JOURNAL OF NATURAL PRODUCTS

Article

Cite This: J. Nat. Prod. 2018, 81, 1451−1459

pubs.acs.org/jnp

Isolation, Synthesis, and Semisynthesis of Amaryllidaceae Constituents from *Narcissus* and *Galanthus* sp.: De Novo Total Synthesis of 2-*epi*-Narciclasine

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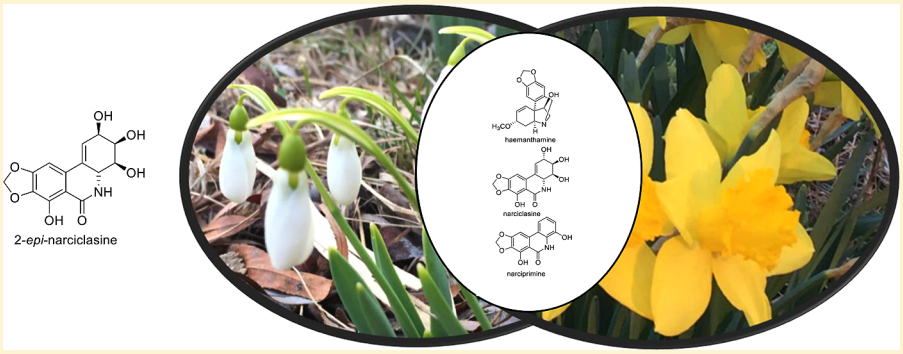
Supporting Information



ABSTRACT: An efficient protocol for the isolation of narciclasine from common Amaryllidaceae bulbs, separation from haemanthamine, and the occurrence of a trace alkaloid, 2-*epi*-narciclasine, are reported. Attempts to convert natural narciclasine to its C-2 epimer by Mitsunobu inversion or oxidation/reduction sequences were compromised by rearrangement and aromatization processes, through which a synthesis of the alkaloid narciprimine was achieved. The methylation of the 7-hydroxy group of natural narciclasine followed by protection of the 3,4-diol function and oxidation/reduction sequence provided the target C-2 epimer. A de novo chemoenzymatic synthesis of 2-*epi*-narciclasine from *m*-dibromobenzene is also described. Haemanthamine and narciprimine were readily detected in the crude extracts of *Narcissus* and *Galanthus* bulbs containing narciclasine, and the occurrence of 2-*epi*-narciclasine as a trace natural product in *Galanthus* sp. is reported for the first time.

Narciclasine (**1**), isolated in 1967,[1] is one of the potent biologically active Amaryllidaceae constituents shown in Figure 1. Originally described as antimitotic,[2] narciclasine induces apoptosis by activating death receptors FAS and DR4 and mitochondrial pathways in tumor cells but not in normal cells.[3] The targeting of eEF1A protein by narciclasine has been reported.[4] The potent anticancer activity led to the intense interest of the organic chemistry community in synthetic approaches to narciclasine, which is slightly more abundant (30−140 mg/kg wet weight)[5] than pancratistatin (**2**) (∼19 mg/kg), isolated by Pettit in 1984.[6]

Many total syntheses of narciclasine have been accomplished to date since the first three reports by Rigby in 1997[7] and Keck[8] and Hudlicky in 1999.[9] Other syntheses followed,[10,11] and the interest in this Amaryllidaceae consitutent continues unabated, in view of the medicinal chemistry potential of the natural product and its derivatives.[10a,b,e−h] In this paper an optimized procedure for isolation of narciclasine from *Narcissus pseudonarcissus* bulbs is reported. A solvent partition sequence has been developed to separate narciclasine from related constituents. Attempts to invert the C-2 configuration employing Mitsunobu chemistry, which has instead led to a synthesis of the natural product narciprimine (**7**) via aromatization of the C-ring, are also discussed. We also report the identification of 2-*epi*-narciclasine as a natural product for the first time in an extract of *Galanthus* sp., the occurrence of narciprimine (**7**) in both *Narcissus* and *Galanthus*, and the conversion of narciclasine to its C-2 epimer as well as a de novo chemoenzymatic total synthesis of this compound.

RESULTS AND DISCUSSION

Optimized Isolation Protocol. At least five different extraction protocols for the isolation of narciclasine from *Narcissus* bulbs have been reported.[10e] The narciclasine content

Received: March 16, 2018
Published: May 22, 2018

DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451−1459

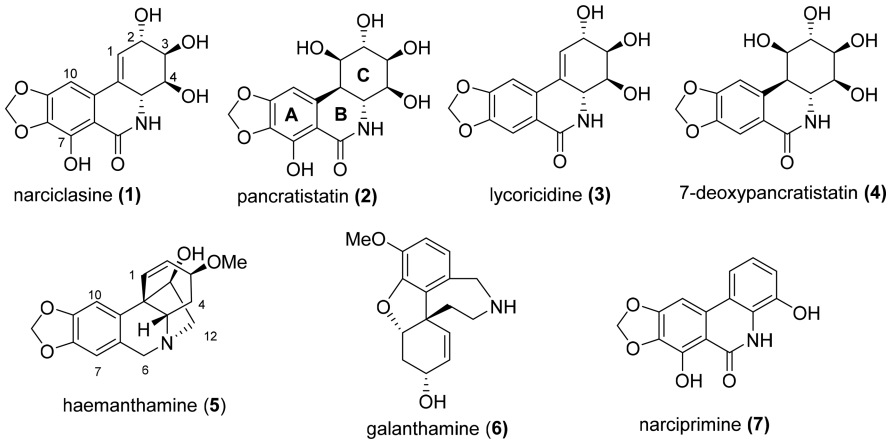
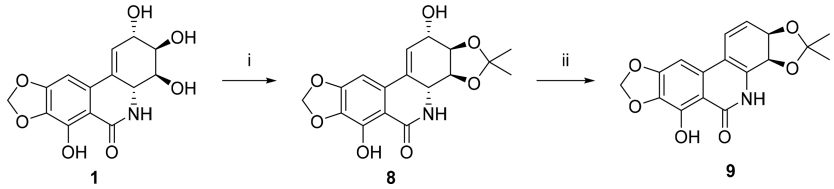


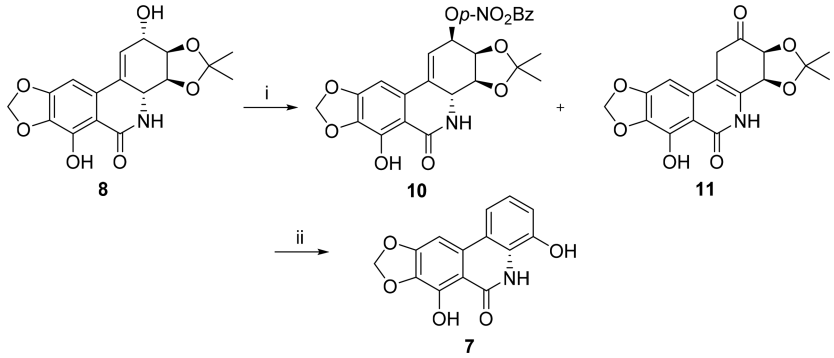
Figure 1. A selection of Amaryllidaceae constituents.

Scheme 1. Attempted Mitsunobu Reaction of Narciclasine-3,4-acetonide[a]



[a]Reagents: (i) 2,2-DMP, *p*-TSA (cat), DCM, rt (65−80%); (ii) PBu_3, BzOH, DEAD, THF, rt (30%).

