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Preparation and conversion of chiral *O*-isopropylidene-protected 4-aminocyclohexenol to various key intermediates toward narcissus alkaloids

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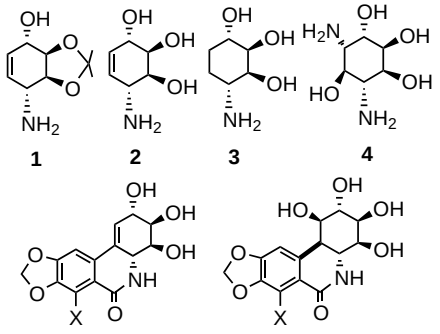
Abstract—Enantiomerically pure 4-amino-5,6-*O*-isopropylidenedioxycyclohex-2-en-1-ol, conveniently prepared by the union of *O*-isopropylidenedioxycyclohexadiene with camphor-based chloronitroso ester, was employed in the synthesis of versatile key intermediates toward narcissus alkaloids.

Chiral *O*-isopropylidene-protected 4-aminocyclohexenol **1** is an ideal substrate in the construction of narcissus ring skeleton as it has close relations both structurally and stereochemically. But most of the uses have been demonstrated for aminocyclitol derivatives such as conduramine A-1 **2**, dihydroconduramine A-1 **3** and *cis*-1,3-diamino-1,3-dideoxycyclitols **4**,[1] and a few reported applications deal with the asymmetric synthesis of (+)-lycoricidine only.[2]



1 **2** **3** **4**

X = H: **Lycoricidine** X = H: **Deoxypancratistatin**
X = OH: **Narciclasine** X = OH: **Pancratistatin**

As part of an effort directed toward the asymmetric synthesis of narcissus alkaloids, we had the occasion to develop possible protocols for the asymmetric formation of **1**. We report here the preparation of an enantiomerically pure **1** and its efficient transformation to versatile key intermediates toward narcissus alkaloids such as lycoricidine, narciclasine, and pancratistatin. Camphor-based chiral controller molecules have previously been shown to exhibit high asymmetric induction in aldol addition and cycloaddition reactions.[4a,b] We envisioned employing the chiral chloronitroso **6a** derived from camphor-based keto ester **6** as a practical dienophile synthon in the asymmetric cycloaddition step as the nitroso functionality in **6a** is rigidly fixed because of the camphor skeleton.[4c] The requisite chloronitroso **6** was readily prepared from the ketopinic acid via a three-step protocol: (a) esterification ($SOCl_2$/MeOH), (b) formation of oxime ($HONH_2{\cdot}HCl$/MeOH/NaOAc), and (c) oxidation (*t*-BuO-Cl/CH_2Cl_2). The overall isolated yield of **6** from ketopinic acid is 88%. One-pot treatment of a cooled (0°C) solution of **6a** in CH_2Cl_2 with diene **5**[3] for 12 h, followed by water treatment at 25°C for 3 h to effect hydrolysis of the resulting adduct; the aqueous layer containing **7** after hexane wash was treated with activated Al(Hg)/acetonitrile at 10–15°C for 2 h to provide a 86% isolated yield of chiral conduramine **1**[5] (Scheme 1). While hydrolysis of the cycloaddition adduct led to the desired oxazine hydrochloride **7**, keto ester **6** could be recovered in 93% yield by hexane extraction of the aqueous reaction mixture. The enantiomeric purity 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 **7** 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 **7** showing the enantiomeric purity in >99%. To have a look at the synthetic efforts expended for this kind of molecule in the literature, Ogawa and Weinreb, in their approach to **3** utilized the protected conduramines being synthesized in eight steps

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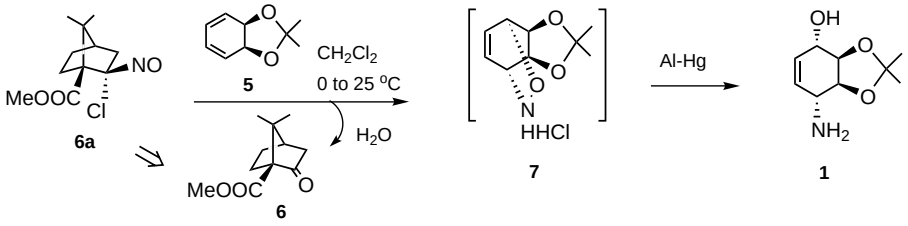
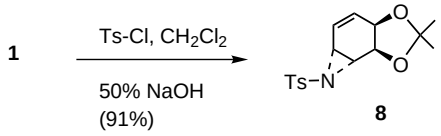


