matrix, or by APCI with a polyethylene glycol reference. The $^1H$ and $^{13}C$ spectra were recorded with Varian Gemini 300 or 400 MHz instruments.

**2,3,4,7-*O*-Tetraacetoxynarciclasine (2b).** To a stirred solution of narciclasine (**2a**, 1.00 g, 3.25 mmol) in pyridine (3 mL under nitrogen) was added acetic anhydride (6 mL). After stirring for 16 h at rt, ice (50 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined extract was dried, filtered, and evaporated in vacuo to afford the title compound (**2b**) as a light brown powder (1.4 g, 90% yield; *Caution: this compound can cause contact dermatitis*): $[\alpha]^{24}_D$ +224 (*c* 1.03, $CHCl_3$); mp 230−231 °C; {lit.[18] mp 220−231 °C, $[\alpha]^{24}_D$ +229 (*c* 0.33, $CHCl_3$)}; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 6.94 (1H, s, H-10), 6.51 (1H, bs, 5-NH), 6.16 (1H, m, H-1), 6.12 and 6.11 (each 1H, d, $J$ = 1 Hz, $OCH_2O$), 5.44 (1H, m, H-3), 5.35 (1H, m, H-2), 5.23 (1H, dd, $J$ = 2 Hz, 8 Hz, H-4), 4.60 (1H, d, $J$ = 8 Hz, H-4a), 2.34 (3H, s, OAc), 2.14 (6H, s, 2 OAc), 2.10 (3H, s, OAc); $^{13}C$ NMR ($CDCl_3$, 75 MHz) 170.3 (C═O), 169.5 (C═O), 169.3 (C═O), 168.9 (C═O), 162.3 (C═O), 152.4 (C), 141.5 (C), 131.4 (C), 133.7 (C), 131.6 (C), 118.1 (CH), 114.7 (C), 103.1 ($CH_2$), 101.9 (CH), 71.3 (CH), 71.3 (CH), 68.3 (CH), 50.2 (CH), 20.93 ($CH_3$), 20.92 ($CH_3$), 20.88 ($CH_3$), 20.78 ($CH_3$); HRMS (FAB) *m*/*z* 498.1003 [(M + $Na^+$)] (calcd for $C_{22}H_{21}NO_{11}Na$, 498.1003 [(M + $Na^+$)]).

**2,3,4,7-Tetraacetoxy-*trans*-dihydronarciclasine (1b). Method 1.** To a solution of narciclasine tetraacetate (**2b**) (0.97 g, 2.04 mmol) in glacial acetic acid (120 mL) was added 5% Pd/C catalyst (0.56 g, 26 mol %). The mixture was stirred under an atmosphere of hydrogen at rt for 3 h and the solution filtered through fluted filter paper. The filtrate was dried, again filtered, and evaporated in vacuo. The residue was separated by column chromatography (CC) on silica gel eluting with 99.5:0.5 $CH_2Cl_2-CH_3OH$ to afford the product (**1b**) as a powder (0.290 g, 30%) along with the *cis*-dihydroperacetate (**3b**) as a solid (0.60 g, 62%). Analysis of **1b** by comparison of NMR data found it to be identical with an authentic sample.[1b]

**Method 2.** To a solution of narciclasine tetracetate (**2b**, 0.200 g, 0.42 mmol) in 1:1 $CH_2Cl_2-CH_3CH_2OH$ was added 10% Pd/C catalyst (0.004 g, 0.042 mmol). The mixture was stirred under 1 atm of hydrogen at room temperature for 4 h and filtered through a pad of silica, and the solvent was removed in vacuo. The residue was separated by CC (flash silica; eluant 45:55 hexanes−EtOAc) to afford the *trans*-dihydroperacetate (**1b**) as a solid (0.131 g, 65%), along with the *cis*-dihydroperacetate (**3b**) as a solid (0.050 g, 25%).

***trans*-Dihydronarciclasine (1a).** *trans*-Dihydronarciclasine-2,3,4,7-tetraacetate (**1b**, 0.512 g, 1.07 mmol) was dissolved in $CH_3OH-H_2O$ (9:1, 20 mL) with $CH_2Cl_2$ (12 mL) added to increase solubility. Potassium carbonate (9 mg, 0.06 mmol) was added and the mixture stirred at rt for 3 days when TLC (4:96 $CH_2Cl_2-CH_3OH$) showed complete deprotection.