Scheme 2. Second Attempt at a Mitsunobu Inversion at C-2 in Narciclasine-3,4-acetonide 8[a]



[a]Reagents: (i) Ph_3P, DIAD, *p*-NO_2BzOH, THF; (ii) TFA/H_2O, 2:1, THF (35%, over 2 steps).

in the bulbs and leaves varies considerably with season, reaching a maximum content as the plant approaches full flowering.[5a] Plant material is normally processed with MeOH or EtOH, and narciclasine is separated through solvent partitioning and chromatographic purification. In our hands, narciclasine has been isolated over several years following literature procedures in quantities approaching 50 mg/kg wet bulbs. We have now developed an optimized, alternative isolation protocol in which extraction of the plant material into MeOH (48 h), dilution with 250 mL of H_2O, and concentration yield an aqueous extract from which the less polar materials are removed by extraction into dichloromethane (DCM). The optimized process involves extraction of the remaining aqueous residue with a mixture of EtOAc and MeOH (9:1). This process allows clean extraction of narciclasine and a trace contaminant into the EtOAc phase from the polar aqueous phase. A single chromatographic purification then allows isolation of narciclasine in pure form.

The initial DCM extraction process completely removes other compounds such as galanthamine (**6**) and a contaminant that has a similar R_f to narciclasine. This compound was identified as the crinane alkaloid haemanthamine (**5**). The ^1H and ^{13}C NMR data of haemanthamine proved identical to the reported data.[12,13] However, analysis of the $^1H-^1H$ and $^1H-^{13}C$ 2D spectra showed that the C-6 and C-12 methylene signals have been previously misassigned. The C-12 methylene (^{13}C: 63.4 ppm; ^1H: 2.9, 3.3 ppm) correlates to the C-11 signals (^{13}C: 79.8 ppm; ^1H: 3.8 ppm), in contrast to the isolated resonances observed for the C-6 methylene (^{13}C: 60.4 ppm; ^1H: 4.2, 3.6 ppm). The assignment of these carbon and proton signals should therefore be reversed.[12,13]

Analysis of the EtOAc content from *Narcissus* by TLC showed essentially single-spot separation; however, the ^1H NMR data show the presence of narciclasine and a trace of an unidentified contaminant. The NMR data of narciclasine and the trace contaminant did not permit identification by comparison with known co-metabolites.[5a] The presence of

DOI: 10.1021/acs.jnatprod.8b00218
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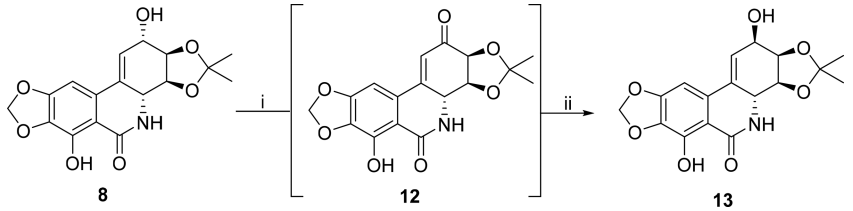
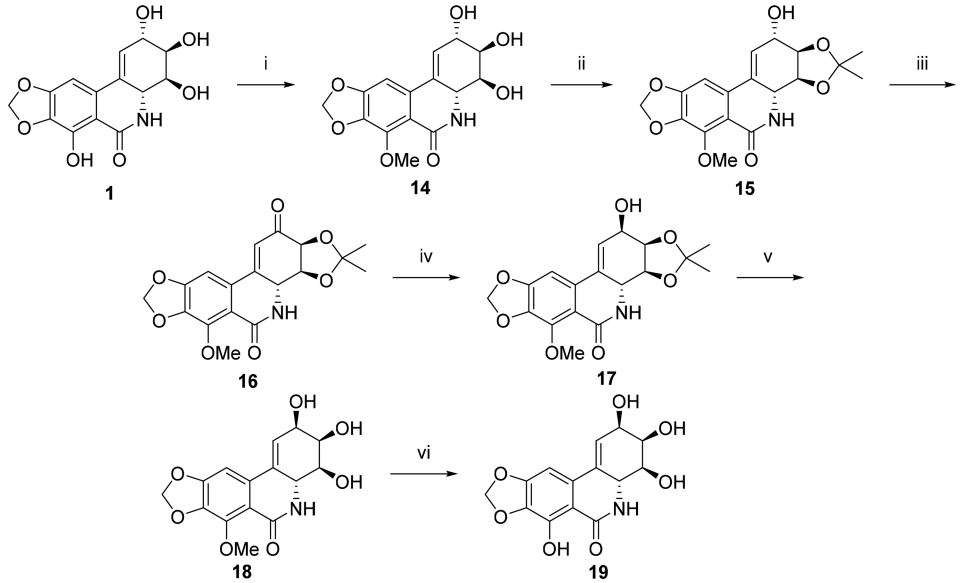
Scheme 3. Oxidation/Reduction of Protected Narciclasine (Free Phenol at C-7)[a]



[a]Reagents: (i) MnO_2, THF; (ii) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH (30% over 2 steps).

Scheme 4. Conversion of Narciclasine (1) to 2-*epi*-Narciclasine 19



[a]Reagents: (i) CH_2N_2, EtOH, Et_2O; (ii) 2,2-DMP, *p*-TSA, DCM: (iii) DMP, DCM; (iv) L-Selectride, DCM, THF (50% over two steps); (v) HCl (2 M), DCM, THF (30%); vi) TMSCl, KI, MeCN (51%).

minor peaks for a methylenedioxy $-CH_2-$ and an olefinic proton (^{1}H NMR: 6.06−6.12 ppm) led to a hypothesis that this material may be a minor epimer of narciclasine. Purification of the EtOAc-soluble portion from *Narcissus* by chromatography on silica yields off-white narciclasine in high yield (120 mg/kg). The disappearance of the minor metabolite upon a single silica gel column led to the assumption that the compound may be the C-2-allylic alcohol epimer. Thus, 2-*epi*-narciclasine became a target for semisynthesis from narciclasine and also for a de novo total synthesis (vide infra). This work and a direct comparison provided proof that the minor isomer from *Narcissus* is *not* the C-2-epimer, and this unstable minor compound remains unidentified. Access to authentic 2-*epi*-narciclasine obtained by semisynthesis (vide infra) and also by de novo total synthesis (Scheme 4) and comparison with extracts of *Narcissus* by LC-MS confirmed the absence of this metabolite in *Narcissus*. However, surprisingly, an identical analysis of an extract of *Galanthus* by LC-MS allowed confirmation of the presence of the 2-epimer by comparison of MS and LC-MS data.

Conversion of Narciclasine to 2-*epi*-Narciclasine. *A. Mitsunobu Inversion.* In an attempt to convert narciclasine to its C-2 epimer Mitsunobu reaction conditions with tributylphosphine and benzoic acid were first applied to the 3,4-acetonide-protected allylic alcohol **8**. Although starting material was consumed, none of the target product was isolated. Instead, elimination took place, most likely from the C-2-alkoxyphosphonium intermediate, and yielded the mixture of dienamine **9** and benzoic acid (1:1) in 30% yield (Scheme 1).