Scheme 1. Preparation of enantiopure *O*-isopropylidene-protected 4-aminocyclohexenol **1**.

from D-glucose and in twelve steps from L-arbinose, respectively.[2b,c] Enzymatic resolution of halobenzenes was employed by Hudlicky efficiently to achieve optically pure conduramines and later this protocol was applied in his total synthesis of (+)-lycoricidine.[2a]

With enantiopure conduramine **1** in hand, we present the following preliminary examples of its transformations to illustrate the broad range of applications (Scheme 2). Chiral vinyl *N*-*p*-toluenesulfonyl aziridine **8** has been demonstrated to be a key intermediate for the enantioselective synthesis of (+)-pancratistatin.[6] In a most interesting and productive retrosynthetic maneuver, intermediate **8** could be traced in one step from 4-amino alcohol **1**. We now describe a one-step transformation of **1** to the desired chiral aziridine **8**. Indeed, reaction of **1** (1 mmol) and *p*-toluenesulfonyl chloride (2.3 mmol) in the presence of 50% NaOH (4 mL) and *n*-Bu_4NHSO_4 (0.05 mmol) at room temperature in CH_2Cl_2 for 8 h gave a 91% isolated yield of vinylaziridine **8**[7], $[\alpha]_D^{25}$ −183.1 (*c* 0.6, CH_2Cl_2) [lit.[6b] $[\alpha]_D^{25}$ −183 (*c* 2.3, $CHCl_3$)], as shown in Scheme 2. This high-yielding route just under aqueous condition to effect conversion of **1** to **8** represents an attractive alternative to the literature method.[6b,8]

For construction of the tricyclic framework of narcissus alkaloids, we envisioned the introduction of the piperonyl moiety on the nitrogen of the amino alcohol **1** followed by tosylation and intramolecular arylation. Thus, tosylamide **10a** was readily available in 92% yield from **1** upon doing tosylation initially followed by piperonylation (Scheme 3). Intramolecular cyclization

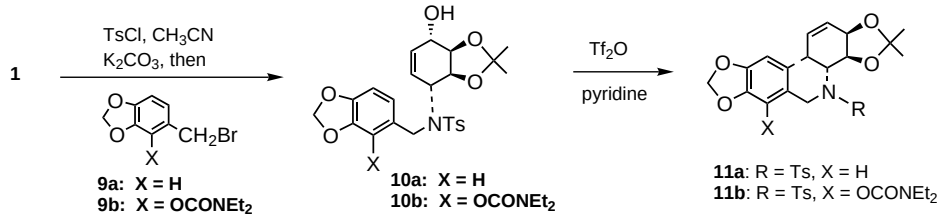


Scheme 2. Conversion of **1** to **8**.

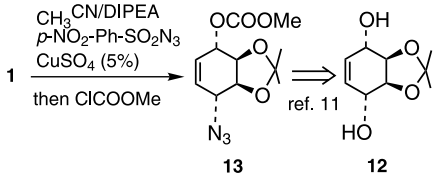
of tosylamide **10a** was effected using triflic anhydride (2.5 equiv.) in the presence of an organic base pyridine (8 equiv.) in dichloromethane at −40°C for 1 h and at 0°C for 4 h leading to the tricyclic molecule **11a** (81% yield) as expected.[9] Piperonyl moiety with an additional carbamate function was also briefly explored. Thus, cyclization onto **10b** was equally effective to yield the desired tricyclic *N*-Ts sulfonamide **11b**[10] (76% yield), being important in the case of narciclasine. NOE examination of the cyclized derivatives revealed that only *cis* fusion occurred against the required *trans* fusion for saturated alkaloids like pancratistatin and deoxypancratistatin. Now efforts are underway to functionalize the double bond and to oxidize the benzylic methylene thereby establishing a new method for narciclacine and lycoricidine. To further demonstrate the synthetic utility of the chiral conduramine **1**, attention was directed to develop an efficient transformation of **1** to the unsaturated azido-carbonate **13**, a key intermediate toward (+)-pancratistatin. Trost has used the palladium-catalyzed desymmetrization of unsaturated cyclic 1,4-diol **12** in an enantioselective synthesis of chiral azide **13**.[11] We envisioned employing diazotransfer on the amine followed by acylation of the alcohol to prepare azido-carbonate **13** (Scheme 4). Thus, treatment of a CH_3CN solution of 1,4-amino alcohol **1** (1 equiv.), 4-nitrobenzenesulfonyl azide (1 equiv.), and DIPEA (2.5 equiv.) with a catalytic amount of anhydrous $CuSO_4$ (5%) at 0°C for 1.5 h followed by direct esterification at 0°C (6 h) with methyl chloroformate (3 equiv.) afforded the desired azido-carbonate **13** (84%).[12]

