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Improved total synthesis of (±)-*trans*-dihydronarciclasine, devised for large-scale preparation

Young-Suk Cho, Cheon-Gyu Cho*

Department of Chemistry, Hanyang University, Seoul 133-791, Republic of Korea

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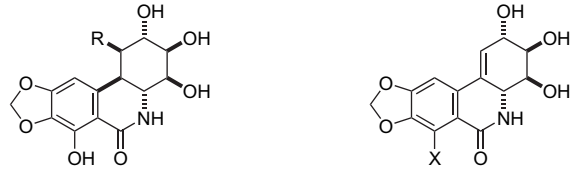
Abstract

New synthetic route to (±)-*trans*-dihydronarciclasine, more suitable for a large-scale preparation, has been devised with the early stage incorporation of ester functionality for direct assembly of the B-ring lactam.

Keywords: Cycloaddition reaction; Amaryllidaceae; *trans*-Dihydronarciclasine; Isocarbostyrils; 3,5-Dibromo-2-pyrone

1. Introduction

Isolated by Pettit and co-workers from the Chinese medicinal plant *Zephyranthes candida* in 1990,[1] *trans*-dihydronarciclasine **1** holds a tricyclic lactam skeleton in common with pancratistatin **2**, lycoricidine **3**, and narciclasine **4** (Fig. 1).[2,7,9a] It has been shown to exhibit highly potent anticancer property, 2–10 fold higher than pancratistatin, the most active member of the lycorine-type *Amaryllidaceae* constituents, against selected human cancer cell lines.[3] In contrast to pancratistatin, *trans*-dihydronarciclasine **1** has attracted little attention despite the structural analogy and highly potent antitumor activities.[4]



1: R = H, *trans*-dihydronarciclasine
2: R = OH, pancratistatin
3: X = H, lycoricidine
4: X = OH, narciclasine

Figure 1. Selected examples of naturally occurring isocarbostyrils.

As a part of our ongoing research program exploring the synthetic utility of 3,5-dibromo-2-pyrone **5** as an ambident enophile,[5] we have recently reported the first total synthesis of (±)-*trans*-dihydronarciclasine, via the highly *endo*-selective Diels–Alder cycloaddition reaction of **5** with styrene dienophile **6** (Scheme 1).[5b] The debromination reactions followed by methanolysis of the resultant cycloadduct **7** afforded the key intermediate **8** containing all the essential functional groups with correct relative stereochemistry present in *trans*-dihydronarciclasine. Subsequent transformations including dihydroxylation, Curtius rearrangement, and Bischler–Napieralski reaction completed the first total synthesis of (±)-*trans*-dihydronarciclasine.

However, the overall efficiency of our synthesis is hampered by the formation of undesired regio-isomer at the B-ring assembly step. Under the conditions shown in Scheme 2, the Bischler–Napieralski reaction of carbamate **11** provided an inseparable mixture of **12a** and **12b** (^{1}H NMR ratio, 3:1) in the combined yield of 81%.[6] The actual isolation of **12a** was made after the BBr_3 mediated selective removal of phenolic methyl group (**12b** remained intact under the conditions). In conjunction with the collaborative investigation searching for anti-leukemic agents with better therapeutic profile, we needed to devise a new route more suitable for a gram-scale synthesis.

* Corresponding author. Tel.: +82 2 2220 0936; fax: +82 2 2299 0762.
E-mail address: ccho@hanyang.ac.kr (C.-G. Cho).

