JOC Article

A Short Synthesis of (+)-Narciclasine via a Strategy Derived from Stereocontrolled Epoxide Formation and $SnCl_4$-Catalyzed Arene-Epoxide Coupling

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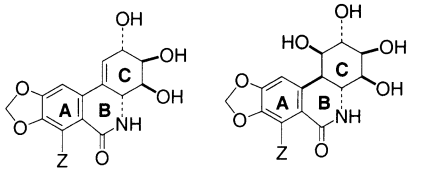
Received March 7, 2002

A facile construction of the typical framework of narcissus alkaloids has been realized by virtue of the development of a practical route involving stereocontrolled epoxide formation and $SnCl_4$-catalyzed arene−epoxide coupling. To achieve this goal, it proved to be necessary to devise a strategy that would enable chemical transformations to install an epoxy moiety in a congested environment. The successful preparation of a hindered epoxide from *O*-isopropylidene-protected 4-aminocyclohexenol required three steps consisting principally of controlled bromohydration and base-promoted closure and N-alkylation. It was found that a catalytic amount of $SnCl_4$ not only maintained the catalytic cycle but also effected clean arylation to form a fused BC ring system. Several tactics that ultimately proved to be unsatisfactory are also discussed in an effort to set important boundary limits on arene−epoxide coupling. The requisite enantiopure 4-aminocyclohexenol was available via an asymmetric cycloaddition of diene to camphor-based chloronitroso. The total synthesis of (+)-narciclasine was realized in nine steps with an overall yield of 19%.

Introduction

There has been considerable interest in recent years in the development of new methodology suitable for the synthesis of narcissus alkaloids such as (+)-narciclasine **1**, (+)-lycoricidine **2**, (+)-pancratistatin **3**, and (+)-deoxypancratistatin **4** because of the reputed biological activity



1: Z = OH, Narciclasine
2: Z = H, Lycoricidine
3: Z = OH, Pancratistatin
4: Z = H, Deoxypancratistatin

and low natural abundance of these compounds. In this regard, the literature provides numerous strategies such as asymmetric syntheses based upon nitroso cycloadditions from chiral diene derived from whole-cell oxidation of bromobenzene with *Pseudomonas putida* 39/D,[1a] Pd-catalyzed desymmetrization of the symmetric dicarbonate,[1b] Pd-catalyzed desymmetrization of the prochiral cyclohexanone,[1c] intramolecular coupling of arene to the allyl triflate[1d] and carbamate,[1e] radical cyclization of the oxime ether,[2] aryl enamide photocyclization,[3] and Pd-catalyzed Heck cyclization.[4] The principal hurdles to synthesis include introduction of the aryl group and stereocontrolled construction of the fused BC ring system. Recently, because the majority of the stereochemical interrelationships and pendent functional groups in these alkaloids share a striking similarity, a synthetic conversion of narciclasine **1** to pancratistatin **3** has been disclosed by Pettit.[5] To explore some of the important structure−activity relationships, the related *cis*-epimer of saturated narcissus alkaloid has also garnered attention from the synthetic community. During the preparation of this manuscript, Hudlicky reported the total synthesis of *epi*-7-deoxypancratistatin via aza-Payne rearrangement and Me_2AlCl-assisted intramolecular cyclization.[6] We describe herein a short synthesis of (+)-narciclasine[2c,3,7] from the readily available chiral *O*-isopropylidene-protected 4-aminocyclohexenol **11** by a route involving stereocontrolled installation of the bromohydrin

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(2) (a) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (b) Keck, G. E.; Wage, T. T. *J. Org. Chem.* **1996**, *61*, 8366. (c) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176.

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(4) (a) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525. (b) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (c) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441. (d) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823. (e) Hudlicky, T.; Olivo, H. F.; Mckibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

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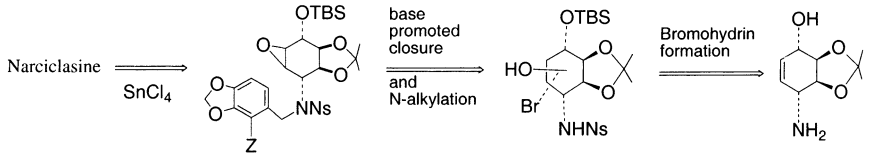
(6) Uwe, R.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115.

(7) (a) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077. (b) For the isolation of narciclasine, see: Piozzi, F.; Modelli, R.; Fuganti, C.; Ceriotti, G. *Tetrahedron* **1968**, *24*, 1119.

10.1021/jo020155k CCC: $22.00
Published on Web 09/07/2002

CHART 1

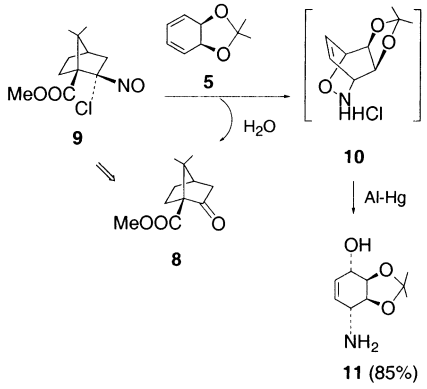


unit, base-promoted epoxide formation, and $SnCl_4$-catalyzed arene−epoxide coupling (Chart 1).[7]

