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A Versatile Strategy for Divergent and Diastereoselective Synthesis of Natural Product-Like Polyhydroxylated Indolizidines

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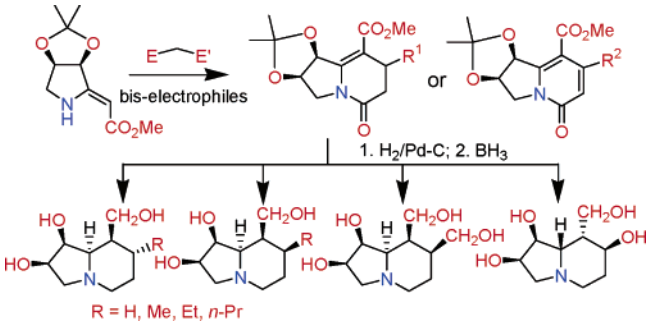

A general and versatile method for the divergent and diastereoselective synthesis of polyhydroxylated indolizidines has been established. The annulation reactions of a readily available enantiopure dihydroxylated cyclic secondary enamine with α,β-unsaturated carboxylates including methyl acrylate, methyl crotonate, methyl 2-hexenoate, allenoate, and dimethyl acetylenedicarboxylate and with malonyl chloride produced hexahydro- or tetrahydro-5-indolizinone-8-carboxylates in high yields. The resulting 5-indolizinone derivatives were converted into diverse polyhydroxylated indolizidines in good yields through practical hydrogenation and reduction reactions.

Introduction

Polyhydroxylated indolizidine alkaloids,[1] such as lentiginosine **1**,[2] swainsonine **2**,[3] castanospermine **3**,[4] and 7-deoxy-6-epi-castanospermine **4**[5] (Figure 1), have attracted continued interest from both organic and medicinal chemists owing to their unique structures and powerful biological activities.[1] For example, swainsonnine and castanospermine have potent inhibitory action toward various glycosidase enzymes[6] and therefore exhibit considerable anti-HIV,[7] antimetastatic immunoregulating,[8] antitumor, and anticancer activities.[9] Although the synthesis of the naturally occurring polyhydroxylated indolizidines is increasing, one of the recent developments in this field is the construction of novel derivatives, including compounds **5**,[10a] **6**,[10b] **7**,[10c] and **8**,[10d] in order to search for glycosidase inhibitors of improved biological activity and of diminished toxicity. In literature, very large numbers of studies on the synthesis of both natural and un-natural polyhydroxylated indolizidines have been reported.[1,11] The majority of these known syntheses are based on one-directional synthetic strategy using carbohydrates as the starting materials,[12] although asymmetric synthesis through noncarbohydrate substrates is becoming popular.[13] To meet the ever-growing demands for diverse polyhydroxylated indolizidine derivatives in the structure−activity relationship study and in

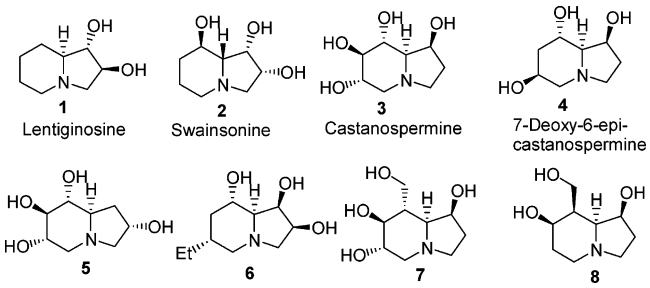

FIGURE 1. Some polyhydroxylated indolizidine alkaloids and their analogues.

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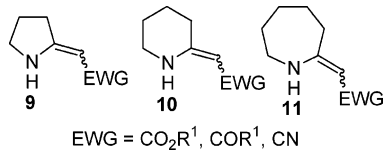
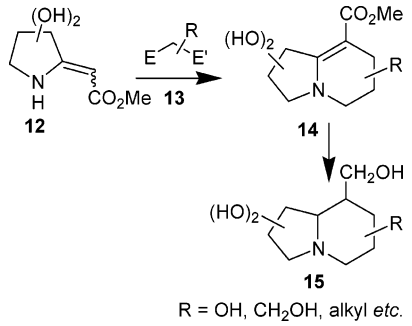


FIGURE 2. Heterocyclic secondary enamines.