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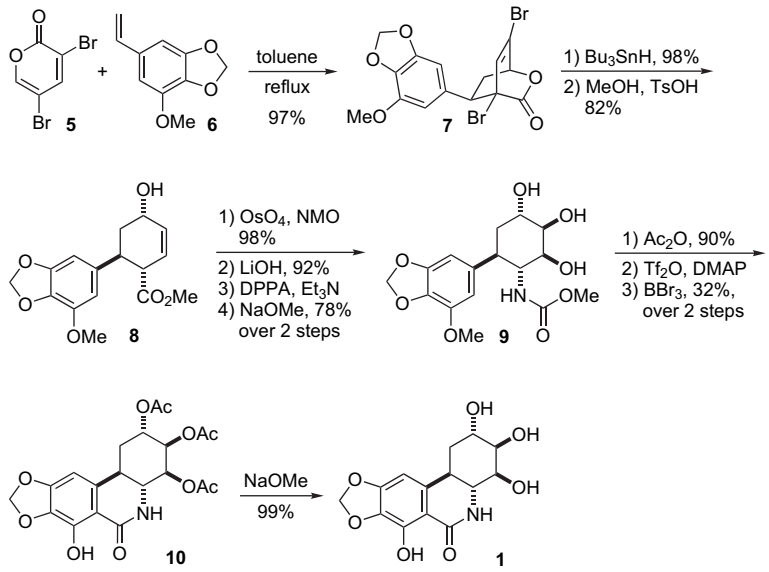
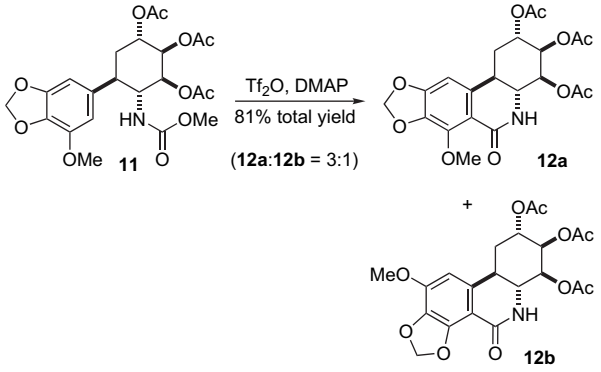


Scheme 1. First-generation synthesis of (±)-*trans*-dihydronarciclasine.



Scheme 2. The Bischler–Napieralski reaction for the B-ring lactam assembly in the first-generation synthesis.

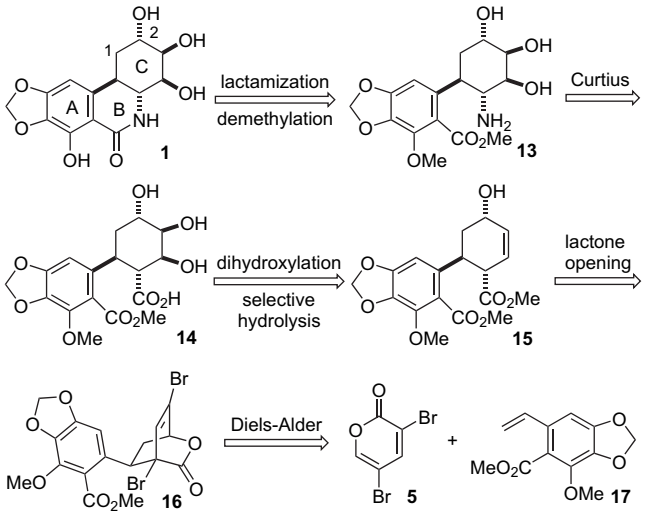
2. Results and discussion

In this context, we have envisioned that the prior installation of an ester group at the aryl subunit (as in **11**) would permit straightforward assembly of B-ring lactam,[7] avoiding the need for the problematic Bischler–Napieralski reaction (Scheme 3).