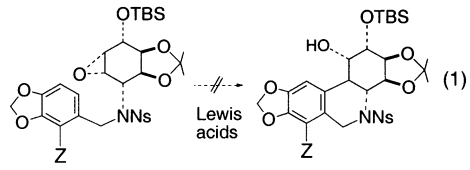
Results and Discucssion

Camphor-based chiral controller molecules have previously been shown to exhibit high asymmetric induction in aldol addition and cycloaddition reactions.[8a−c] We envisioned employing the previously reported chiral chloronitroso **9**[8d] as a practical nitroso synthon.[9] Chloronitroso **9** was readily prepared from the ketopinic acid via a three-step protocol: (a) esterification ($SOCl_2$/MeOH), (b) formation of oxime ($HONH_2$·HCl/MeOH/NaOAc), and (c) oxidation (*t*-BuO-Cl/CH_2Cl_2). The overall isolated yield of **9** from ketopinic acid was 88%. The requisite enantiopure *O*-isopropylidene-protected 4-aminocyclohexenol **11** was prepared in one-pot by cycloaddition of **9** to diene **5**[10] (CH_2Cl_2, 0 °C, 12 h) followed by treatment with water and Al-Hg (CH_3CN, 0 to 25 °C, 2 h) (Scheme 1).[11] While hydrolysis of the cycloaddition adduct led to the desired oxazine hydrochloride **10**, keto ester **8** could be recovered in 93% yield by hexane extraction of the aqueous reaction mixture. The enantiomeric purity (>99%) of bicyclic oxazine was determined by ^{1}H NMR of its D-camphor-10-sulfonyl derivative and also by comparing the achiral oxazine with our adduct **10** in HPLC (Chiracel OD; 95% hexane/isopropyl alcohol; flow rate 1 mL/min; UV 254 nm). Only a single peak (t_R = 19.2 min) was observed for the chiral oxazine **10**. Because of the sensitivity of **11**, it was generally used directly in the next step without purification. Subsequent protection of the amino and hydroxyl moieties with *p*-nitrobenzenesulfonyl chloride (Ns-Cl) and TBS-Cl delivered the silylated sulfonamide **12** in 78% isolated yield.

SCHEME 1



Stereocontrolled Epoxide Formation and Arene−Epoxide Coupling. With enantiopure unsaturated sulfonamide **12** in hand, the stage was set for diastereocontrolled introduction of the epoxy unit in order to permit intramolecular coupling of an aryl ring to the epoxide. Experience had shown that all attempts to effect Lewis acid-promoted arene−epoxide coupling of **7** failed to



provide the desired fused ring system (eq 1).[12] They either decomposed, failed to react, or produced halohydrins, through an epoxide ring-opening process. Apparently, in these instances, the cyclization process cannot compete with ring opening. It was felt that the acetonide moiety might repel the arene ring, thereby preventing cyclization. Attention was then centered upon intramolecular arylation of epoxides **14**, where the epoxy unit and acetonide ring are syn to each other (Scheme 2). In the absence of a potent directing group for peracids,[13] the more hindered epoxide can usually be prepared by bromohydrin formation and base-promoted closure.[14] Generation of bromohydrin **13** was not anticipated to present complications and did not. Thus, exposure of **12**

(8) (a) For a review concerning camphor derivatives as chiral auxiliaries, see: Oppolzer, Z. *Tetrahedron* **1987**, *43*, 1969−2004. (b) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (c) Lin, C.-C.; Wang, Y.-C.; Hsu, J.-L.; Chiang, C.-C.; Su, D.-W.; Yan, T.-H. *J. Org. Chem.* **1997**, *62*, 3806. (d) Extensive studies have revealed that camphor-based chloronitroso **9** has shown exceptionally high stereoselection in cycloadditions. Elango, S.; Wang, Y.-C.; Cheng, C.-L.; Yan, T.-H. *Tetrahedron Lett.* **2002**, *43*, 3757.

(9) For chloronitroso dienophiles derived from steroid, D-mannofuranose, D-xylofuranose, L-xylose, and D-xylose, see: (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron, Lett.* **1984**, *31*, 5091. (b) Schurrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407. (c) Braun, H.; Felber, H.; Kresze, G.; Schmidtchen, F. P.; Prewo, R.; Vasella, A. *Liebigs Ann. Chem.* **1993**, 261, and earlier references therein. (d) Adrian, H.; Bailey, P. D.; Rees, D. C.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1998**, 2251. (e) Faitg, T.; Soulie, J.; Lallemand J.-Y.; Ricard, L. *Tetrahedron: Asymmetry* **1999**, 2165. (f) Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 329.