The Mitsunobu reaction was next attempted on compound **8** under alternative conditions using triphenylphosphine and diisopropyl diazodicarboxylate (DIAD) (Scheme 2). These conditions resulted in the formation of the target product **10** (16%) and the product of allylic alcohol oxidation, followed by olefin migration to give the stable conjugated enamine **11** (84%). This rearrangement of the double bond into the lactam moiety has previously been reported.[14] In the present case, the reaction produced an inseparable mixture of the products **10** and **11**. Most interestingly, treatment of the mixture with trifluoroacetic acid (TFA), in an attempt to remove the acetonide, yielded a major product in 35% isolated yield from acetonide **8**. This product proved to be identical with the minor Amaryllidaceae constituent narciprimine (**7**), a compound that exhibits acetylcholinesterase inhibitory activity.[2,15]

B. Oxidation/Reduction Sequence. Because of the failure of the direct C-2-inversion reactions, an alternative attempt at the conversion of narciclasine to its C-2 epimer was investigated involving the oxidation of the C-2 allylic alcohol group and stereoselective reduction. This sequence also proved problematic: Oxidation of compound **8** was unsuccessful under Swern as well as Dess-Martin conditions. Enone **12** was prepared by oxidation of narciclasine with MnO_2, but its isolation was arduous because of its instability. As noted in the original publication by Krohn, enone **12** readily rearranges to its

DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451−1459

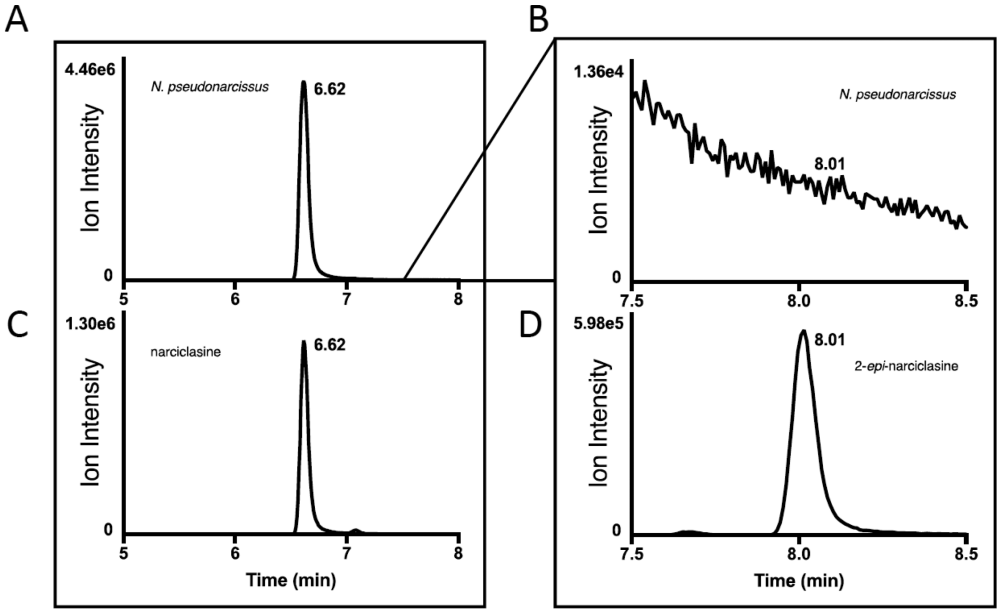
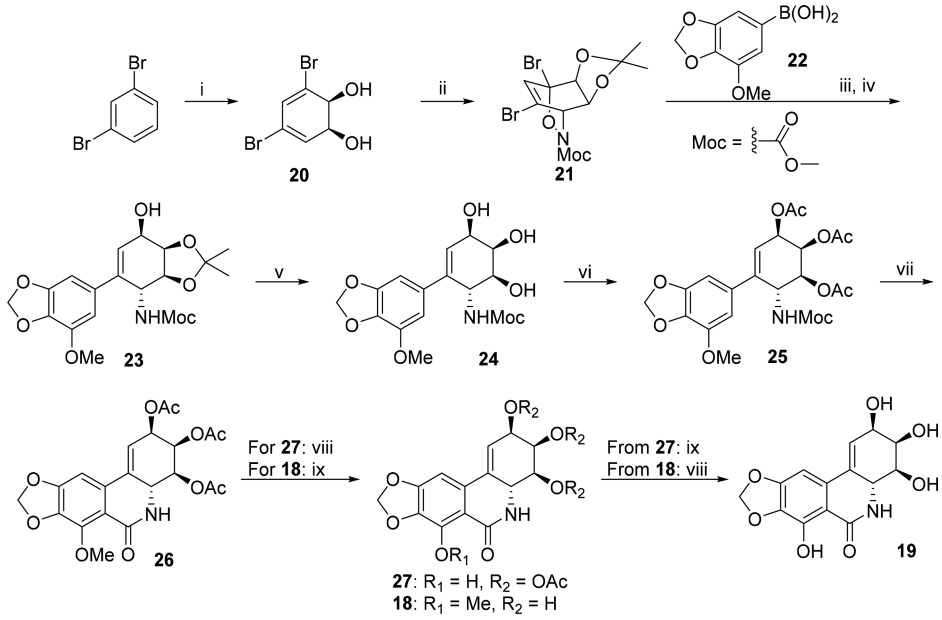


Figure 2. Extracted ion chromatograms (m/z 306.0614) for narciclasine (A, C) and 2-*epi*-narciclasine (B, D) from *N. pseudonarcissus* extracts (A, B) compared to synthesized standards (C, D).

Scheme 5. Synthesis of 2-*epi*-Narciclasine (19)[a]



[a]Reagents: (i) toluene dioxygenase in *E. coli* JM109(pDTG601A) (0.5−0.8 g/L); (ii) DMP, *p*-TsOH, then MocNHOH, $NaIO_4$, MeOH, H_2O (45−70%); (iii) $Pd(PPh_3)_4$, Na_2CO_3, PhH, H_2O, EtOH, then $Mo(CO)_6$, MeCN, H_2O (60−72%); (iv) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH (68−90%); (v) HCl (2 M), DCM, THF (95%); (vi) Ac_2O, Et_3N, DMAP, DCM (84%); (vii) Tf_2O, DMAP, DCM (31%); (viii) TMSCl, Kl, MeOH (40−60%); (ix) K_2CO_3, MeOH (60−95%).

deconjugated isomer **11** (Scheme 3).[14] Attempts to perform a one-pot oxidation/reduction without isolation of enone **12** proved irreproducible, and only traces of allylic alcohol **13** were observed in reaction mixtures.

We suspected that the free phenolic moiety might be contributing to the problem encountered in oxidations of the C-2 allylic alcohol moiety and to the instability of enone **12**. Thus, narciclasine was treated with diazomethane to produce the methyl ether **14**, whose protection as an acetonide yielded compound **15**, Scheme 4. The allylic alcohol was oxidized under Dess-Martin conditions to enone **16**, followed by in situ reduction. The Luche reduction of **16** yielded a mixture of both diastereomers **15** and **17** in 45% yield and a 6:1 ratio. The reduction with a bulkier reagent, L-selectride, provided only the allylic alcohol **17** in 50% yield. Acetonide deprotection and O-demethylation of **18** furnished 2-*epi*-narciclasine (**19**). UPLC analysis of the crude extract from *Narcissus* bulbs revealed the absence of 2-*epi*-narciclasine, as evidenced by co-injection comparison with the synthetic sample (Figures 2B and 2D).