SCHEME 1. General Strategy for Synthesis of Polyhydroxylated Indolizidines from Hydroxylated Heterocyclic Enaminoester

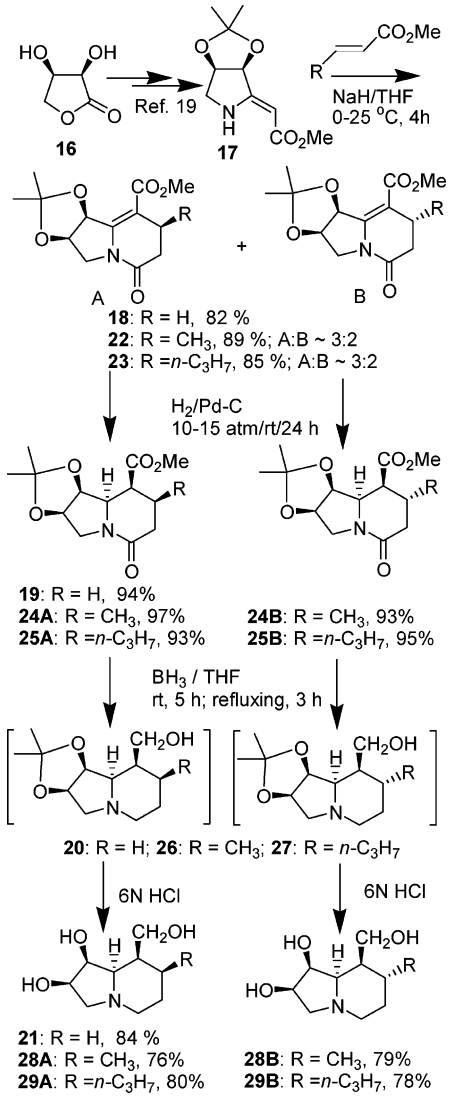


the drug discovery, a general and efficient method that could deliver different isomers and analogues is of highly importance.

Heterocyclic secondary enamines, such as enamino esters **9**−**11** (Figure 2), are the versatile building blocks for the preparation of fused *N*-heterocycles.[14] For example, we have previously shown that enamines **9**−**11** underwent annulation reactions with ethyl propiolate,[15] dimethyl acetylenedicarboxylate (DMAD),[15] and malonyl chloride[16] to afford various tetrahydro-5-indolizinones. Having considered the highly efficient and controllable annulation reactions, we envisioned that the dihydroxyl heterocyclic enaminoester **12** could be the versatile intermediates for the preparation of polyhydroxylated indolizidines bearing additional substituents on the fused ring skeleton, which are not readily obtainable by other methods (Scheme 1). Herein, we report a general and useful divergent and diastereoselective synthesis of new polyhydroxylated indolizidines from the easily available protected dihydroxylated enaminoester **17** and biselectrophilic reagents.

To assemble the same stereochemistry of the five-membered ring in swainsonine, the enantiopure methyl (3*S*,4*R*)-3,4-isopropylidenedioxypyrrolidin-2-ylidene acetate **17** was prepared following a literature method[17] from commercially available D-erythronic acid γ-lactone **16** that can be obtained in a large scale by oxidation of the very cheap D-(−)-isoascorbic acid.[18] We first studied the reaction of enamine **17** with electron-deficient olefins. In the presence of NaH at 0 °C to ambient temperature, enamine **17** and methyl acrylate underwent Michael addition followed by intramolecular cyclization to provide hexahydroindolizinone-8-carboxylate **18** in 82% yield. Palladium-catalyzed hydrogenation under atmospheric pressure did not reduce the carbon−carbon double bond of **18**. Efficient reduction was performed at 10−15 atm, affording 94% yield of octahydroindolizinone **19**. The hydrogenation occurred from the less sterically hindered face of fused heterocycles. Reduction of carbonyls of **19** using borane−dimethyl sulfide or $LiAlH_4$ only gave a mixture of **20** and amide-reduced product. The complete reduction of both amide and ester carbonyls was finally achieved by using a large excess amount of fresh prepared borane. After treatment of the crude product with 6 N HCl, (1*S*,2*R*,8*S*,9*R*)-octahydro-8-hydroxymethyl-1,2-indolizinediol **21** that was a homologous of 8-episwainonine was obtained in 84% yield (Scheme 2). We then tried the annulation of **17** with methyl crotonate and with methyl 2-hexenoate under identical condi-