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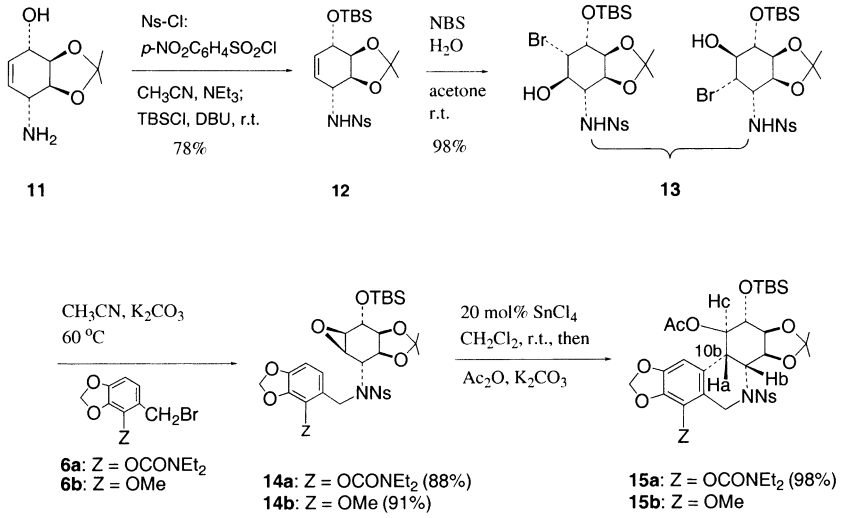
(11) For additional examples of preparation of conduramine synthons, see refs 4 and 9b.

(12) Yan, T.-H.; Wang, Y.-C. Unpublished observations.

(13) Stereoselective preparation of epoxides can be achieved by the aid of the structure of the substrates, especially in the cyclic systems. The presence of a hydroxyl group close to the olefinic bond strongly determines the epoxide stereochemistry. For studies of the directive effect of the hydroxyl group, see: (a) Henbest, H. B. *Proc. Chem. Soc.* **1963**, 159. (b) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc., B* **1970**, 1374. (c) Prat, D.; Delpech, B.; Lett, R. *Tetrahedron Lett.* **1986**, *27*, 711.

(14) Hanselaer, R.; Samson, R.; Vandewalle, M. *Tetrahedron* **1978**, *34*, 2393.

SCHEME 2. Stereocontrolled Epoxide Formation and Arene−Epoxide Coupling



to NBS in aqueous acetone at room temperature gave rise to bromohydrins **13** as a 1:1 mixture of two regioisomers. The resulting mixture was used as such for the epoxide formation. Epoxides **14** could be prepared in one step from **13** through base-promoted epoxide formation and N-piperonylation. Thus, reaction of bromohydrin **13** with the requisite piperonyl bromides **6**[15,16] in the presence of K_2CO_3 at 60 °C for 4 h led to clean internal S_N2 reaction and N-alkylation to give the desired epoxides **14** in 91−95% isolated yields. With epoxides **14** in hand, the stage was set to establish the feasibility of Lewis acid as a catalyst to effect intramolecular arene−epoxide coupling. After an extensive survey of Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, $AlCl_3$, and $MgBr_2$, we were disappointed to discover that none of catalysts led to acceptable levels of arene−epoxide coupling. Surprisingly, a catalytic amount of $SnCl_4$ (10−20 mol %) not only maintained the catalytic cycle but also effected clean intramolecular arylation of **14** to form the fused BC ring system. Thus, exposure of **14a** to $SnCl_4$ in dry CH_2Cl_2 at room temperature for 10 min followed by addition of Ac_2O provided after chromatography on silica gel the desired tetracyclic ester **15a** in 93% yield. The assignment of the cis-fused ring stereochemistry of **15a** follows by comparison to the known compounds pancratistatin **3** and deoxypancratistatin **4**. The ^{1}H NMR absorptions for benzylic proton (H−C-10b) in **3** (δ 2.96, br d, J = 11.5−12.9 Hz) and **4** (δ 2.98, d, J = 9.8−12.0 Hz) are diagnostic of the trans-fused BC ring system.[1−3,5] The corresponding absorptions for **15a** (δ 3.05, t, J_{ab} = 6.4 Hz, J_{ac} = 6.4 Hz) establish the cis-fused ring stereochemistry as depicted, which, in turn, confirms our tentative assignment of the stereochemistry of the initial bromohydrin products **13**. We next investigated the arene−epoxide coupling of **14b**. Due to well-documented para-directing effect of the methoxy substituent, we were not surprised to discover a poor selectivity (intra- and intermolecular coupling) in this cyclization. A 1:1 mixture of **15b** and dimer (not shown) was obtained as judged by ^{1}H NMR spectrum. All attempts to enhance the relative proportion of the desired ester **15b** in this cyclization were to no avail.

(+)-Narciclasine. The ready accessibility to tetracyclic intermediate **15a** by the preceding protocol set the stage for completion of the synthesis (Scheme 3). Thus, exposure of **15a** to 2 equiv of mercaptoacetic acid in the presence of LiOH (5 equiv) at room temperature in DMF for 1 h led to clean removal of the nosyl (*p*-nitrobenzenesulfonyl) moiety to liberate the free amine **16** (78% isolated yield),[17] which upon treatment with Boc_2 followed by addition of $RuCl_3$ and aqueous $NaIO_4$ to effect benzylic oxidation provided the solid imide **17** in 67% yield. The imide **17** possessing the typical framework of pancratistatin is lacking the stereochemistry only at the benzylic position (C-10b). There remained the task of eliminating acetic acid from **17** to obtain the unsaturated alkaloid. Dreiding models of **17** indicate the acetoxy and benzylic hydrogen (H−C-10b) attached to a cis-fused bicyclic framework (BC ring system) are not syn-periplanar in its ground-state geometry. For this reason, base-promoted syn-elimination most likely would require some degree of heating. Thus, exposure of **17** with DBU at 70 °C led to clean syn-elimination to give **18** in 97% yield. Subsequent exposure of the elimination product **18** to formic acid at 60 °C followed by solvent removal and immediate treatment with a solution of $LiAlH_4$ in THF resulted in efficient deprotection of all the protecting groups to give the target molecule **1**, which was identical in all aspects to the literature report.[2c,3,18] The total synthesis of narciclasine **1** was thus realized in nine steps with an overall yield of 19%.