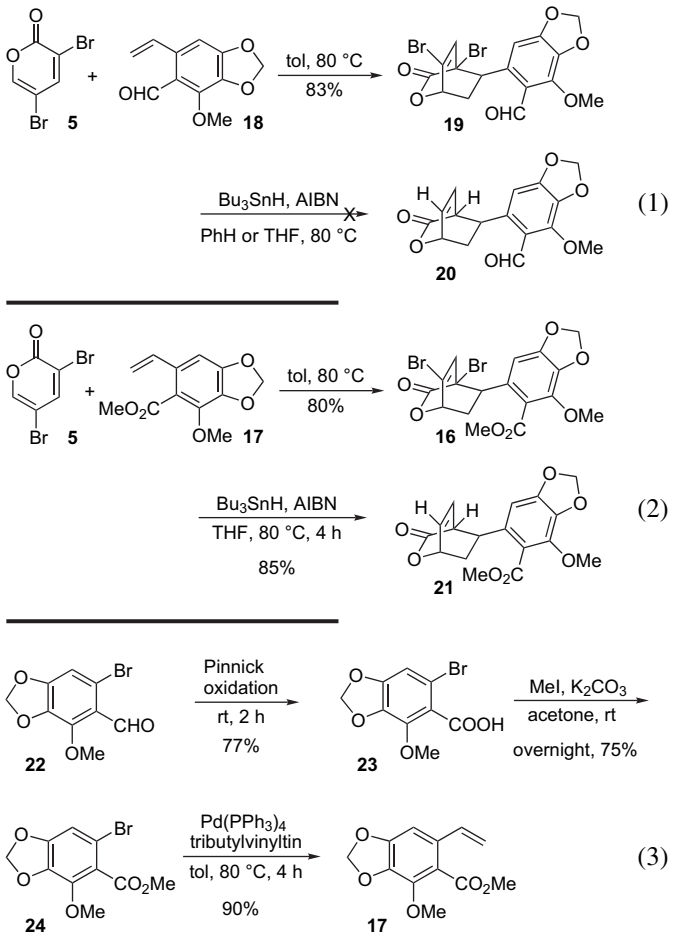
Further retrosynthetic analysis called for the elaboration of the styrene dienophile **17** containing the ester group at the *ortho* position. Such modification would also make the protection of the hydroxyl groups unnecessary, further condensing the synthetic route.

In initiating our synthetic program, the styrene dienophile **18** containing aldehyde group was first employed (Eq. 1, Scheme 4), anticipating the potential difficulty in the selective hydrolysis of the cyclohexenyl methyl ester in the presence of aryl methyl ester during the synthesis of intermediate **14** from **15** (Scheme 3). The Diels–Alder cycloaddition with 3,5-dibromo-2-pyrone **5** provided *endo*-cycloadduct **19** in 83% yield. Interestingly, the isolated **19** remained intact under the standard Bu_3SnH/AIBN debromination conditions. A prolonged heating with excess Bu_3SnH gave a complex product mixture. Turning back to our original plan (Eq. 2), the styrene dienophile **17**[8] was prepared and reacted with **5** to afford the corresponding *endo*-cycloadduct **16** in 80% yield. Unlike **19**, cycloadduct **16** was readily debrominated to furnish **21** in good yield (85%), when subjected to our standard debromination conditions. The requisite styrene dienophile **17** was prepared from bromobenzaldehyde **22**[8] (Eq. 3). The Pinnick oxidation followed by the methylation with MeI provided methyl ester **24** in good overall yield. The Stille coupling reaction with vinyltin afforded dienophile **17** in 90% yield.

Lactone ring opening reaction with NaOMe was accompanied with the olefin isomerization to produce the conjugated enoate as observed in the similar lactone utilized in our first-generation synthesis.[5b] After the acidic methanolysis, the resultant methyl ester **15** was dihydroxylated with OsO_4/NMO to provide **25** in 95% yield. Again, the dihydroxylation