The reaction solution was concentrated under reduced pressure and the residue separated by CC on silica gel (96:4 $CH_2Cl_2-CH_3OH$) to give **1a** as an amorphous solid (0.134 g, 40%): mp 260 °C (dec), 285 °C (melts) {lit.[2] mp 290−291 °C} $[\alpha]^{22}_D$ +2.8 (*c* 0.97, THF), {lit.[2] $[\alpha]^{25}_D$ +4.7 (*c* 0.27, THF)}; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 13.0 (s, 1H), 7.56 (s, 1H), 6.46 (s, 1H), 6.04 and 6.01 (each 1H, d, $J$ = 1.2 Hz, $OCH_2O$), 4.96−4.84 (m, 3H), 3.38 (nm, 1H), 3.70 (nm, 2H), 3.34−3.26 (m, 1H), 2.84 (td, 1H, $J$ = 3.9, 12.3 Hz, H-10b), 2.07 (m, 1H), 1.65−1.57 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) 174.4, 156.8, 150.1, 143.2, 136.6, 111.6, 106.5, 101.2, 76.3, 74.2, 73.2, 59.8, 3.5, 32.8; HRMS ($APCI^+$) *m*/*z* 310.0925 [M + H]$^+$ (calcd for $C_{14}H_{16}NO_7$, 310.0927 [M + H]$^+$).

**3,4-Isopropylidene-7-deoxynarciclasine (2e).** 7-Deoxynarciclasine (**2c**, 0.205 g, 0.704 mmol)[3a,9] and TsOH (0.133 g, 0.704 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL), and 2′,2′-dimethoxypropane (0.864 mL, 7.04 mmol) was added. The resulting solution was stirred for 16 h, poured into water (50 mL), and extracted with ethyl acetate (4 × 30 mL). The combined organic extract was dried, filtered, and concentrated in vacuo to yield a pale yellow solid, which was separated by CC (flash silica; eluant 3:7 hexanes−EtOAc) to afford product **2e** as a solid (0.215 g, 92%): recrystallized from methanol as needles; mp 251−253 °C; $[\alpha]^{25}_D$ −32.6 (*c* 0.61, $CH_3OH$); {lit.[21] $[\alpha]^{25}_D$ −34.3 (*c* 0.76, $CH_3OH$)}; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.59 (1H, s, H-7), 7.02 (1H, s, H-10), 6.28 (2H, bs, H-1, N*H*), 6.04 (2H, s, $-OCH_2O-$), 4.35−4.45 (1H, m, H-2), 4.10−4.20 (3H, m, H-3,4,4a), 3.04 (1H, d, $J$ = 4.5 Hz, $-OH$), 1.53 (3H, s, $-CH_3$), 1.39 (3H, s, $-CH_3$); $^{13}C$ NMR ($CDCl_3$, 75 MHz) 162.4, 151.8, 148.6, 128.3, 127.5, 124.0, 120.8, 111.4, 107.6, 101.9, 101.4, 79.5, 78.9, 72.8, 55.9, 27.0, 24.7; HRMS ($APCI^+$) *m*/*z* 332.1147 (calcd for $C_{17}H_{18}NO_6$, 332.1134).

**2-[*tert*-Butyldimethylsilyl]oxy-3,4-isopropylidene-7-deoxynarciclasine (2f).** To 3,4-isopropylidene-7-deoxynarciclasine (**2e**, 0.024 g, 0.0725 mmol) in *N*,*N*-dimethylformamide (3 mL) were added *tert*-butyldimethylsilyl chloride (TBDMSCl, 0.016 g, 0.109 mmol) and imidazole (0.007 g, 0.109 mmol). The resulting solution was stirred for 5 h, and the dimethylformamide was removed in vacuo to afford a pale yellow oil. The residue was separated by CC (flash silica; eluant 3:2 hexanes−EtOAc) to provide the silyl ether as a solid (0.028 g, 87%): mp 269 °C; $[\alpha]^{27}_D$ +20.2 (*c* 0.45, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.60 (H, s, H-7), 7.04 (1H, s, H-10), 6.15−6.25 (2H, m, H-1, N*H*), 6.03 (2H, s, $OCH_2O-$), 4.30−4.35 (1H, m, H-2), 4.00−4.15 (3H, m, H-3, 4, 4a), 1.50 (3H, s, $-CH_3$), 1.36 (3H, s, $-CH_3$), 0.96 (9H, s, $-C(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); $^{13}C$ NMR ($CDCl_3$, 75 MHz) 162.3, 151.7, 148.4, 128.4, 126.8, 126.1, 120.8, 110.8, 107.6, 101.8, 101.4, 79.4, 79.1, 73.4, 55.6, 27.1, 25.8, 24.8, 18.1, −4.5, −5.0; HRMS ($APCI^+$) *m*/*z* 446.1997 (calcd for $C_{23}H_{32}NO_6Si$, 446.1999): *anal*. C, 61.96%, H, 7.32%, N, 3.12%, calcd for $C_{23}H_{31}NO_6Si$, C, 62.00%; H, 7.01%; N, 3.14%.