Conclusions

In summary, asymmetric chloronitroso cycloaddition, application of the stereocontrolled epoxide formation, and

(15) (a) Piperonyl bromide **6a** was prepared in three steps from the corresponding 2-hydroxy-3,4-methylenedioxybenzaldehyde:[16a] (i) $ClCONEt_2$ (1 equiv), K_2CO_3 (3 equiv), CH_3CN, 85 °C, 2 h. (ii) $NaBH_4$ (2 equiv), MeOH, from 0 to 25 °C. (iii) HBr (48 wt % in H_2O), CH_2Cl_2, 25 °C, 86% yield (three steps). (b) Reaction of 2-methoxy-3,4-methylenedioxybenzyl alcohol[16b] with HBr (48 wt % in H_2O) in CH_2Cl_2 at 25 °C afforded the corresponding piperonyl bromide **6b** in 96% yield.

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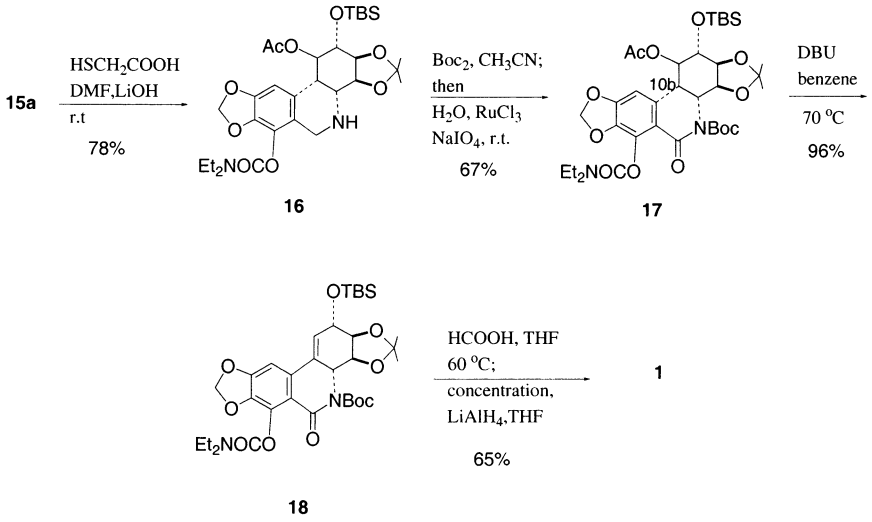
(17) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.

(18) (a) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860. (b) Piozzi, F.; Modelli, R.; Fuganti, C.; Ceriotti, G. *Tetrahedron* **1968**, *24*, 1119.

SCHEME 3



implementation of a $SnCl_4$-catalyzed intramolecular arylation led efficiently to the tetracyclic ester. (+)-Narciclasine was available in nine steps by this route. Tetracyclic sulfonamide **15** might also serve as a synthetic intermediate toward pancratistatin **3** and its epimer. The conversion of tetracyclic intermediate **15** to pancratistatin **3** requires inversion at C-10b (benzylic carbon). Now, efforts are directed toward inverting the stereochemistry of C-10b.

Experimental Section

General. Reactions were generally conducted under a positive pressure of dry nitrogen within oven-dried glassware. THF and ether were distilled from sodium/benzophenone ketyl prior to use. Methylene chloride and acetonitrile were distilled from CaH_2 prior to use. Flash chromatography was done on E. Merck silica gel 60 (230−400 mesh). Melting points (Pyrex capillary) are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent.

(1*S*,2*R*,3*S*,6*R*)-6-Amino-1,2-*O*-isopropylidene-4-cyclohexene-1,2,3-triol (11). To a solution of chloronitroso ester **9** (5.4 g, 20.0 mmol) in CH_2Cl_2 (40 mL) in a round-bottom flask covered with aluminum foil at 0 °C was added cyclohexadiene acetonide **5** (3.1 g, 20.0 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 12 h at the same temperature. Then, the solvent was removed in vacuo to yield a solid residue that was dissolved in water (60 mL) and stirred at room temperature for 30 min. This aqueous solution was thoroughly washed with hexane and directly treated with Al-Hg (3.1 g) and CH_3CN (230 mL). [From the hexane solution was recovered pure camphor ester in 85−90% yield.] After stirring at room temperature for 1.5 h, the reaction mixture was filtered over a Celite pad and washed the residue with CH_3CN (30 mL × 2). The filtrate was completely concentrated in vacuo to afford the amino alcohol **11**, which was generally found to be pure by ^{1}H NMR spectroscopy. If necessary, the crude product is redissolved in CH_3CN, dried with K_2CO_3, and evaporated in vacuo to afford 2.36 g (85% yield) of **11** as a colorless oil: IR (neat) 3354, 2986, 1602, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, J = 9.6, 4.4 Hz, 1 H, *H*C═CH), 5.94 (dd, J = 9.6, 4.4 Hz, 1 H, HC═C*H*), 4.41 (dd, J = 7.6, 3.6 Hz, 1 H, *H*C−OH), 4.16−4.13 (m, 2 H, O−C*H*−C*H*−O), 3.57 (t, J = 4.0 Hz, 1 H, *H*C−N), 2.24−2.15 (bs, 3 H, O*H*, NH_2), 1.40 (s, 3 H, H_3C−C−CH$_3$), 1.33 (s, 3 H, H$_3$C−C−CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.01, 131.58, 108.70, 79.76, 79.72, 68.45, 56.62, 26.58, 24.37; $[\alpha]^{25}_D$ +11.2° (*c* 0.75, CH_2Cl_2); high-resolution MS *m*/*e* calcd for $C_9H_{15}NO_3$ 185.2234, found 185.2235. Anal. Calcd for $C_9H_{15}NO_3$: C, 49.22; H, 6.20; N, 3.59. Found: C, 49.31; H, 6.16; N, 3.62.