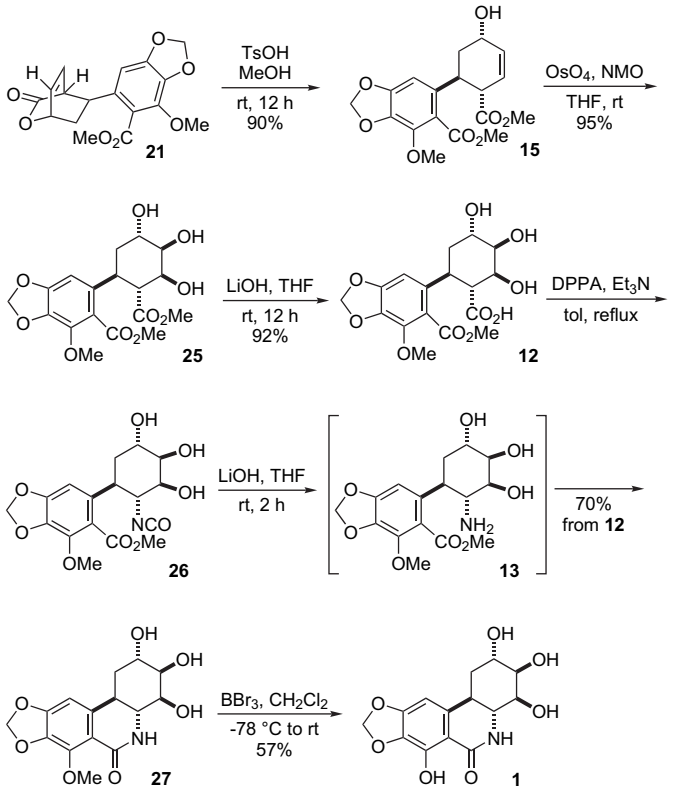


Scheme 3. Retrosynthesis of second-generation synthetic route.



Scheme 4. Diels–Alder reaction and preparation of dienophile **17**.

reaction took place exclusively on the less hindered β-face.[9] Despite our initial concern, the aliphatic methyl ester was selectively hydrolyzed to the corresponding mono-acid **12** in 92% yield, when subjected to simple hydrolysis conditions (1 N LiOH in THF). The isolated carboxylic acid **12** was then carried through the Curtius rearrangement reaction by reacting with DPPA in the presence of triethylamine. After the reaction, the reaction mixture containing isocyanate **26** was concentrated and directly treated with 1 N LiOH in THF, which effected the hydrolysis of the isocyanate group to **13**, and lactamization in a tandem fashion, to provide lactam **27** in 70% overall yield from **12**. Finally, the deprotection of methyl ether with BBr_3 furnished (±)-*trans*-dihydronarciclasine **1** in 57% yield (Scheme 5).



Scheme 5. Synthesis of (±)-*trans*-dihydronarciclasine.

3. Conclusion

In summary, we have devised a new synthetic route to (±)-*trans*-dihydronarciclasine **1**, more suitable for a large-scale preparation, highlighted with a direct assembly of the B-ring lactam unit through the incorporation of ester group onto the dienophile. Overall, the title compound was prepared from 3,5-dibromo-2-pyrone in 21% total yield over eight steps (15 longest steps, starting from the preparation of dienophile **17**). Further work is necessary to cut down the lengthy synthetic steps to the dienophile **17**.

4. Experimental

4.1. General methods

Reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents used were dried and purified before use in a Grubbs column, except for methanol, which was used as received. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck precoated silica gel plates. Flash column chromatography was performed with 230–400 mesh grade silica gel or neutral alumina. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon-13 NMR spectra were recorded on a Varian 400 MHz spectrometer. High-resolution mass spectra were measured by using FAB method at the Korean Basic Research Center, Seoul, Republic of Korea.

4.2. Synthesis of dienophile *17*

4.2.1. 6-Bromo-4-methoxybenzo[d][1,3]dioxole-5-carboxylic acid (*23*)

To a flask were added 3.6 g (13.9 mmol) of **22**,[8] 2.5 g of NaH_2PO_4 (20 equiv), 5.0 g of $NaClO_2$ (4 equiv), 8.8 mL of 2-methyl-2-butene (6 equiv), and *t*-BuOH/H_2O (5:1, 0.25 M). After 3 h at rt, the reaction mixture was acidified to pH 2

with 3 N HCl (aqueous) and extracted with EtOAc several times. The combined organic solution was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give 2.94 g of **23** as a white solid in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.00 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.2, 141.6, 136.3, 121.8, 111.3, 107.8, 102.2, 60.6.

*4.2.2. Methyl 6-bromo-4-methoxybenzo[d][1,3]dioxole-5-carboxylate (**24**)*

To a solution of carboxylic acid **23** (2.5 g, 9.1 mmol) and anhydrous K_2CO_3 (1.9 g, 13.6 mmol) in reagent acetone (90 mL) was added methyl iodide (17 mL, 271 mmol). After 12 h at rt, the resultant reaction mixture was treated with 10% K_2CO_3 solution and extracted with Et_2O. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc=10:1) to provide 1.97 g of **24** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 5.97 (s, 2H), 3.99 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.3, 141.8, 136.5, 123.4, 111.4, 107.73, 102.6, 60.9, 53.3; HRMS Calcd for $C_{10}H_9BrNaO_5$ $(M+23)^+$: 310.9531, found: 310.9533.