De Novo Synthesis to 2-*epi*-Narciclasine. A total synthesis of 2-*epi*-narciclasine was accomplished from 1,3-dibromobenzene via enzymatic dihydroxylation to diol **20**,

DOI: 10.1021/acs.jnatprod.8b00218
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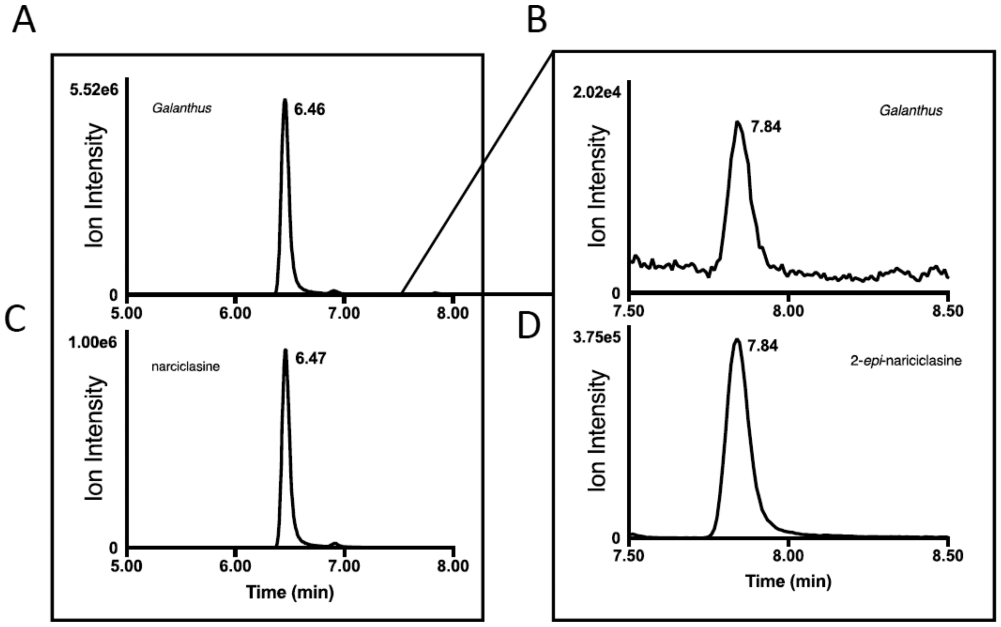

Figure 3. Extracted ion chromatograms (m/z 306.0614) for narciclasine (A, C) and 2-*epi*-narciclasine (B, D) from *Galanthus* sp. extracts (A, B) compared to synthesized standards (C, D).

which was converted in five steps to the allylic alcohol **23** [acetonide protection, nitroso Diels–Alder reaction, Suzuki coupling, $Mo(CO)_6$ and Luche reductions] (Scheme 5). Details of these transformations were recently published [up to the allylic alcohol **23**].[16] The allylic alcohol **23** was deprotected with 2 M HCl, and the resulting triol **24** was reprotected as triacetate **25**. Formation of ring B of the narciclasine backbone was achieved employing the Banwell-modified Bishler–Napieralski reaction and yielded phenantridone **26**.[17] Deprotection of **26** can be accomplished in two ways: (a) O-demethylation (yielding compound **27**), followed by hydrolysis of acetoxy groups, or (b) hydrolysis of acetoxy groups (yielding compound **18**), followed by O-demethylation. The initial pathway was combined in one pot and furnished 2-*epi*-narciclasine (**19**) in 50% yield over the two steps. As stated above, 2-*epi*-narciclasine was not detected in the crude extract from Narcissus (Figures 2B and 2D).

The literature contains a few misleading references to this epimer, including the structure as represented by **19**.[18] This arose from initial misassignment of the structure of narciclasine (**1**), which was corrected by Krohn and Mondon in 1972.[19] They synthesized oxygenated derivatives and compared their ^{1}H NMR data with those of the isomerized narciclasine derivative. In this manner the correct C-2 configuration was reassigned for the natural product, as shown in Figure 1.

Detection of 2-*epi*-Narciclasine in *Amaryllidaceae* Crude Extracts. Narciclasine was detected in extracts of both *N. pseudonarcissus* and *Galanthus* sp. (Figures 2A and 3A, respectively) as compared to an authentic standard (Figures 2C and 3C). However, as indicated by coelution with synthesized 2-*epi*-narciclasine (Figures 2D and 3D), this compound was only detected in extracts of *Galanthus* sp. (Figure 3B), and not extracts of *N. pseudonarcissus* (Figure 2B). 2-*epi*-Narciclasine has not been reported as a natural product. Narciclasine, haemanthamine, and narciprimine were readily detectable in LC-MS chromatograms of the crude extract from both *N. pseudonarcissus* and *Galanthus* sp. and alignment of retention time and mass spectrum with standard compounds (see HRMS data in Figure S2-1 in the Supporting Information). Analysis of the relative content of 2-*epi*-narciclasine in *Galanthus* sp. showed it to be approximately 100-fold less abundant than narciclasine (Figure S2-2 in the Supporting Information), indicating its presence at sub-ppm level (<1.0 mg/kg) in *Galanthus* bulbs. The compound would have been identified only with much difficulty through standard isolation protocols but was readily matched with a sample of synthesized 2-*epi*-narciclasine. On the other hand, significant amounts of narciprimine (Figure S2-3, Supporting Information) and haemanthamine (Figure S2-4, Supporting Information) were detected in the extracts of both species.

An efficient solvent extraction and single-column protocol for the isolation of narciclasine from bulbs of *N. pseudonarcissus* is reported in high (>100 mg/kg wet weight) yield. The crinane alkaloid haemanthamine was also isolated, and several resonances in the NMR spectrum of **5** were reassigned on the basis of 2D NMR correlations. Clean separation of narciclasine from haemanthamine is achieved during this solvent-extraction process. A trace contaminant co-occurring with narciclasine in the EtOAc extract of *N. pseudonarcissus* was hypothesized to be 2-*epi*-narciclasine, leading to both the semi- and total syntheses of this 2-epimer. This compound proved *not* to be identical to a minor metabolite, whose constitution is as-yet unidentified. Nonetheless, through an interesting twist of fate, 2-*epi*-narciclasine was identified as a trace metabolite (<1.0 ppm) in an extract of *Galanthus* sp. and is here reported as a natural product for the first time. Attempted Mitsunobu inversions of the allylic alcohol functionality in narciclasine as an entry to the C-2 epimer were complicated by side reactions; however this work resulted in a serendipitous synthetic entry to the natural product narciprimine. Analysis of the crude extracts of *N. pseudonarcissus* and *Galanthus* sp. using LC-MS and synthesized standards confirmed the presence of narciclasine, haemanthamine, and narciprimine in both extracts and the trace occurrence of 2-*epi*-narciclasine in only the *Galanthus* sample. Given the low natural abundance of 2-*epi*-narciclasine, the optical rotation data or a detailed analysis on a chiral support

DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451–1459

and comparison with the racemate could not be obtained. The overall absolute configuration is assumed to be in accord with related lycoranes such as narciclasine and pancratistatin. Of special note is the rare fact that this total synthesis of 2-*epi*-narciclasine preceded its identification as a natural product

EXPERIMENTAL SECTION

General Experimental Procedures. All solvents were dried and distilled before usage. Reactions were done in an inert atmosphere (Ar or N_2). All reagents were obtained from commercial sources. Before using, all glassware was oven- or flame-dried. NMR analysis was carried out on 400, 600, and Bruker AV-III 700 mHz spectrometers running Topspin 2.1 and 3.5 software. Probes were equipped with gradients and variable-temperature accessories. Chemical shifts are given in δ, and coupling constants J are given in Hz. Melting points were determined using a capillary melting point apparatus. HRMS data were recorded using an LTQ Orbitrap XL or double focusing sector mass spectroscopy, and the mass ion was determined by electrospray ionization, fast atom bombardment, or electron ionization. Infrared spectra were recorded on an FT-IR spectrophotometer as $CHCl_3$ solutions or neat and are reported in wave numbers (cm^{-1}). Optical rotations were determined on an Autopol IV automatic polarimeter and a PerkinElmer 241-MC polarimeter. Flash grade 60 silica gel was used for column chromatography unless otherwise noted. Deactivated silica was prepared by stirring it with 10% H_2O for 5 h. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets and visualized with UV and CAM or $KMnO_4$ solutions. UPLC-ESIMS analysis of crude extracts obtained from TEVA and synthesized standards was performed on an Acquity UPLC Class I equipped with an Acquity BEH C18 1.7 μm column coupled to a Waters Xevo-G2XS QTOF. Leucine enkephalin (200 pg/μL in acidified 50:50 MeCN/H_2O) was used as a reference calibrant with a Waters LockSpray ion source for exact mass measurement. Narciprimine, narciclasine, and 2-*epi*-narciclasine standards were diluted in acidified 5% MeCN/H_2O (0.1% formic acid) and hemeanthamine standard diluted in DCM for UPLC-MS analysis. Crude extracts obtained from TEVA were prepared in MeOH at 2 mg/mL and diluted (1:10) in acidified 5% MeCN/H_2O (0.1% formic acid) or DCM.