**7-Deoxy-2-[*tert*-butyldimethylsilyl]oxy-3,4-isopropylidene-*trans*-dihydronarciclasine (1d).** To a solution of 2-(*tert*-butyldimethylsilyl]-oxy-3,4-isopropylidene-7-deoxynarciclasine (**2f**, 0.050 g, 0.112 mmol) in 1:1 $CH_2Cl_2-CH_3CH_2OH$ (8 mL) was added 10% Pd/C (1.2 mg,

0.0112 mmol). The resulting mixture was stirred under 1 atm of hydrogen for 4 h and then passed through a short column of silica gel, eluting with EtOAc. Removal of solvent in vacuo afforded a solid, which was separated by CC (gravity, silica gel; eluant 7:3 hexanes−EtOAc) to yield a solid (0.028 g, 56%): mp 181.5−182.5 °C; $[\alpha]_D$ −23.8 (*c* 0.52, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.59 (1H, s, H-7), 6.76 (1H, s, H-10), 6.02 (2H, s, −OC*H*$_2$O−), 6.01 (1H, s, N*H*), 4.41 (1H, d, $J$ = 2 Hz, H-2), 4.12−4.20 (1H, m, H-4), 4.04−4.12 (1H, m, H-4), 3.42 (1H, dd, $J$ = 13 Hz, 9, H-4a), 3.11 (1H, dt, $J$ = 13 Hz, 2, H-10b), 2.20−2.25 (1H, m, H-1), 1.70−1.84 (1H, m, H-2), 1.45 (3H, s, −C*H*$_3$), 1.40 (3H, s, −C*H*$_3$), 0.90 (9H, s, −C(C*H*$_3$)$_3$), 0.14 (6H, s, −Si(C*H*$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 75 MHz) 165.3, 151.2, 146.6, 136.4, 123.1, 109.8, 108.4, 104.2, 101.6, 77.6, 77.4, 67.0, 57.8, 31.9, 31.6, 28.2, 26.4, 25.6, 17.8, −4.9, −5.0; HRMS (APCI$^+$) *m*/*z* 448.2169 (calcd for $C_{23}H_{34}NO_6Si$, 448.2155); *anal*. C 61.74%, H 7.78%, N 3.11%, calcd for $C_{23}H_{33}NO_6Si$, C 61.72%, H 7.43%, N 3.13%.

Continued elution of the column led to 7-deoxy-2-[*tert*-butyldimethylsilyl]oxy-3,4-isopropylidene-*cis*-dihydronarciclasine (**3c**) as a solid (0.013 g, 26%): mp 237.5−238.5 °C; $[\alpha]_D$ +82.2 (*c* 0.51, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) 7.49 (1H, s, H-7), 6.68 (1H, s, H-10), 6.08 (1H, s, N*H*), 6.02 and 6.00 (each 1H, d, $J$ = 1.2 Hz, $OCH_2O$), 4.10−4.20 (2H, m, H-4, 4a), 3.94−4.02 (1H, m, H-3), 3.79 (1H, ddd, $J$ = 12 Hz, 7, 5, H-2), 2.94−3.08 (1H, m, H-10b), 1.84 (1H, q, $J$ = 13 Hz, H-1), 1.55−1.65 (1H, m, H-1), 1.55 (3H, s, −C*H*$_3$), 1.41 (3H, s, −C*H*$_3$), 0.85 (9H, s, −C(C*H*$_3$)$_3$), 0.11 (3H, s, −SiC*H*$_3$), 0.07 (3H, s, −SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) 165.9, 151.3, 147.2, 137.8, 121.7, 108.6, 107.9, 107.0, 101.6, 79.9, 77.1, 72.6, 51.8, 35.8, 35.4, 28.4, 26.4, 25.7, 17.9, −4.4, −4.8; HRMS (APCI$^+$) *m*/*z* 448.2168 (calcd for $C_{23}H_{34}NO_6Si$ 448.2155); *anal*. C 61.72%, H 7.81%, N 3.11%, calcd for $C_{23}H_{33}NO_6Si$, C 61.72%, H 7.43%, N 3.13%.