*4.2.3. Methyl 4-methoxy-6-vinylbenzo[d][1,3]dioxole-5-carboxylate (**17**)*

A mixture of 1.28 g (4.43 mmol) of **24**, 1.9 mL (1.5 equiv) of tributylvinyltin, 256 mg (0.05 equiv) of $Pd(PPh_3)_4$, and toluene (44 mL) was heated at 100 °C for 4 h. Upon cooling to rt, the reaction mixture was treated with saturated KF (aqueous), diluted with dichloromethane, and filtered through a plug of Celite. The filtrate was dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc=8:1) to provide 940 mg of **17** in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.60 (dd, J=17.2, 11.1 Hz, 1H), 5.96 (s, 2H), 5.60 (d, J=17.2 Hz, 1H), 5.23 (d, J=11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 150.6, 140.5, 136.1, 133.1, 130.9, 120.5, 115.7, 101.6, 99.7, 60.3, 52.5; FTIR (CH_2Cl_2) 3003, 2965, 2901, 1731, 1599, 1504, 1468, 1432, 1265 cm^{-1}; HRMS Calcd for $C_{12}H_{12}NaO_5$ $(M+23)^+$: 259.0582, found: 259.0585.

*4.3. Synthesis of (±)-**1***

*4.3.1. Methyl 6-(4,7-dibromo-3-oxo-2-oxa-bicyclo[2.2.2]-oct-7-en-5-yl)-4-methoxybenzo[d][1,3]dioxole-5-carboxylate (**16**)*

A mixture of 1.20 g (4.7 mmol) of 3,5-dibromo-2-pyrone **5** and 1.67 g (7.1 mmol) of **17** in anhydrous toluene (16 mL) was heated at 100 °C in a sealed tube for 1 day. The reaction mixture was cooled to rt, concentrated, and purified by column chromatography (hexane/EtOAc=6:1) to provide 1.97 g of the *endo* isomer **16** as a yellow solid in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, J=2.2 Hz, 1H), 6.27 (s, 1H), 6.00 (s, 1H), 5.99 (s, 1H), 5.24 (br s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.48 (dd, J=9.4, 5.0 Hz, 1H), 2.95 (ddd, J=13.9, 9.5, 4.4 Hz, 1H), 2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.8, 150.9, 140.6, 136.1, 134.0, 132.1, 123.5, 121.0, 101.9, 100.6, 80.8, 62.8, 60.3, 52.8, 41.9, 37.9; FTIR (CH_2Cl_2) 3072, 3004, 2945, 2897, 1774, 1711, 1621, 1483, 1345, 1260 cm^{-1}; HRMS Calcd for $C_{17}H_{14}Br_2NaO_7$ $(M+23)^+$: 510.9004, found: 510.9009.

*4.3.2. Methyl 4-methoxy-6-(3-oxo-2-oxa-bicyclo[2.2.2]-oct-7-en-5-yl)benzo[d][1,3]dioxole-5-carboxylate (**21**)*

To a sealed tube charged with 200 mg (0.41 mmol) of **16** and 4 mL of THF were added 40 mg (0.24 mmol) of AIBN and 0.44 mL (1.64 mmol) of tributyltin hydride at rt. The resulting solution was heated at 80 °C for 4 h. After cooling, the mixture was taken up in diethyl ether, washed with 25% aqueous ammonia solution and water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc=4:1) to provide 116 mg of **21** as a white solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (ddd, J=7.3, 5.1, 1.4 Hz, 1H), 6.37–6.34 (m, 1H), 6.20 (s, 1H), 5.942 (s, 1H), 5.939 (s, 1H), 5.32–5.30 (m, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.67–3.66 (m, 1H), 3.25 (ddd, J=9.1, 4.4, 1.8 Hz, 1H), 2.68 (ddd, J=13.9, 9.5, 4.0 Hz, 1H), 1.76–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 167.8, 150.3, 140.5, 135.3, 133.6, 133.1, 130.1, 121.5, 101.6, 101.4, 74.6, 60.3, 52.8, 47.5, 34.2, 33.2; FTIR (CH_2Cl_2) 3054, 2998, 2947, 1768, 1712, 1622, 1499, 1432, 1354 cm^{-1}; HRMS Calcd for $C_{17}H_{16}NaO_7$ $(M+23)^+$: 355.0794, found: 355.0792.