Extraction and Purification of Narciclasine (1) and Haemanthamine (5) from *Narcissus pseudonarcissus* Bulbs. Finely chopped bulbs of *Narcissus pseudonarcissus* (1.0 kg wet weight) were soaked in MeOH (3.0 L) for 2 days at ambient temperature. Considerable darkening of the material and decomposition is observed if bulbs are allowed to soak for longer periods. The resulting solution and suspended plant parts were filtered through a bed of Celite and washed with MeOH (3 × 250 mL). The combined filtrate was concentrated at 45 °C under reduced pressure to give approximately 250 mL of an aqueous residue, which was further diluted with water (250 mL). The aqueous phase was extracted with DCM (3 × 250 mL). The combined DCM phases were concentrated *in vacuo*, giving a residue (12.8 g) that was purified by column chromatography (DCM/MeOH, 24:1 to 19:1). Haemanthamine (**5**) was obtained as a pale yellow solid (11 mg, 0.0011%).

*Haemanthamine (**5**):* R_f = 0.3 [DCM/MeOH (9:1)]; mp = 200–204 °C, lit.[20] 199–202 °C; $[\alpha]_D^{20}$ +41 (*c* 0.2, $CHCl_3$); lit.[20] $[\alpha]_D^{24}$ +42 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.96 (s, 1H), 6.59 (s, 1H), 6.46 (d, J = 10.1 Hz, 1H), 6.11 (dd, J = 10.0, 5.0 Hz, 1H), 5.92 (s, 2H), 5.75 (s, 1H), 5.03 (s, 1H), 4.17 (d, J = 16.8 Hz, 1H), 3.82–3.78 (m, 1H), 3.77–3.74 (m, 1H), 3.65–3.60 (m, 1H), 3.37–3.28 (m, 2H), 3.22 (s, 3H), 3.07 (dd, J = 13.4, 4.0 Hz, 1H), 2.97–2.93 (m, 1H), 2.01 (td, J = 13.3, 4.2 Hz, 1H), 1.76 (d, J = 9.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 145.9, 145.4, 136.2, 129.2, 128.8, 106.8, 103.3, 100.5, 79.8, 72.2, 63.4, 62.5, 60.4, 55.6, 54.9, 49.9, 28.0; HRMS (ESI) (M + H)$^+$ calcd for $C_{17}H_{20}NO_4$ 302.1392; found 302.1387.

The aqueous phase from the DCM extraction was extracted with EtOAc/MeOH (9:1, 3 × 250 mL). The combined organic phase was concentrated in vacuo to give a residue (1.53 g), which was further purified by column chromatography (DCM/MeOH, 19:1 to 13:1). Narciclasine (**1**) was isolated as an off-white solid (0.12 g, 0.012%).

*Narciclasine (**1**):* Specific rotation and other physical data were in accord with the literature. R_f = 0.3 [DCM/MeOH (9:1)]; mp = 236–240 °C (dec > 245 °C), lit.[11c] 246 °C; $[\alpha]_D^{20}$ +111 (*c* 0.4, MeOH), lit.[8] $[\alpha]_D^{20}$ +112 (*c* 0.6, MeOH); ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.26 (s, 1H), 7.89 (s, 1H), 6.86 (s, 1H), 6.17–6.14 (m, 1H), 6.08 (d, J = 2.4 Hz, 2H), 5.18 (dd, J = 16.0, 5.8 Hz, 2H), 5.02 (d, J = 3.8 Hz, 1H), 4.19 (d, J = 8.5 Hz, 1H), 4.02 (s, 1H), 3.81–3.77 (m, 1H), 3.70 (d, J = 2.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 168.9, 152.4, 144.8, 133.4, 132.1, 129.3, 124.8, 105.6, 102.1, 95.8, 72.4, 69.1, 68.8, 52.9; HRMS (ESI) (M+Na)$^+$ calcd for $C_{14}H_{13}NO_7Na$ 330.0590; found 330.0581.

*(3aS,3bR,12S,12aR)-6,12-Dihydroxy-2,2-dimethyl-3b,4,12,12a-tetrahydrobis[1,3]dioxolo[4,5-c:4′,5′-j]phenanthridin-5(3aH)-one (**8**).* Protocol A: Narciclasine (**1**) (10 mg, 0.032 mmol) was suspended in DCM (3 mL), and 2,2-DMP (0.3 mL) added followed by addition of *p*-toluenesulfonic acid (*p*-TSA, cat.). The mixture was stirred at room temperature for 2 h. The reaction mixture was adsorbed on deactivated silica and purified by flash column chromatography (EtOAc/hexanes, 1:2 to 1:1). The product was isolated as a colorless, oily solid, 8 mg, 71%.

8: R_f = 0.6 [EtOAc/hexanes (2:1)]; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.76 (s, 1H), 8.83 (s, 1H), 7.03 (s, 1H), 6.49 (t, J = 3.0 Hz, 1H), 6.07 (dd, J = 5.1, 0.8 Hz, 2H), 5.82 (s, 1H), 4.19–4.14 (m, 1H), 4.14–4.09 (m, 1H), 4.07 (t, J = 7.8 Hz, 1H), 3.97 (dd, J = 7.9, 6.2 Hz, 1H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.7, 152.6, 145.2, 133.4, 128.9, 128.3, 126.0, 109.8, 104.3, 102.1, 94.3, 79.0, 78.5, 71.0, 54.6, 27.1, 24.8; HRMS (EI) calcd for $C_{17}H_{17}O_7N$ 347.1005; found 347.1004.

Protocol B: To a stirred solution of narciclasine (**1**) (10 mg, 0.032 mmol) and 2,2-DMP (0.3 mL) in DMF (0.3 mL) was added pyridinium *p*-toluene sulfonate (0.8 mg, 0.0032 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was poured into H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with cold H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting mixture was purified by silica gel column (DCM/MeOH, 250:1 to 165:1). Acetonide **8** was obtained as a white solid (9 mg, 82%).

8: R_f = 0.6 [DCM/MeOH (19:1)]; mp = 270–274 °C, lit. 270–273[5b] and 275–276 °C;[14] $[\alpha]_D^{20}$ −11.4 (*c* 1.2, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ −33 (*c* 0.35, THF) and lit.[8] $[\alpha]_D^{20}$ −24 (*c* 0.35, THF); ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.73 (s, 1H), 8.79 (s, 1H), 7.00 (s, 1H), 6.46 (t, J = 2.9 Hz, 1H), 6.05 (d, J = 5.0 Hz, 2H), 5.79 (d, J = 5.7 Hz, 1H), 4.17–4.12 (m, 1H), 4.11–4.08 (m, 1H), 4.07–4.02 (m, 1H), 3.95 (dd, J = 7.8, 6.3 Hz, 1H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 152.5, 145.2, 133.3, 128.9, 128.3, 125.9, 109.8, 104.2, 102.0, 94.2, 79.0, 78.4, 71.0, 54.6, 27.0, 24.8; HRMS (ESI) (M+H)$^+$ calcd for $C_{17}H_{18}NO_7$ 348.1083; found 348.1075.