(1*S*,2*S*,3*S*,6*R*)-3-((*t*-Butyldimethylsilyl)oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-nitrobenzenesulfonyl)amino)-cyclohexene-1,2-diol (12). To a solution of **11** (1.85 g, 10.0 mmol) and NEt_3 (4.2 mL, 30 mmol) in CH_3CN (20 mL) was added *p*-nitrobenzenesulfonyl chloride (2.3 g, 10 mmol). After the mixture was stirred at 25 °C for 8 h, a solution of DBU (2.3 mL, 15 mmol) and TBS−Cl (1.69 g, 11 mmol) in CH_3CN (10 mL) was added and the mixture was stirred further for a period of 9 h. The reaction was quenched with aqueous $NaHCO_3$, and CH_3CN was removed under vacuum. The aqueous solution was extracted with CH_2Cl_2 (40 mL × 3). The combined organic extracts were washed with dilute HCl and brine, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (silica gel, 20% EtOAc/hexane) to give 3.78 g (78%) of **12** as a white solid: mp 78−79 °C; IR (neat) 3280, 3106,1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2 H), 8.02 (d, J = 8.8 Hz, 2 H), 6.06 (dd, J = 9.6, 5.2 Hz, 1 H), 5.88 (d, J = 10.4 Hz, 1 H), 5.83 (dd, J = 9.6, 5.6 Hz, 1 H), 4.38 (dd, J = 7.2, 2.8 Hz, 1 H), 4.31 (dt, J = 7.2, 2.8, 1.6 Hz, 1 H), 4.16 (dd, J = 4.8, 1.6 Hz, 1 H), 3.95−3.93 (m, 1 H), 1.23 (s, 6 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.01, 147.27, 133.15, 130.30, 128.18, 124.30, 108.62, 78.21, 77.30, 66.18, 50.12, 26.09, 25.71, 24.32, 17.93, −4.80, −4.92; high-resolution MS (FAB+) *m*/*e* calcd for $C_{21}H_{32}N_2O_7SSi$ 485.1699. found 485.1704; $[\alpha]^{25}_D$ −23.0° (*c* 0.8, CH_2Cl_2). Anal. Calcd for $C_{21}H_{32}N_2O_7SSi$: C, 52.04; H, 6.65; N, 5.78. Found: C, 51.97; H, 6.56; N, 5.92.

(1*S*,2*S*,3*S*,4S,5S,6*S*)-5-Bromo-3-((*t*-butyldimethylsilyl)-oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-nitrobenzenesulfonyl)amino)cyclohexane-1,2,4-triol and (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-4-Bromo-3-((*t*-butyldimethylsilyl)oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-nitrobenzenesulfonyl)amino)cyclohexane-1,2,5-triol (13). To a solution of **12** (4.84 g, 10.0 mmol) in acetone (10 mL) and water (40 mL) was added NBS (2.67 g, 15 mmol). After stirring at 25 °C for 10 h, the reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with water, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (silica gel, 17% EtOAc/hexane) to give 5.71 g (98%) of **13** as a sticky solid (two regioisomers, found by 400 MHz ^{1}H NMR to be in a 3:2 ratio). Major isomer: mp 82−83 °C; IR (neat) 3528, 3277 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2 H), 8.06 (d, J = 8.8 Hz, 2 H), 6.20 (d, J = 10.4 Hz, 1 H), 4.43 (dd, J = 6.8, 3.2 Hz, 1 H), 4.31 (dd, J = 6.4, 3.6 Hz, 1 H), 4.20 (dd, J = 7.6, 3.6 Hz, 1 H), 4.05 (t, J = 2.4 Hz, 1 H), 3.85 (dd, J = 8.0, 2.4 Hz, 1 H), 3.76 (dt, J = 10.4, 3.2 Hz, 1 H), 1.42 (s, 3 H), 1.29 (s, 3 H), 0.93 (s, 9 H), 0.17 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.08, 146.14,