SCHEME 2. Preparation of Homologues of 8-Episwainonine and 7-Alkyl-8-hydroxymethyl-1,2-indolizinediols from Enaminoester 17 and Alkenoates



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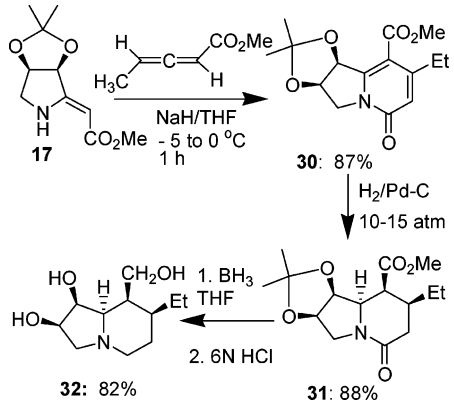
SCHEME 3. Preparation of 7-Alkyl-8-hydroxymethyl-1,2-indolizinediols from Enaminoester 17 and Allenoate



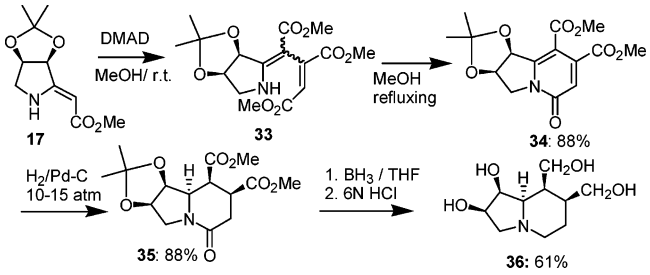
tions as those for methyl acrylate in order to introduce an additional substituent at the 7 position. The reaction proceeded smoothly and efficiently to afford products **22** and **23**, respectively. Unfortunately, the diastereoselectivity was low with the ratio of (7*S*) isomer **A** over (7*R*) isomer **B** being around 3:2. The pairs of diastereoisomers of **22** and **23** can be separated by column chromatography, and the structure of major product **22A** that featured the alkyl group and dioxy substituents in a cis relationship was determined by X-ray diffraction study (See Supporting Information, Figure S1). Similar stereospecific hydrogenation, exhaustive reduction followed by deprotection of hydroxyl groups in **26** and **27**, gave enantiomeric pure 7-alkylated 8-homoswainonine stereoisomers **28A**, **28B**, **29A** and **29B**, in good yields (Scheme 2).

It is worth noting that the chiral moiety of **17** showed weak unsymmetrical induction in the addition reactions, but it has a remarkable induction effect in the following hydrogenation process. All hexahydro-5-indolizinone **18**, **22**, and **23** produced predominantly one diastereoisomer (**19**, **24**, and **25**, respectively), even if 7-alkyl group has an opposite steric hindrance to the double bond (**22B** and **23B**). (See Figure S2 in Supporting Information for crystal structure of **24B**)

Since the annulation reaction of **17** with α,β-unsaturated carboxylates gave two diastereoisomers of hexahydroindolizinones with poor selectivity, a highly diastereoselective synthesis of 7-substituted 8-homoswainonine derivatives was explored by taking the advantage of highly selective hydrogenation reaction. We then synthesized the hexahydro-5-indolizinone **30** in high yield from annulation reaction of **17** with methyl allenoate. Gratifyingly, hydrogenation of **30** afforded the fully cis-substituted octahydroindolizinone **31** as a single diastereoisomer, which was converted into 7-ethyl-8-hydroxymethylindolizine-1,2-diol **32** in good yield by borane reduction and deprotection (Scheme 3).