*(3aS,12aR)-6-Hydroxy-2,2-dimethyl-4,12a-dihydrobis[1,3]-dioxolo[4,5-c:4′,5′-j]phenanthridin-5(3aH)-one mixture with benzoic acid (**9**):* Allylic alcohol **8** (15 mg, 0.043 mmol), PBu_3 (17.5 mg, 0.086 mmol, 21.3 μL), and benzoic acid (10.6 mg, 0.086 mmol) were suspended in tetrahydrofuran (THF) (1 mL). It was followed by slow dropwise addition of diethyl azodicarboxylate (DEAD) (15 mg, 0.086 mmol, 13.7 μL). The reaction mixture was stirred at room temperature for 1.5 h (full consumption of starting material). The reaction mixture was adsorbed on deactivated silica and purified by column chromatography (EtOAc/hexanes, 1:4 to 2:3). The product was isolated as a 1:1 mixture with benzoic acid, 6 mg, 30%.

9: R_f = 0.4 [EtOAc/hexanes (1:2)]; $[\alpha]_D^{23}$ −109 (*c* 0.05, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81–6.73 (m, 2H), 6.12 (d, J = 1.0 Hz, 2H), 6.05 (dd, J = 9.9, 4.5 Hz, 1H), 5.09 (d, J = 7.7 Hz, 1H), 4.82 (dd, J = 7.6, 4.5 Hz, 1H), 1.51 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 165.8, 154.5, 144.6, 133.8, 132.8, 132.4, 131.6, 130.3, 129.6, 128.6, 122.9, 120.9, 108.6, 108.5, 102.6, 92.8, 71.3, 70.8, 27.2, 25.6; LRMS (ESI+) calcd for $C_{17}H_{15}O_6N$+Na 352.1; found 352.0.

*Narciprimine 4,7-Dihydroxy-[1,3]dioxolo[4,5-j]phenanthridin-6(5H)-one (**7**):* Ph_3P (60 mg, 0.23 mmol) and *p*-nitrobenzoic acid (38 mg, 0.23 mmol) were added to a stirred solution of the acetonide

DOI: 10.1021/acs.jnatprod.8b00218
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8 (20.0 mg, 0.057 mmol) in THF (2 mL), followed by the dropwise addition of DIAD (0.051 mL, 0.25 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was then cooled to 0 °C and quenched with slow addition of 1 M HCl (0.2 mL) and H_2O (5.0 mL). The mixture was extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude mixture was purified by silica gel column (EtOAc/hexanes, 1:5 to 1:4) and afforded an inseparable mixture of **10** and **11**[16] (1:6, 10 mg), which was characterized by ^{1}H NMR and COSY data. R_f = 0.70 [DCM/MeOH (19:1)]. The mixture of **10** and **11** was used directly in the next step.

To a solution of the above mixture (10.0 mg) in THF (2.0 mL) was added TFA/H_2O (2:1, 0.9 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. The solvent was evaporated by flushing with a stream of nitrogen. The crude product was purified by silica gel column (DCM/MeOH, 199:1 to 140:1). Narciprimine (**7**) was obtained as a white solid (5 mg, 35% over 2 steps), the physical data of which were fully consistent with the literature.[15]

7: R_f = 0.45 [DCM/MeOH (19:1)]; mp = 309−313 °C, lit.[17] 310−315 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.78 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.20 (s, 2H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 165.0, 153.6, 144.8, 144.4, 132.3, 131.9, 123.9, 123.2, 119.4, 113.8, 113.5, 107.1, 102.3, 93.7; HRMS (ESI) (M + H)$^+$ calcd for $C_{14}H_{10}NO_5$ 272.0559; found 272.0555.

(2S,3R,4S,4aR)-2,3,4-Trihydroxy-7-methoxy-3,4,4a,5-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (***14***)*:* *N*-Nitroso-*N*-methylurea (1.3 g, 13 mmol) was added portionwise to a cold (0 °C) mixture of aqueous KOH solution (8 M, 4 mL) and Et_2O (14 mL). The organic layer containing freshly prepared diazomethane solution was decanted onto 2 g of cold KOH pellets and added to the suspension of narciclasine (**1**) (100 mg, 0.325 mmol) in EtOH (17 mL) at 0 °C. The reaction flask was covered with a loose rubber septum and left to warm to room temperature, and the mixture stirred for 16 h. After full consumption of starting material (TLC, DCM/MeOH, 10:1), the mixture was stirred for another 16 h under atmospheric conditions and then quenched with the addition of glacial acetic acid (1 mL). The reaction mixture was concentrated and used for acetonide formation without further purification. The crude product was purified by column chromatography (DCM/MeOH, 10:1 to 5:1) to afford **14** (83 mg, 79%).

14: R_f = 0.1 [DCM/MeOH (10:1)]; mp = 208 °C, lit.[2] 206 °C; $[\alpha]_D^{23}$ +256 (c 0.7, $CHCl_3$/MeOH, 1:1), lit.[11b] $[\alpha]_D^{26}$ +204 (c 0.3, DMSO); IR (neat) 3379, 2980, 2912, 1359, 1650, 1611, 1478 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.15 (s, 1H), 7.00 (s, 1H), 6.13 (d, J = 0.9 Hz, 1H), 6.11−6.09 (m, 1H), 6.07 (d, J = 0.9 Hz, 1H), 5.19 (d, J = 5.8 Hz, 1H), 5.15 (d, J = 5.5 Hz, 1H), 4.96 (d, J = 3.8 Hz, 1H), 4.04−3.99 (m, 2H), 3.84 (s, 3H), 3.77 (ddd, J = 7.8, 5.5, 2.0 Hz, 1H), 3.69−3.65 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.1, 151.4, 143.5, 139.2, 133.5, 131.3, 123.6, 115.3, 102.0, 99.5, 72.5, 69.2, 69.2, 60.5, 52.6; HRMS (EI) calcd for $C_{15}H_{15}O_7N$ 321.0849; found 321.0847.

(2S,3R,4S,4aR)-2,3,4-Trihydroxy-7-methoxy-3,4,4a,5-tetrahydro-3,4-[a][2,2-dimethyl-1,3-dioxolanyl]-[1,3]dioxolo[4,5-j]-phenanthridin-6(2H)-one (***15***)*:*[16] 7-Methoxynarciclasine (**14**) (22 mg, 0.07 mmol) was suspended in DCM (2 mL), and 2,2-DMP (0.2 mL) was added, followed by the addition of a catalytic amount of *p*-TSA. The reaction mixture was stirred at room temperature for 2 h, adsorbed on deactivated silica, and purified by gravity column chromatography [DCM/MeOH (100:1 to 30:1)] to afford **15** as a colorless, oily solid, 17 mg, 68%.

15: R_f = 0.3 [DCM/MeOH (50:1)]; $[\alpha]_D^{24}$ +47.9 (c 0.5, $CHCl_3$); IR (neat) 3338, 2988, 2923, 2853, 1655, 1611, 1478 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.31−6.27 (m, 1H), 6.04−6.02 (m, 3H), 4.37 (m, 1H), 4.16−4.05 (m, 3H), 4.02 (s, 3H), 2.77 (d, J = 4.5 Hz, 1H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 152.5, 145.3, 139.8, 130.4, 128.2, 125.0, 113.7, 111.4, 102.1, 97.7, 79.8, 79.0, 72.9, 61.2, 55.6, 27.2, 25.0; HRMS (EI) calcd for $C_{18}H_{19}O_7N$ 361.1162; found 361.1165.