128.76, 124.09, 109.74, 78.43, 77.31, 76.10, 73.96, 56.99, 52.97, 26.46, 25.64, 23.93, 17.93, −5.02, −5.23; $[\alpha]^{25}_D$ −10.7° (*c* 1.5, CH_2Cl_2). Minor isomer: mp 99−100 °C; IR (neat) 3508, 3280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2 H), 8.10 (d, J = 8.8 Hz, 2 H), 5.68 (d, J = 8.8 Hz, 1 H), 4.25−4.20 (m, 2 H), 4.18 (dd, J = 9.2, 1.2 Hz, 1 H), 4.15−4.11 (m, 1 H), 3.80 (dd, J = 8.8, 6.8 Hz, 1 H), 3.62 (dq, J = 6.4, 1.6 Hz, 1 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 0.90 (s, 9 H), 0.19 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.97, 146.79, 128.55, 124.04, 110.19, 77.30, 72.96, 72.36, 59.96, 56.26, 27.31, 25.76, 25.64, 25.29, 18.02, −4.66, −4.74; $[\alpha]^{25}_D$ −50.7° (*c* 2.2, CH_2Cl_2); high-resolution MS (FAB+) *m/e* calcd for $C_{21}H_{33}BrN_2O_8SSi$ 581.0988, found 581.0984.

(1*S*,2*S*,3*S*,4*R*,5*R*,6*S*)-3-((*t*-Butyldimethylsilyl)oxy)-6-(*N*-(*o*-carbamoyloxypiperonyl)-*N*-(*p*-nitrobenzenesulfonyl)-amino)-4,5-epoxy-1,2-*O*-isopropylidenecyclohexane-1,2-diol (14a). To a solution of **13** (1.16 g, 2.0 mmol) and **6a** (0.66 g, 2.0 mmol) in CH_3CN (15 mL) was added K_2CO_3 (2.8 g, 20.0 mmol). The reaction mixture was heated at 60 °C for 4 h, allowed to cooled to room temaerature, and then concentrated in vacuo. The residue was taken in CH_2Cl_2 and washed with water, dilute HCl, and brine. The organic layer was dried, concentrated, and purified by flash chromatography (silica gel, 25% EtOAc/hexane) to give 1.32 g (88%) of **14a** as a white solid: mp 92−93 °C; IR (neat) 3105, 1725, 1531, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 2 H), 8.01 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 8.4 Hz, 1 H), 6.60 (d, J = 8.4 Hz, 1 H), 5.97 (d, J = 1.6 Hz, 1 H), 5.96 (d, J = 1.6 Hz, 1 H), 4.48 (s, 2 H), 4.40 (t, J = 8.8 Hz, 1 H), 4.10 (dd, J = 8.0, 6.8 Hz, 1 H), 3.69−3.64 (m, 2 H), 3.43−3.29 (m, 4 H), 3.11 (t, J = 4.4 Hz, 1 H), 3.01 (dd, J = 4.4, 3.2 Hz, 1 H), 1.24 (s, 3 H), 1.22 (t, J = 7.6 Hz, 3 H), 1.16 (t, J = 7.2 Hz, 3 H), 1.14 (s, 3 H), 0.85 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.54, 149.82, 149.05, 146.29, 139.52, 133.07, 128.72, 123.87, 122.84, 122.75, 109.71, 105.90, 102.20, 79.99, 74.07, 72.78, 61.91, 56.61, 53.46, 44.81, 42.55, 42.16, 26.77, 25.68, 24.18, 18.05, 14.12, 13.25, −4.82, −4.99; $[\alpha]^{25}_D$ −6.4° (*c* 4.0, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{34}H_{47}N_3O_{12}SSi$ 750.2728, found 750.2736. Anal. Calcd for $C_{34}H_{47}N_3O_{12}SSi$: C, 54.45; H, 6.32; N, 5.60. Found: C, 54.60; H, 6.54; N, 5.76.

(1*R*,2*R*,3*S*,4*R*,4a*R*,10b*S*)-1-Acetoxy-2-((*t*-butyldimethylsilyl)-oxy)-7-(*o*-carbamoyloxypiperonyl)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-5-(*p*-nitrobenzenesulfonyl)-1,1a,2,3,4,4a,6-heptahydrophenanthridine (15a). To a solution of epoxide **14a** (0.75 g, 1.0 mmol) in CH_2Cl_2 (50 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 0.2 mL). After the reaction mixture was stirred at 25 °C for 20 min, K_2CO_3 (1.73 g, 12.5 mmol) was added followed by the addition of a solution of DMAP (0.11 g, 0.9 mmol), pyridine (7.5 mmol), and acetic anhydride (0.8 mL, 8.5 mmol) in CH_2Cl_2. Stirring was continued for 6 h, and the reaction mixture was diluted with water (20 mL). The organic layer was washed with dilute HCl and brine. Concentration and purification by flash chromatography (silica gel, 17% EtOAc/hexane) to afford 0.77 g (98%) of **15a** as a white solid: mp 110−111 °C; IR (neat) 3112, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2 H), 7.96 (d, J = 8.8 Hz, 2 H), 6.50 (s, 1 H), 5.90 (dd, J = 4.0, 1.6 Hz, 2 H), 5.03 (dd, J = 8.4, 6.4 Hz, 1 H), 4.80 (d, J = 17.2 Hz, 1 H), 4.35 (t, J = 8.4 Hz, 1 H), 4.27 (dd, J = 8.4, 6.4 Hz, 1 H), 4.16 (d, J = 17.2 Hz, 1 H), 4.01−3.93 (m, 2 H), 3.43 (q, J = 7.2 Hz, 1 H), 3.37 (q, J = 7.2 Hz, 1 H), 3.05 (t, J = 6.4 Hz, 1 H), 2.03 (s, 3 H), 1.46 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.19 (t, J = 7.2 Hz, 3 H), 0.81 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.47, 152.10, 149.88, 148.65, 145.27, 138.30, 130.65, 128.80, 126.52, 123.81, 118.84, 109.78, 105.13, 102.06, 78.18, 74.44, 72.83, 72.18, 52.89, 42.70, 42.20, 40.23, 39.15, 27.45, 25.58, 25.18, 21.30, 17.89, 14.25, 13.31, −4.41, −4.90; $[\alpha]^{25}_D$ −26.9° (*c* 2.1, CH_2Cl_2); high-resolution MS (FAB+) *m/e* calcd for $C_{36}H_{49}N_3O_{13}SSi$ 792.2834, found 792.2831. Anal. Calcd for $C_{36}H_{49}N_3O_{13}SSi$: C, 54.60; H, 6.24; N, 5.30. Found: C, 54.54; H, 6.42; N, 5.50.