Encouraged by the highly diasteroselective synthesis of **32**, we then extended our synthesis to tetrahydroxylated indolizidine derivatives. At ambient temperature, the reaction of **17** with DMAD proceeded rapidly to form a yellow-colored compound, which was isolated and identified as the adduct **33** of **17** to DMAD. In warm methanol, the intermediate **33** was converted smoothly and efficiently into 5-indolinzinone-7,8-dicarboxylate **34** in a total yield of 88% from enamine **17**. Hydrogenation of **34** employing the aforementioned reaction conditions gave a fully cis-substituted product **35**, whose structure was confirmed by the single-crystal X-ray diffraction analysis (See Supporting

SCHEME 4. Preparation of 7,8-Dihydroxymethyl-1,2-indolizinediols from Enaminoester 17 and DMAD



Information, Figure S3). Simple operations comprising complete reduction and deprotection yielded tetrahydroxylated indolizidine product **36** in 61% yield (Scheme 4).

To synthesize 7-hydroxyl-8-homoswainsonine **40**, we first prepared 7-hydroxyl-5-indolinzinone-8-carboxylate **37** in 81% yield by treating cyclic enamine **17** with malonyl dichloride. The hydrogenation of **37** produced two reduction products **38A** and **38B** in a total yield of 74%. Surprisingly, in contrast to the catalytic hydrogenation of **30** and **34**, which all formed fully cis-substituted reduction products, the same catalytic hydrogenation of **37** led to the formation of the (7*S*,8*S*) diastereoisomer **39A** as the major product in 63% yield, while the (7*S*,8*R*) diastereoisomer **39B**, the expected all-cis-configured product, was isolated only in 11% yield. The structure of **39A** was unambiguously determined by X-ray diffraction analysis (See Figure S4 in Supporting Information). The unusual stereoselective hydrogenation of **37** suggested a directing effect of a free hydroxyl group of **38**, which was generated from the initial hydrogenation of **37**. In other words, the free hydroxyl group most probably interacted with catalyst to accelerate the hydrogenation from the same side of the hydroxyl group. Similar hydroxyl-directed homogeneous[19a−c] and heterogeneous[19d,e] hydrogenation of carbon−carbon double bonds were reported in literatures. It is interesting to note that no directing effect was observed in the catalytic hydrogenation of 7-methoxycarbonyl substituted 5-indolinzinone **34**. 7-Hydroxyl-8-homoswainsonine **40A** was obtained from reduction and deprotection of **39A** (Scheme 5).

In summary, we have provided a new strategy for the divergent synthesis of chiral polyhydroxylated indolizidine compounds. Being different from the well-documented methods that mainly require the preformation of a polyhydroxylated chain or heterocycle, our cyclic enamine protocol showed versatility in the construction of indolizidines bearing multihydroxyl, hydroxymethyl, and alkyl groups in a highly diastereoselective manner. The easy availability of chiral dihydroxyl heterocyclic enaminoester, cheap and ready available biselectrophilic reagents, and simple chemical manipulations render our approach powerful and practical in the synthesis of diverse polyhydroxylated indolizidines. Having considered the easy access to various chiral cyclic enamines from carbohydrates or synthetic γ- and δ-lactones and their annulation reactions with numerous bise-

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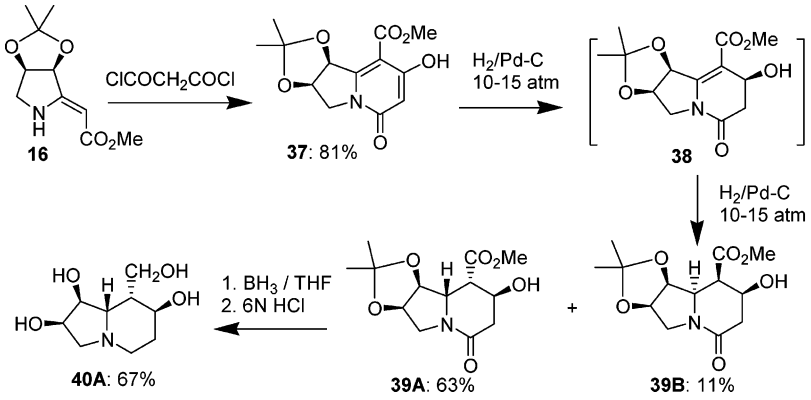
SCHEME 5. Preparation of 7-Hydroxyl-8-homoswainsonine from Enaminoester 17 and Malonyl Dichloride



lectrophiles, the generation of polyhydroxylated pyrrolizidines, indolizidines, and quinolizidines at will can be anticipated in future.