The third minor component isolated was 7-deoxy-2-[*tert*-butyldimethylsilyl]oxy-3,4-isopropylidene-iso-dihydronarciclasine (**4c**) as a solid (0.005 g, 10%): mp 246.5−248.0 °C; $[\alpha]_D$ −47.3 (*c* 0.92, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.87 (1H, bs, N*H*), 7.81 (1H, s, H-7), 7.00 (1H, s, H-10), 6.09, (2H, s, −OC*H*$_2$O−), 4.92 (1H, d, $J$ = 4.5 Hz, H-4), 4.12−4.18 (2H, m, H-2, 3), 2.86 (1H, dd, $J$ = 16 Hz, 4, H-1), 2.62 (1H, dd, $J$ = 16 Hz, 5, H-1), 1.44 (3H, s, −C*H*$_3$), 1.27 (3H, s, −C*H*$_3$), 0.85 (9H, s, −C(C*H*$_3$)$_3$), 0.12 (3H, s, −SiC*H*$_3$), 0.08 (3H, s, −SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) 162.3, 152.3, 147.5, 134.6, 130.6, 121.6, 110.5, 107.4, 105.9, 101.8, 101.1, 77.4, 72.1, 68.4, 28.9, 27.8, 26.2, 25.7, 17.9, −4.7, −4.8; HRMS (APCI$^+$) *m*/*z* 446.1999 (calcd for $C_{23}H_{32}NO_6Si$ 446.1998); *anal.* C 61.89%, H 7.35%, N 3.09%, calcd for $C_{23}H_{31}NO_6Si$, C 62.00%, H 7.01%, N 3.14%.

**7-Deoxy-*trans*-dihydronarciclasine (1c). 1d** (0.02 g, 0.045 mmol) was dissolved in tetrahydrofuran (2 mL), and formic acid (2 mL, 60%) was added at rt. The reaction was heated to 60 °C for 3 h. TLC (85:15 EtOAc−hexanes) showed complete conversion to a slower moving product. The solution was concentrated to a white residue, which was separated by silica gel flash CC (90:10 $CH_2Cl_2$−$CH_3OH$) to yield a white solid (13.1 mg, 71.4%), mp 230 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) showed the silyl ether was still present, which was confirmed by HRMS (APCI$^+$) *m*/z = 408.1845 (calcd for $C_{20}H_{30}NO_6Si$ 408.1842). Then the silyl ether intermediate, 7-deoxy-2-[*tert*-butyldimethylsilyl]-oxy-*trans*-dihydronarciclasine (0.037 g, 0.09 mmol), was dissolved in THF (5 mL), tetrabutylammonium fluoride (TBAF, 0.01 mL, 0.01 mmol) was added, and the mixture was stirred at rt under argon. After 6 h, TLC (1:9 $CH_3OH$−$CH_2Cl_2$) showed incomplete conversion of starting material to product. Additional TBAF (0.1 mL, 0.1 mmol) was added, the reaction was continued for 24 h, more TBAF (0.1 mL, 0.1 mmol) was added, and stirring continued for 5 days. Ethyl acetate (35 mL) was added, and the organic phase washed with brine (25 mL), dried, filtered, and concentrated in vacuo to a yellow oil. The oil in THF was passed into a column of silica gel and chromatographed using a gradient elution (9:1 $CH_2Cl_2$−$CH_3OH$ to 7:3 $CH_2Cl_2$−$CH_3OH$). The product (**1c**) was isolated as a white solid, 13.4 mg (50%), and was identical by $^1$H NMR with a natural sample of 7-deoxy-*trans*-dihydronarciclasine.[4]

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