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A concise synthetic method towards (−)-swainsonine and its 8-epimer by using palladium-catalyzed asymmetric hydroamination of alkoxyallene as the key strategy

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ABSTRACT

A concise and flexible formal synthesis of (−)-swainsonine and the 8-epimer is reported. The synthesis features sequential Pd-catalyzed asymmetric hydroamination of alkoxyallene and the Ru-catalyzed ring-closing-metathesis as the key strategy, which generates cyclic allylic *N,O*-acetal as the pivotal intermediate. Notably, this reaction could be performed on a multigram-scale. In addition, both the natural product and its 8-epimer could be obtained with comparable synthetic efficiency.

1. Introduction

Over the past decades, polyhydroxylated indolizidine alkaloids have drawn considerable attention from the field of synthetic organic chemistry because of their unique biological activities.[1] A series of these indolizidine alkaloids including (−)-swainsonine, (+)-castanospermine, (−)-lentiginosine, (−)-uniflorine-A, and (−)-steviamine are commonly found in plants and fungi (Fig. 1).

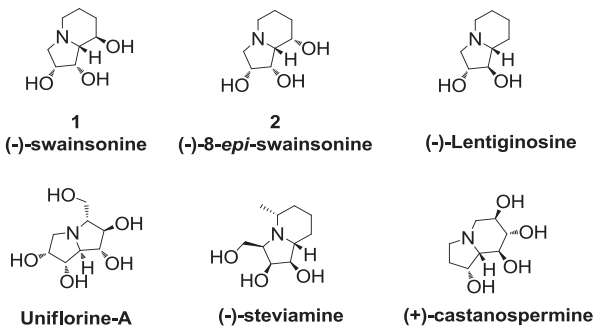

Fig. 1. Examples of polyhydroxylated indolizidine alkaloids.

Among them (−)-swainsonine **1** was first isolated from the fungus *Rhizoctonia leguminicola* in 1973.[2] Since then, it has also been found from several plants and fungi.

(−)-Swainsonine is known to be a potent inhibitor of the lysosomal α-mannosidase and mannosidase II.[3] It also has anticancer,[4] antimetastatic,[5] immunoregulating[6] and *anti*-HIV activities.[7] Moreover, (−)-swainsonine has potential uses as an adjuvant for protection from *anti*-cancer drug and chemotherapeutic toxicity.[8] Due to these promising activities, numerous synthetic methods toward swainsonine and its analogs have been reported.[9] In fact, (−)-swainsonine was one of the most popular targets in synthetic organic community, for more than 40 synthetic methods have been reported until now.[10] Due to the presence of various hydroxyl and amine functional groups, most syntheses of (−)-swainsonine utilize abundant commercially available carbohydrate chiral pools as the starting material. These methods usually rely on extensive protective group strategy, and thus require lengthy synthetic sequences (12–18 steps). Recently, asymmetric syntheses starting from achiral starting materials have gained significant interest. These new methods have unique advantage in that the absolute and relative stereochemistry of the natural product can be easily altered.

In this article, we wish to report a highly concise and flexible formal asymmetric synthesis of (−)-swainsonine and its 8-epimer. The absolute stereochemistry of the natural product was introduced by the enantioselective palladium-catalyzed hydroamination of

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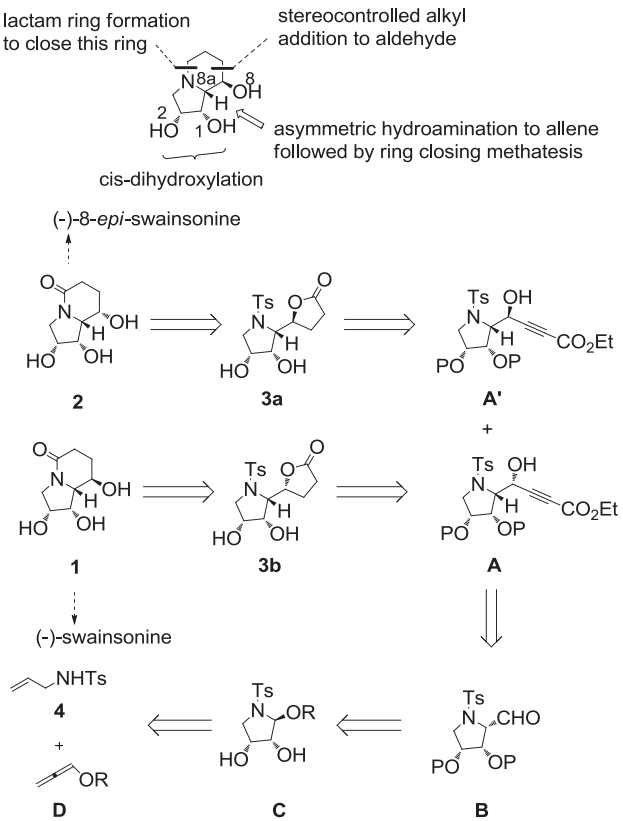
alkoxyallene, which was recently developed by us.[11] The synthetic method uses minimal protective groups. In addition, the 8-epimer of the natural product could be obtained with comparable efficiency to the natural product.