(1*R*,2*R*,3*S*,4*R*,4a*R*,10b*S*)-1-Acetoxy-2-((*t*-butyldimethylsilyl)oxy)-7-(*o*-carbamoyloxypiperonyl)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-1,1a,2,3,4,4a,5,6-octahydrophenanthridine (16). To a solution of **15a** (0.6 g, 0.76 mmol) in DMF (4.0 mL) was added LiOH (0.07 g, 3 mmol) followed by mercaptoacetic acid (0.11 mL, 1.52 mmol). After stirring at 25 °C for 1 h, the solution was diluted with ether (30 mL) and washed with aqueous $NaHCO_3$ followed by brine. The ether layer was dried, concentrated, and purified by flash chromatography (silica gel, 25% EtOAc/hexane) to afford 0.36 g (78%) of **16** as a white solid: mp 114−115 °C; IR (neat) 3330, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1 H), 5.93 (d, J = 1.6 Hz, 1 H), 5.89 (d, J = 1.6 Hz, 1 H), 5.13 (t, J = 9.6 Hz, 1 H), 4.15−4.08 (m, 2 H), 4.06 (d, J = 16.0 Hz, 1 H), 3.91 (d, J = 16.0 Hz, 1 H), 3.80 (dd, J = 9.2, 6.4 Hz, 1 H), 3.46 (dd, J = 1.6, 1.2 Hz, 1 H), 3.42−3.27 (m, 4 H), 2.81 (dd, J = 10.4, 3.2 Hz, 1 H), 1.95 (s, 3 H), 1.73 (br s, i H), 1.53 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H), 1.16 (t, J = 7.2 Hz, 3 H), 0.81 (s, 9 H), 0.12 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.54, 152.45, 146.96, 138.34, 130.96, 127.32, 122.13, 108.61, 107.26, 101.65, 80.20, 78.20, 76.15, 74.43, 53.44, 43.81, 42.47, 42.05, 39.32, 28.18, 26.22, 25.66, 21.37, 17.93, 14.15, 13.34, −4.20, −4.86; $[\alpha]^{25}_D$ +38.2° (*c* 1.9, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{30}H_{46}N_2O_9Si$ 607.3051, found 607.3054. Anal. Calcd for $C_{30}H_{46}N_2O_9Si$: C, 59.38; H, 7.64; N, 4.62. Found: C, 59.22; H, 7.69; N, 4.44.

(1*R*,2*R*,3*S*,4*R*,4a*R*,10b*S*)-1-Acetoxy-5-(*t*-butoxycarbonyl)-2-((*t*-butyldimethylsilyl)oxy)-7-(*o*-carbamoyloxypiperonyl)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-1,1a,2,3,4,4a-pentahydrophenanthridone (17). A solution of **16** (0.3 g, 0.5 mmol) and di-*tert*-butyl dicarbonate (0.12 g, 0.5 mmol) in CH_3CN (9 mL) was stirred at 25 °C until the starting amine disappeared on TLC (ca. 4 h). To this vigorously stirred solution was added CCl_4 (9 mL) followed by an aqueous solution of $NaIO_4$ (0.45 g in 13.5 mL H_2O) and $RuCl_3$ (20 mg, 0.10 mmol). After being stirred for 3 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), and the aqueous phase was extracted with CH_2Cl_2 (15 mL × 3) and EtOAc (15 mL × 3). The combined organic extracts were dried and concentrated in vacuo. The residue was diluted with ether (20 mL), filtered through a Celite pad, concentrated, and purified by flash chromatography (silica gel, 15%, 25%, and 33% EtOAc/hexane) to afford 0.24 g (67%) of **17** as a white solid: mp 100−101 °C; IR (neat) 1728 (broad), 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1 H), 6.04 (d, J = 0.8 Hz, 1 H), 6.02 (d, J = 0.8 Hz, 1 H), 5.34 (dd, J = 7.6, 3.2 Hz, 1 H), 4.83 (dd, J = 9.2, 5.6 Hz, 1 H), 4.25 (dd, J = 8.8, 7.2 Hz, 1 H), 4.00 (t, J = 7.6 Hz, 1 H), 3.83 (t, J = 7.2 Hz, 1 H), 3.46 (q, J = 6.8 Hz, 2 H), 3.42−3.29 (m, 2 H), 2.10 (s, 3 H), 1.52 (s, 9 H), 1.46 (s, 3 H), 1.24 (t, J = 7.6 Hz, 1 H), 1.23 (s, 3 H), 1.18 (t, J = 6.8 Hz, 1 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.03, 159.19, 152.84, 152.68, 152.23, 140.33, 135.27, 133.02, 117.81, 109.71, 103.55, 102.73, 83.19, 77.70, 75.29, 74.79, 72.89, 53.05, 42.26, 41.99, 41.91, 27.88, 27.26, 25.65, 25.14, 21.22, 17.98, 13.85, 13.17, −4.47, −4.92; $[\alpha]^{25}_D$ −11.9° (*c* 1.9, $CHCl_3$); high-resolution MS (FAB+) *m/e* calcd for $C_{35}H_{52}N_2O_{12}Si$ 721.3368, found 721.3371. Anal. Calcd for $C_{35}H_{52}N_2O_{12}Si$: C, 58.31; H, 7.27; N, 3.89. Found: C, 58.38; H, 6.98; N, 3.83.