This one-pot conversion of amino alcohol into the azido-carbonate **13** is noteworthy for its simplicity and efficiency.

The findings reported herein provide critical information for extensive applications of unsaturated 1,4-amino alcohol **1** for narcissus alkaloids. We plan to report some interesting synthetic applications toward the total synthesis from **1** in the near future.



Scheme 3. Construction of tricyclic framework of narcissus alkaloids.



Scheme 4. A one-step conversion of **1** to **13**.

Acknowledgements

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5. Selected data for **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, $J=9.6$, 4.4 Hz, 1H, *H*C=CH), 5.94 (dd, $J=9.6$, 4.4 Hz, 1H, HC=C*H*), 4.41 (dd, $J=7.6$, 3.6 Hz, 1H, *H*C-OH), 4.16–4.13 (m, 2H, O-C*H*-C*H*-O), 3.57 (t, $J=4.0$ Hz, 1H, *H*C-N), 2.24–2.15 (bs, 3H, O*H*, NH_2), 1.40 (s, 3H, H_3C-C-CH$_3$), 1.33 (s, 3H, H$_3$C-C-CH_3).
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7. Selected data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $J=6.8$ Hz, 2H), 7.31 (d, $J=6.8$ Hz, 2H), 5.91 (ddd, $J=10.0$, 4.4, 0.8 Hz, 1H), 5.72 (ddd, $J=10.0$, 2.0, 0.8 Hz, 1H), 4.50 (dd, $J=6.4$, 1.6 Hz, 1H), 4.36 (dt, $J=6.8$, 2.0 Hz, 1H), 3.34 (dd, $J=6.4$, 1.6 Hz, 1H), 3.23 (dd, $J=6.4$, 4.4 Hz, 1H), 2.41 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H).
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10. Selected data for **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, $J=8.0$ Hz, 2H), 7.16 (d, $J=8.0$ Hz, 2H), 6.51 (s, 1H), 6.39 (s, 1H), 6.05 (dd, $J=10.0$, 5.2 Hz, 1H), 5.92 (dd, $J=9.6$, 3.6 Hz, 1H), 5.85 (s, 2H), 4.63 (d, $J=16.8$ Hz, 1H), 4.54 (dd, $J=4.4$, 4.0 Hz, 1H), 4.27 (d, $J=16.8$ Hz, 1H), 4.26–4.21 (m, 2H), 3.48 (dd, $J=4.8$, 4.4 Hz, 1H), 2.34 (s, 2H), 1.45 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 146.88, 146.20, 143.20, 136.78, 131.33, 129.33, 128.59, 127.55, 125.67, 124.85, 109.51, 107.37, 106.11, 100.96, 72.31, 71.55, 53.81, 44.02, 36.46, 27.89, 26.13, 21.41; $[\alpha]_D^{25}$ −101.7 (*c* 1.7, CH_2Cl_2).
11. Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc*. **1995**, *117*, 10143 and references cited therein.
12. Selected data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, $J=10.0$, 2.8 Hz, 1H), 5.73 (dt, $J=10.0$, 2.8 Hz, 1H), 5.13 (m, 1H), 4.30 (dd, $J=8.0$, 4.8 Hz, 1H), 4.14 (dd, $J=7.6$, 6.0 Hz, 1H), 3.97 (m, 1H), 3.81 (s, 3H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.88, 128.61, 127.33, 109.93, 76.59, 76.11, 75.32, 60.63, 55.02, 27.01, 24.72, $[\alpha]_D^{25}$ −33.8 (*c* 0.9, CH_2Cl_2) [lit.[11]. $[\alpha]_D^{25}$ −34.0 (*c* 2.1, CH_2Cl_2)]; high-resolution MS (FAB+) *m*/*e* Calcd for $C_{11}H_{16}N_3O_5$: 270.1089. Found: 270.1093.