Experimental Section

1. Reaction of Heterocyclic Enamine 17 with Methyl Acrylate. Under nitrogen atmosphere, a solution of heterocyclic enamine **17** (213 mg, 1 mmol) in dry THF (10 mL) was added dropwise to the suspension of NaH (24 mg, 0.5 mmol, 50% in mineral oil) in THF (10 mL) cooled in an ice bath. The resulting mixture was stirred at 0 °C until no evolution of hydrogen gas. To this mixture, the solution of methyl acrylate (108 mg, 1.25 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for another 4 h at ambient temperature. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (4:1 to 1:1) to give hexahydro-5-indolizinone-8-carboxylate **18** in 82% yield.

Methyl (1*S*,2*R*)-1,2-*O*-Isopropylidenedioxy-1,2,3,5,6,7-hexahydro-5-indolizinone-8-carboxylate 18. 219 mg, 82%, 122−123 °C, $[\alpha]_D^{20} = -204.3^o$ ($c = 0.635$, $CHCl_3$). IR ν (cm^{-1}) 1700, 1675, 1656; ^{1}H NMR δ (ppm) 5.75 (d, $J = 6.1$ Hz, 1H), 4.84 (dt, $J =$ 5.9, 1.7 Hz, 1H), 3.97(dd, $J = 13.1$, 1.6 Hz, 1H), 3.81 (s, 3H), 3.77 (dd, $J = 13.1$, 5.8 Hz, 1H), 2.78−2.84 (m, 1H), 2.56−2.65 (m, 3H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C NMR δ (ppm) 169.0, 166.2, 149.9, 112.4, 105.0, 80.3, 75.1, 51.7, 50.9, 30.4, 27.2, 25.4, 21.5. MS (FT-ICR): 268 (M+1). Anal. Calcd for $C_{13}H_{17}NO_5$ C 58.42, H 6.41, N 5.24; Found: C 58.43, H 6.50, N 5.08.

2. Hydrogenation of the Hexahydro-5-indolizinone-8-carboxylate 18. The hexahydro-5-indolizinone **18** (200 mg, 0.75 mmol) was dissolved in methanol (20 mL), and palladium on activated carbon (10%) (0.2−0.5 g) was added. The reaction mixture was stirred under hydrogen (10−15 atm) for 24 h at room temperature. The catalyst was filtered off and washed with methanol (2 × 10 mL). The filtrate was concentrated under vacuum, and the residue was purified on a silica gel column eluting with ethyl acetate and acetone (9:1) to give octahydro-5-indolizinone **19** in 94% yield.

Methyl (1*S*,2*R*,8*S*,8a*R*)-1,2-*O*-Isopropylidenedioxy-octahydro-5-indolizinone-8-carboxylate 19. 190 mg, 94%, mp 90−93 °C, $[\alpha]_D^{20} = -114.3^o$ ($c = 0.545$, $CHCl_3$). IR ν (cm^{-1}) 1732, 1626; ^{1}H NMR δ (ppm) 4.78 (t, $J = 5.5$ Hz, 1H), 4.67 (t, $J = 5.2$ Hz, 1H), 4.42 (d, $J = 13.3$ Hz, 1H), 3.77 (s, 3H), 3.67 (dd, $J = 7.4$, 3.6 Hz, 1H), 3.09−3.12 (m, 1H), 2.90 (dd, $J = 13.2$, 4.4 Hz, 1H), 2.60 (dt, $J = 16.4$, 3.9 Hz, 1H), 2.13−2.30 (m, 3H), 1.37 (s, 3H), 1.26 (s, 3H); ^{13}C NMR δ (ppm) 171.7 169.8, 111.8, 80.5, 77.6, 60.0, 52.0, 50.0, 39.4, 31.2, 26.0, 24.3, 22.4; MS (EI): 152 (100), 194 (95), 211 (50), 270 (M+1, 92%). Anal. Calcd for $C_{13}H_{19}NO_5$: C 57.98, H 7.11, N 5.20; Found: C 57.93, H 7.04, N 5.22.