(2*S*,3*S*,4*R*,4a*R*)-5-(*t*-Butoxycarbonyl)-2-((*t*-butyldimethylsilyl)oxy)-7-(*o*-carbamoyloxypiperonyl)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-2,3,4,4a-tetrahydrophenanthridone (18). To a solution of **17** (0.22 g, 0.3 mmol) in benzene (3 mL) was added DBU (0.45 mL, 3 mmol). After being heated at 70 °C for 40 h, the reaction mixture was cooled, diluted with ether (15 mL), and washed with aqueous $NaHCO_3$ followed by brine. Drying, solvent evaporation, and silica gel chromatography (elution with 15% EtOAc/hexane) gave 0.19 g (96%) of **18** as a white solid: mp 202−203 °C; IR (neat) 1730 (broad), 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1 H), 6.17 (t, J = 2.8 Hz, 1 H), 6.05 (d, J = 1.2 Hz, 1 H), 6.04 (d, J = 1.2 Hz, 1 H), 4.76 (dt, J = 8.0, 2.4 Hz, 1 H), 4.36 (dt, J = 5.6, 2.4 Hz, 1 H), 4.05 (t, J = 8.0

Hz, 1 H), 3.96 (dd, J = 8.0, 6.4 Hz, 1 H), 3.61−3.25 (m, 4 H), 1.51 (s, 9 H), 1.45 (s, 3 H), 1.27 (t, J = 7.6 Hz, 1 H), 1.26 (s, 3 H), 1.19 (t, J = 7.2 Hz, 1 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.10, 153.52, 153.06, 152.53, 141.56, 134.79, 129.72, 128.38, 127.43, 115.14, 111.44, 102.80, 98.88, 83.14, 79.81, 79.76, 73.68, 57.56, 42.20, 41.99, 27.71, 26.91, 25.86, 25.03, 18.19, 13.69, 13.12, −4.50, −5.02; $[\alpha]^{25}_D$ +1.3° (*c* 3.1, $CHCl_3$); high-resolution MS (FAB+) *m/e* calcd for $C_{33}H_{48}N_2O_{10}Si$ 661.3078, found 661.3083. Anal. Calcd for $C_{33}H_{48}N_2O_{10}Si$: C, 59.98; H, 7.32; N, 4.24. Found: C, 60.19; H, 7.18; N, 4.27.

(+)-Narciclasine 1. To a solution of **18** (0.10 g, 0.15 mmol) in THF was added 60% HCOOH (8 mL) at 25 °C, and the mixture was heated at 60 °C for 45 min. After solvent evaporation, the residue was dissolved in dry THF (20 mL) and a solution of $LiAlH_4$ (1.0 M in THF, 0.75 mL) was introduced dropwise. After the reaction mixture was stirred at room temperature for 12 h, the reaction was quenched with aqueous Na_2SO_4 solution and acidified with dilute HCl. The product was extracted with EtOAc (5 × 15 mL). Drying, solvent evaporation, and silica gel chromatography (elution with 15% EtOAc/hexane) gave 0.06 g (65%) of **1** as a white solid: mp 246 °C dec (lit.[2c] 216 °C dec; lit.[3b] 248 °C dec; lit.[11a] 217−221 °C; lit.[11b] 250−251 °C dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.90 (s, 1 H), 6.85 (s, 1 H), 6.14 (t, J = 2.8 Hz, 1 H), 6.074 and 6.070 (2s, 2 H), 5.26−5.16 (m, 2 H), 5.04 (br s, 1 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.01 (br s, 1 H), 3.78 (d, J = 8.0 Hz, 1 H), 3.69 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.97, 152.38, 144.85, 133.46, 132.16, 129.28, 124.78, 105.58, 102.11, 95.86, 72.40, 69.17, 68.85, 52.92; $[\alpha]^{25}_D$ +126.5° (*c* 0.5, MeOH) [lit.[2c] +112° (*c* 0.57, MeOH); lit.[3b] +141.8°; lit.[11a] +142.8° (*c* 0.7, MeOH); lit.[11b] +145° (*c* 1.5, EtOH)].

Acknowledgment. Support from the National Science Council of the Republic of China (NSC 90-2113-M-005-017) is gratefully acknowledged.

JO020155K