(2R,3R,4S,4aR)-2,3,4-Trihydroxy-7-methoxy-3,4,4a,5-tetrahydro-3,4-[a][2,2-dimethyl-1,3-dioxolanyl]-[1,3]dioxolo[4,5-j]-phenanthridin-6(2H)-one (***17***)*:* A solution of allylic alcohol **15** (15 mg, 0.042 mmol) in DCM (2 mL) was cooled to 0 °C, and Dess-Martin periodinane (20 mg, 0.045 mmol) added. The mixture was left to warm to room temperature for 1.5 h. To the cooled reaction mixture (0 °C) was added L-selectride (1 M solution in THF, 0.2 mL) in a dropwise manner. The mixture was left to warm to room temperature. After consumption of the intermediate enone **16** [TLC, DCM/MeOH (50:1)], the reaction mixture was quenched with a saturated NH_4Cl solution (1 mL) and filtered through a plug of Celite. Compound **17** was purified by column chromatography [DCM/MeOH (100:1 to 50:1)] (6 mg, 40%, yellow oil).

17: R_f = 0.3 [DCM/MeOH (50:1)]; $[\alpha]_D^{24}$ +119 (c 0.1, $CHCl_3$/MeOH, 92:8); IR (neat) 3306, 2924, 2854, 1659, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.47 (dd, J = 5.9, 3.5 Hz, 1H), 6.04 (dd, J = 8.1, 1.3 Hz, 2H), 5.97 (s, 1H), 4.79 (ddd, J = 7.0, 3.5, 1.2 Hz, 1H), 4.68 (dd, J = 6.4, 4.6 Hz, 1H), 4.31 (dd, J = 8.3, 4.5 Hz, 1H), 4.27−4.19 (m, 1H), 4.03 (s, 3H), 2.70 (s, 1H), 1.57 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 152.3, 145.2, 140.2, 134.8, 130.7, 120.1, 114.3, 112.1, 102.2, 98.3, 80.6, 73.4, 63.6 61.2, 54.9, 26.8, 24.8; HRMS (EI) calcd for $C_{18}H_{19}O_7N$ 361.1162; found 361.1153.

2-epi-7-Methoxynaciclasine [(2R,3R,4S,4aR)-2,3,4-Trihydroxy-7-methoxy-3,4,4a,5-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one] (***18***)*: Procedure from Synthesized Intermediate* ***17****:* Acetonide **17** (5 mg, 0.014 mmol) was dissolved in a mixture of DCM and THF (1:2, 0.5 mL), and 2 M HCl (0.3 mL) was added in a dropwise manner at 0 °C. After stirring for 30 min, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with DCM (3 × 4 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The triol was purified by preparative TLC [DCM/MeOH (8:1)]. The reaction yielded 2 mg (44%) of compound **18** as a white, crystalline product.

Procedure from Synthesized Intermediate ***26****.* A round-bottom flask was charged with triacetate **26** (25 mg, 0.056 mmol), K_2CO_3 (23 mg, 0.17 mmol), and MeOH (3 mL). After stirring for 5 min, the reagents dissolved and the mixture became homogeneous. TLC analysis showed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure, and the product was isolated by preparative TLC [DCM/MeOH (8:1)] to yield **18** as a white, crystalline solid (17 mg, 95%).

26b: R_f = 0.4 [DCM/MeOH (5:1)]; $[\alpha]_D^{24}$ +9 (c 0.1, $CHCl_3$/MeOH, 1:1); IR (neat) 3342, 2923, 2852, 1651 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 6.87 (s, 1H), 6.11 (d, J = 0.9 Hz, 1H), 6.06 (d, J = 0.9 Hz, 1H), 6.00 (d, J = 1.4 Hz, 1H), 4.43 (d, J = 2.7 Hz, 1H), 4.33−4.27 (m, 1H), 4.11 (s, 1H), 3.91 (s, 3H), 3.73 (dd, J = 8.7, 1.7 Hz, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 163.6, 153.0, 145.2, 140.4, 134.3, 130.7, 126.2, 116.3, 103.1, 99.9, 74.1, 72.8, 68.8, 61.1, 52.9; HRMS (EI) calcd for $C_{15}H_{15}O_7N$ 321.0849; found 321.0849.

(2R,3R,4S,4aR)-2,3,4,7-Tetrahydroxy-3,4,4a,5-tetrahydro-[1,3]-dioxolo[4,5-j]phenanthridin-6(2H)-one (***19***)*: Procedure from Synthesized Intermediate* ***18****:* Triol **18** (20 mg, 0.062 mmol) was dissolved in MeCN (2 mL), and a solution of trimethylsilyl chloride (TMSCl) in MeCN (0.5 M, 0.16 mL) and KI (11 mg, 0.068 mmol) were added. The reaction mixture was heated at 60 °C for 1 h, cooled to 0 °C, and quenched with H_2O (2 mL). The product was extracted with EtOAc (3 × 5 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography [DCM/MeOH (30:1 to10:1)] yielded 11 mg (60%) of 2-*epi*-narciclasine (**19**).

Procedure from Synthesized Intermediate ***27****:* Triacetate **27** (15 mg, 0.035 mmol) was dissolved in MeOH (3 mL), and K_2CO_3 (20 mg, 0.14 mmol) was added at rt. The reaction mixture was stirred for 10 min until full consumption of starting material (TLC, DCM/MeOH, 10:1). The reaction mixture was quenched with HCl (2 M, 0.2 mL) and diluted with H_2O(10 mL), and the product extracted with DCM (20 mL) over 16 h. The organic layer was dried over Na_2SO_4, filtered, and concentrated on deactivated silica, and the product was

DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451−1459

purified by flash column chromatography [DCM/MeOH (30:1 to 10:1)], to yield 7 mg (66%) of **19** as a white precipitate, 66%.

19: R_f = 0.2 [DCM/MeOH (10:1)]; $[\alpha]_D^{21}$ +69 (*c* 0.1, *i*-PrOH); IR (neat) 3356, 2922, 2852, 1660, 1632 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.92 (s, 1H), 6.73 (s, 1H), 6.08 (d, *J* = 5.2 Hz, 2H), 5.98 (s, 1H), 5.31 (s, 1H), 4.95 (s, 1H), 4.89 (d, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 2.1 Hz, 1H), 4.22 (dt, *J* = 8.5, 3.1 Hz, 1H), 3.89 (s, 1H), 3.64 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.1, 152.4, 144.8, 133.3, 131.9, 127.8, 126.9, 105.6, 102.1, 95.5, 72.0, 71.7, 67.6, 53.2; HRMS (EI) calcd for $C_{14}H_{13}O_7N$ 307.0692; found 307.0691.

*Methyl (1R,4R,5R,6S)-4,5,6-Trihydroxy-2-(7-methoxybenzo[d]-[1,3]dioxol-5-yl)cyclohex-2-enylcarbamate (**24**):* Allylic alcohol **23** (61 mg, 0.16 mmol) was dissolved in a mixture of DCM and THF (1:2, 3 mL), and 6 M HCl (0.5 mL) was added dropwise at room temperature. The reaction mixture was stirred for 15 min, quenched with a saturated solution of $NaHCO_3$ (5 mL), and extracted with DCM (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The triol was purified by column chromatography [DCM/MeOH (100:1 to 10:1)], and compound **24** was isolated by precipitation from $CHCl_3$ as a white solid [52 mg (95%)].