3. Reduction and Deprotection of the Octahydro-5-indolizinone-8-carboxylate 19. At ambient temperature, boron trifluoride etherate (ca. 48% BF_3, 15 mL, 57 mmol) was added dropwise very slowly to the suspension of $NaBH_4$ (4.0 g, 105 mmol) in dry THF (20 mL) within 2 h. During this period, the borane gas generated was continuously bubbled into the solution of octahydro-5-indolizinone-8-carboxylate **19** (135 mg, 0.5 mmol) in THF (10 mL). After addition of boron trifluoride, the mixture of $NaBH_4$ with boron trifluoride in THF was warmed to 60−70 °C, and the vapor of borane ether complex was bubbled into the solution of **19**. The reaction mixture was stirred at room temperature for 3 h and then refluxing for another 3 h. The reaction mixture was cooled in an ice bath, and 10 mL of methanol was added to quench the reaction (Caution: hydrogen evolution). After removal of the solvent, the thick oily residue was dissolved in methanol (20 mL) and refluxed for 3 h to decompose the boron complex of product. The volatiles were removed again under vacuum, and the pure 1,2-*O*-isopropylidenedioxy-octahydroindolizine **20** was isolated by chromatography on a neutral aluminum oxide column eluting with ethyl acetate. Deprotection procedure was performed by the treatment of **20** with 6 N HCl (10 mL) at room temperature for 4 h. The acidic reaction mixture was basified using Na_2CO_3 powder to pH 9 and then concentrated under vacuum to dryness. The octahydro-8-hydroxymethyl-1,2-indolizinediol **21**, a homologous of 8-episwainonine, was isolated in 84% yield from repeating extraction of inorganic salts with dichloromethane (10 × 10 mL).

(1*S*,2*R*,8*S*,9*R*)-Octahydro-8-hydroxymethyl-1,2-indolizinediol 21. 79 mg, 84%, oil, $[\alpha]_D^{20} = -23.8^o$ ($c = 0.630$, $CHCl_3$). IR ν (cm^{-1}) 3279; ^{1}H NMR δ (ppm) 4.10−4.72 (br, 3H), 4.29 (dd, $J =$ 5.5, 3.8 Hz, 1H), 4.28−4.30 (m, 1H), 4.20 (t, $J = 5.1$ Hz, 1H), 4.13 (dd, $J = 10.9$, 8.1 Hz, 1H), 3.17 (d, $J = 10.7$ Hz, 1H), 3.07 (dd, $J = 11.0$, 1.9 Hz, 1H), 2.42 (brs, 1H), 2.26 (brs, 1H), 2.20 (d, $J = 2.8$ Hz, 1H), 2.01 (brs, 1H), 2.01−2.07 (m, 1H), 1.80 (dd, $J =$ 11.0, 1.9 Hz, 1H), 1.59−1.68 (m, 1H), 1.46−1.54 (m, 2H); ^{13}C NMR δ (ppm) 72.0, 69.3, 63.1, 62.6, 61.8, 54.7, 37.5, 29.9, 21.7. HRMS (ESI-TOF): 187.1210, $C_9H_{17}NO_3$ required 187.1208.

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Supporting Information Available: The experimental procedures for preparation of polyhydroxylated indolizidines **21**, **28**, **29**, **32**, **36**, and **40**, full characterization and copies of ^{1}H NMR and ^{13}C NMR spectra of all isolated products **18**−**40**, excluding the 1,2-*O*-isopropylidene protected polyhydroindolizidines such as **20**, **26**, and **27**, as well as single-crystal data of **22A**, **24B**, **35**, and **39A** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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