*4.3.3. Methyl 6-(5-hydroxy-2-(methoxycarbonyl)cyclo-hex-3-enyl)-4-methoxybenzo[d][1,3]-dioxole-5-carboxylate (**15**)*

To a flask charged with 110 mg (0.33 mmol) of **21** were added MeOH (1 mL) and 190 mg (1 mmol) of $TsOH\cdot H_2O$ at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The reaction mixture was quenched with aqueous NH_4Cl, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography (hexane/EtOAc=1:1) to give 110 mg of **15** as a white solid in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.04–6.01 (m, 1H), 5.94 (s, 2H), 5.88 (dd, J=10.3, 1.5 Hz, 1H), 4.21 (br s, 1H), 3.98 (s, 3H), 3.88 (s, 3H), 3.59 (s, 3H), 3.38–3.32 (m, 2H), 2.05–2.02 (m, 1H), 1.83–1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 167.9, 150.5, 140.5, 136.2, 134.8, 130.0, 128.2, 121.9, 101.5, 100.9, 63.5, 60.2, 52.4, 52.2, 48.6, 38.6, 34.4; FTIR (CH_2Cl_2) 3496, 2999, 2949, 2893, 1724, 1618, 1475, 1432, 1283, 1227 cm^{-1}; HRMS Calcd for $C_{18}H_{20}NaO_8$ $(M+23)^+$: 387.1056, found: 387.1061.

*4.3.4. Methyl 4-methoxy-6-(3,4,5-trihydroxy-2-(methoxy-carbonyl)cyclohexyl)benzo[d][1,3]dioxole-5-carboxylate (**25**)*

To a solution of **15** (60 mg, 0.17 mmol) in THF (3.3 mL) were added NMO (30 mg, 0.26 mmol) in H_2O (0.85 mL) and OsO_4 (0.3 mL, 4% in H_2O). The reaction mixture was stirred at rt for 8 h. The reaction was quenched with saturated aqueous $NaHSO_3$ and extracted with EtOAc. The combined organic solution was washed with brine, dried with $MgSO_4$, and concentrated. This crude product was purified by column

chromatography (100% EtOAc) to give 62 mg of **25** as a colorless oil in 95% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 6.63 (s, 1H), 5.960 (s, 1H), 5.957 (s, 1H), 4.09 (dd, J=11.0, 2.6 Hz, 1H), 3.92 (s, 3H and 1H, overlapped), 3.84 (s, 3H), 3.82 (s, 1H), 3.49 (s, 3H), 3.18 (ddd, J=15.8, 12.1, 3.3 Hz, 1H), 2.97–2.92 (m, 1H), 1.89–1.82 (m, 1H), 1.68–1.65 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.5, 169.4, 152.0, 141.2, 136.5, 136.2, 122.0, 102.9, 102.7, 72.9, 70.8, 70.6, 60.5, 52.6, 52.2, 51.9, 37.9, 35.9; FTIR (CH_2Cl_2) 3342, 2964, 2919, 2850, 1732, 1558, 1541, 1500, 1454, 1373, 1257 cm^{-1}; HRMS Calcd for $C_{18}H_{22}NaO_{10}$ $(M+23)^+$: 421.1111, found: 421.1117.