24: R_f = 0.4 [DCM/MeOH (10:1)]; mp = 184−185 °C (MeOH); $[\alpha]_D^{23}$ −145 (*c* 0.3, MeCN); IR (neat) 3366, 2938, 2904, 2851, 1697, 1626 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 7.01 (d, *J* = 9.8 Hz, 1H), 6.59 (d, *J* = 1.4 Hz, 1H), 6.56 (d, *J* = 1.5 Hz, 1H), 5.96 (s, 2H), 5.79−5.76 (m, 1H), 4.89 (d, *J* = 5.9 Hz, 1H), 4.73 (d, *J* = 4.4 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.63−4.58 (m, 1H), 4.14 (dt, *J* = 6.3, 2.9 Hz, 1H), 3.84 (t, *J* = 3.9 Hz, 1H), 3.79 (s, 3H), 3.63−3.57 (m, 1H), 3.45 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.9, 148.2, 142.7, 136.7, 134.1, 133.9, 128.8, 105.7, 101.1, 100.2, 72.8, 71.1, 67.7, 56.0, 52.3, 51.2; HRMS (EI) calcd for $C_{16}H_{19}O_8N$ 353.1111; found 353.1102.

*(1S,2R,3R,6R)-5-(7-Methoxybenzo[d][1,3]dioxol-5-yl)-6-(methoxycarbonylamino)cyclohex-4-ene-1,2,3-triyl triacetate (**25**):* Triol **24** (362 mg, 1.03 mmol) was dissolved in DCM (12 mL), and the solution cooled to 0 °C. Et_3N (570 μL) and Ac_2O (390 μL) were added dropwise. After addition of DMAP (cat., 4.2 mg), the reaction flask was removed from the ice bath. After 10 min TLC (DCM/MeOH, 10:1) showed full consumption of starting material. The reaction mixture was quenched with H_2O (15 mL), the organic layer was separated, and the aqueous phase was washed with DCM (4 × 10 mL). The combined organic phases were washed with saturated NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography [EtOAc/hexanes (gradient 1:2 to 1:1.5)] to yield 412 mg (84%) of triacetate **25** as a white foamy oil.

25: R_f = 0.5 [EtOAc/hexanes (1:1)]; $[\alpha]_D^{22}$ −210 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3333, 2941, 2849, 1744, 1722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.51 (s, 1H), 5.95 (dd, *J* = 7.0, 1.4 Hz, 2H), 5.74 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.70 (dd, *J* = 6.4, 2.8 Hz, 1H), 5.63−5.58 (m, 1H), 5.20 (dd, *J* = 8.5, 1.2 Hz, 1H), 5.12 (t, *J* = 9.0 Hz, 1H), 4.66 (d, *J* = 10.0 Hz, 1H), 3.87 (s, 3H), 3.57 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.5, 170.1, 157.0, 148.9, 143.5, 140.2, 135.5, 132.0, 123.8, 106.2, 101.8, 101.1, 77.2, 71.8, 69.1, 68.0, 56.6, 52.5, 50.6, 21.0, 20.9 × 2; HRMS (EI) calcd for $C_{22}H_{25}O_{11}N$ 479.1422; found 479.1427; anal. calcd for $C_{22}H_{25}O_{11}N$: C, 55.11; H, 5.26; found C, 55.15; H, 5.34.

*(2R,3R,4S,4aR)-7-Methoxy-6-oxo-2,3,4,4a,5,6-hexahydro-[1,3]-dioxolo[4,5-j]phenanthridine-2,3,4-triyl triacetate (**26**):* Triacetate **25** (21 mg, 0.044 mmol) was dissolved in DCM (1 mL), and DMAP (16 mg, 0.132 mmol, 3 equiv) was added. The reaction mixture was cooled to 0 °C, and Tf_2O (37 μL, 0.219 mmol, 5 equiv) was added dropwise. The mixture was stirred for 18 h at 3 °C, poured into a saturated solution of $NaHCO_3$ (5 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was concentrated under reduced pressure. The crude mixture was redissolved in THF (2 mL), 2 M HCl (0.2 mL) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (5 mL), extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography [EtOAc/hexanes (1:3 to 1:1)] to yield 31 mg (48%) of triacetate **26** as a colorless oil.

26: R_f = 0.7 [EtOAc/hexanes (1:1)], $[\alpha]_D^{24}$ +7 (*c* 0.2, $CHCl_3$); IR (neat) 2956, 2926, 2856, 1750, 1669, 1239 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.06 (d, *J* = 1.1 Hz, 1H), 6.03 (d, *J* = 1.1 Hz, 1H), 5.94 (s, 1H), 5.90 (s, 1H), 5.80 (dd, *J* = 6.1, 3.4 Hz, 1H), 5.75−5.72 (m, 1H), 5.08 (dd, *J* = 9.1, 1.8 Hz, 1H), 4.58 (dt, *J* = 9.0, 2.8 Hz, 1H), 4.06 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.3, 169.8, 163.0, 152.5, 144.9, 139.6, 132.3, 132.1, 120.1, 114.7, 102.2, 99.5, 72.8, 68.1, 67.8, 61.2, 50.7, 21.0, 20.9 × 2; HRMS (EI) calcd for $C_{21}H_{21}O_{10}N$ 447.1165; found 447.1156.

*(2R,3R,4S,4aR)-7-Hydroxy-6-oxo-2,3,4,4a,5,6-hexahydro-[1,3]-dioxolo[4,5-j]phenanthridine-2,3,4-triyl triacetate (**27**):* Phenantridone **26** (30 mg, 0.067 mmol) was dissolved in MeCN (3 mL), and a solution of TMSCl in MeCN (0.5 M, 0.17 mL) and KI (12 mg, 0.072 mmol) were added. The reaction mixture was heated at 60 °C for 1 h, cooled to 0 °C, and quenched with H_2O (3 mL). The product was extracted with EtOAc (3 × 5 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography [DCM/MeOH (gradient 100:1 to 10:1)] yielded 15 mg (50%) of phenol **27**.

27: R_f = 0.3 [DCM/MeOH (20:1)]; $[\alpha]_D^{21}$ −28 (*c* 0.2, $CHCl_3$); IR (neat) 3308, 2923, 1749, 1675 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.91 (s, 1H), 6.94 (s, 1H), 6.14−6.09 (m, 3H), 5.88−5.85 (m, 1H), 5.59−5.55 (m, 1H), 5.17 (dd, *J* = 9.4, 1.7 Hz, 1H), 4.61 (dt, *J* = 9.1, 2.8 Hz, 1H), 2.07 (s, 3H), 2.03−2.00 (m, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.2, 170.1, 169.4, 169.1, 152.5, 144.8, 133.9, 130.5, 129.3, 121.6, 105.8, 102.3, 96.1, 71.5, 67.5, 67.4, 50.0, 21.0, 20.6, 20.5; HRMS (EI) calcd for $C_{20}H_{19}O_{10}N$ 433.1009; found 433.1003.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00218.

NMR data and LC-MS results (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the following agencies for financial support of this work: Stanley Medical Research Institute (Grant No. 13R-002), Natural Sciences and Engineering Research Council of Canada (NSERC) (Grant No. RGPIN-2018-03723), Canada Research Chair Program, Canada Foundation for Innovation (CFI), TDC Research, Inc., TDC Research Foundation, the Ontario Partnership for Innovation and Commercialization (OPIC), The Advanced Biomanufacturing Centre (Brock University), and Growing Forward 2. We are thankful to H. Endoma (Brock University) for her skillful assistance in the fermentations. We thank R. Simionescu and Dr. L. Qui for their help with NMR and mass spectrometry analyses. We would like

DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451−1459

to thank Dr. L. Cvak from TEVA [Opava, Czech Republic] for a generous gift of narciclasine and *Galanthus* sp. crude extracts.

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DOI: 10.1021/acs.jnatprod.8b00218
J. Nat. Prod. 2018, 81, 1451−1459