*4.3.5. 2,3,4-Trihydroxy-6-(7-methoxy-6-(methoxycarbonyl)benzo[d][1,3]dioxol-5-yl)cyclohexanecarboxylic acid (**12**)*

To a solution of **25** (90 mg, 0.226 mmol) in THF (1.2 mL) was added 1 N LiOH aqueous solution (1.33 mL). After being stirred at rt overnight, the solution was acidified to pH 2 with 3 N aqueous HCl and extracted with EtOAc several times. The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 80 mg of **12** as a white solid in 92% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.6 (br s, 1H), 6.57 (s, 1H), 6.03 (s, 1H), 6.01 (s, 1H), 4.81 (d, J=3.3 Hz, 1H), 4.70 (d, J=3.3 Hz, 1H), 4.5 (d, J=7.3 Hz, 1H), 3.85 (s, 3H), 3.85–3.83 (m, 1H), 3.73 (s, 3H), 3.71 (br s, 1H), 3.60 (br s, 1H), 3.02 (ddd, J=15.3, 12.1, 3.3 Hz, 1H), 2.73–2.71 (m, 1H), 1.61 (dd, J=13.2 Hz, 1H), 1.49–1.45 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6, 166.7, 149.7, 139.2, 135.8, 134.3, 120.6, 101.5, 101.4, 71.7, 69.2, 68.7, 59.8, 51.8, 49.9, 36.3, 35.2; FTIR (CH_2Cl_2) 3396, 2935, 2833, 1689, 1613, 1486, 1404, 1290 cm^{-1}.

*4.3.6. 2,3,4-Trihydroxy-7-methoxy-1,2,3,4,4a,5-hexa-hydro-[1,3]dioxolo[4,5-j]phenanthridin-6(11bH)-one (**27**)*

The mixture of **12** (50 mg, 0.13 mmol), Et_3N (54 μL, 0.39 mmol), and DPPA (84 μL, 0.39 mmol) in toluene (1.6 mL) was heated to reflux for 2 h and cooled to rt. The mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl, brine, and dried over $MgSO_4$. This crude product was concentrated under reduced pressure and purified by column chromatography (100% EtOAc) to give isocyanate, which was directly dissolved in 2 mL of THF and treated with 4 N LiOH (0.8 mL, 20 equiv). After 2 h at rt, the reaction mixture was neutralized by adding saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic solution was washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (MeOH/EtOAc=10:1) to give 30 mg of **27** as a white solid in 70% yield over two steps. ^{1}H NMR (400 MHz, CD_3OD) δ 6.62 (s, 1H), 6.04 (s, 1H), 6.00 (s, 1H), 4.07–4.08 (m, 1H), 3.99 (s, 3H), 3.89–3.97 (m, 1H), 3.85 (dd, J=9.9, 2.9 Hz, 1H), 3.39–3.35 (m, 2H), 2.94 (dd, J=12.5, 3.7 Hz, 1H), 2.19 (d, J=13.6 Hz, 1H), 1.8 (dd, J=14.0, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.9, 153.9, 145.9, 141.3, 138.1, 116.5, 103.2, 100.4, 73.3, 71.4, 70.6, 60.9, 55.6, 36.6, 29.9; FTIR (CH_2Cl_2) 3379, 2949, 2918, 2845, 1734, 1648, 1537, 1501, 1470, 1372, 1355, 1237 cm^{-1}; HRMS Calcd for $C_{15}H_{17}NNaO_7$ $(M+23)^+$: 346.0903, found: 346.0901.

*4.3.7. (±)-trans-Dihydronarciclasine (**1**)*

To a solution of **27** (45 mg, 0.14 mmol) in CH_2Cl_2 at −78 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.35 mL). The reaction mixture was warmed to 0 °C and stirred for 30 min. Then, 5 mL of 25% NH_4OH was added at 0 °C. After 20 min, the reaction mixture was extracted with CH_2Cl_2 several times. The combined organic solution was washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (MeOH/EtOAc=5:1) to give 25 mg of **1** as a white solid in 57% yield. Spectral data matched the literature values.[4a,9b] ^{1}H NMR (400 MHz, CD_3OD) δ 6.32 (d, J=1.1 Hz, 1H), 6.01 (d, J=1.1 Hz, 1H), 5.99 (d, J=1.1 Hz, 1H), 4.08 (dd, J=6.2, 2.9 Hz, 1H), 3.92–3.88 (m, 1H), 3.86 (dd, J=9.9, 2.9 Hz, 1H), 3.46 (dd, J=12.8, 9.9 Hz, 1H), 3.01–2.98 (m 1H), 2.26–2.19 (m, 1H), 1.88–1.77 (m, 1H).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.031.

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