2. Result and discussion

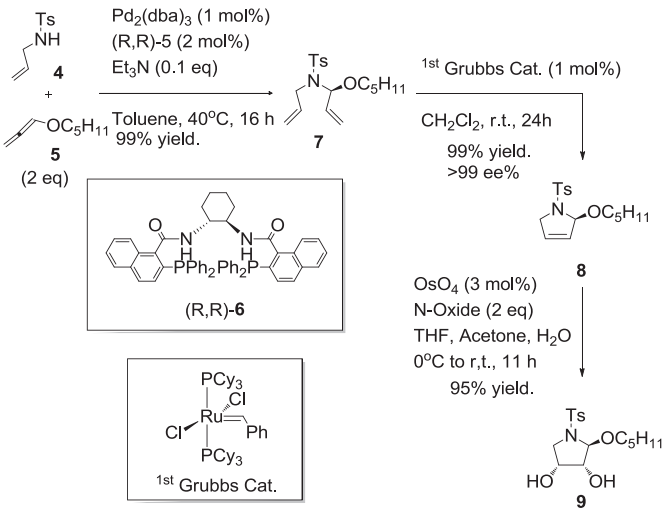
Our retrosynthetic analysis is depicted in Scheme 1. We envisioned that the target compounds could be easily accessed from the corresponding lactam precursors **1** and **2**. The piperidine moiety in **1** and **2** could be formed from the lactone intermediate **3a** (and **3b**), which would be easily prepared the alcohol A (and A′). These alcohols could be obtained by the stereocontrolled addition of the propiolate moiety to the aldehyde B. We then envisaged that B possessing all *cis*-substituents may be efficiently synthesized from the *N*,*O*-acetal intermediate C,[12] which could be accessed by the sequential metal-catalyzed reactions from the allylic amine **4** and the alkoxyallene D.



Scheme 1. Retrosynthetic analysis of (−)-swainsonine.

A key task in the proposed method is to control the stereochemical outcome of the propiolate addition to render a flexible synthetic pathway that can give access to both (−)-swainsonine and (−)-8-*epi*-swainsonine. In our previous study, the nature of the protective group proved to be of critical importance in achieving high *cis*-selectivity in the Lewis acid-mediated C–C bond formation from the *N*,*O*-acetal intermediate D.[11c,13] We decided to use the bis-benzyl ether (OP=OCH_2Ph) because the benzyl moiety can be easily removed under the hydrogenation condition for the formation of the lactone **3a** (and **3b**) from B.

At the outset of the study, we sought to find a reliable synthetic route that potentially allows for large-scale preparation of the target compound. Thus, we decided to investigate first the synthesis of the key intermediate **9** on a multi-gram scale based upon our previous report.[11c] As described in Scheme 2, the reaction of allyl tosyl amine **4** with n-pentyloxyallene **5** (2 equiv)[11c] at 40 °C for 16 h employing $Pd_2(dba)_3$ precatalyst (1 mol %) and (*R*,*R*)-DACH-naphthyl-Trost ligand **6** (2 mol %) produced the acyclic allylic acetal **7** in >99% yield over >99% ee. Remarkably, the reaction on a multigram scale showed a comparable result to our previous study in a reproducible manner. Ring-closing-metathesis reaction of **7** employing the first Grubbs catalyst provided the cyclic *N*,*O*-acetal **8** in near-quantitative yield.[14,15] The subsequent Os-catalyzed dihydroxylation reaction gave **9** with desired absolute configuration in high yield and selectivity, as shown previously.[11c] Thus, the key sequential metal-catalyzed reaction proved to work well on a multigram scale. More than 4 g of intermediate **9** was easily obtained in 94% yield (over three steps) with >99% ee.



Scheme 2. Synthesis of hydroxylated pyrrolidine **9**.

We then investigated the stereodivergent formation of the alcohols **13a**/**13b** (Scheme 3). First, diol **9** was converted into the bis-benzyl ether **10** in 96% yield with no particular event by treatment with NaH and benzyl bromide in the presence of catalytic Bu_4NI. The subsequent Lewis acid-mediated synthesis of the cyanide **11** from **10** also proceeded smoothly in near-quantitative yield by the use of BF_3OEt_2 (4 equiv) and TMSCN (3 equiv). Analysis of the ^1H NMR of the crude product showed over 10:1 stereoselectivity, which is comparable to that observed with the bis-silyl ether in our previous study.[11c] At this point, the stereochemistry of **11** was tentatively assigned to be *cis*. (The stereochemical analysis was confirmed by the synthesis of compound **14**. Please see below). Reduction of **11** to aldehyde **12** was somewhat troublesome, due to the poor stability of **12**.[16] Under the optimized condition, **11** was reacted with DiBAL-H (1.1 equiv) at −78 °C. The resulting imine·aluminum complex was then carefully treated with 1N HCl solution at 0 °C to give the aldehyde **12** in ~88% yield after short-pad chromatography, which was immediately used for the next step.[17] As shown in Scheme 3, the stereodivergent formation of the alcohol **13a**/**13b** from the aldehyde **12** showed fruitful outcome. The reaction with no additive at −100 °C gave a mixture of diastereomeric alcohols in overall 91% yield with moderate (4:1) selectivity towards **13a** (The stereochemistry of the major compound was confirmed by the synthesis of the natural product. Please see below). The use of $MgBr_2$ (2 equiv) that are known to induce chelation-controlled addition significantly improved the diastereoselectivity (over 10:1) with slight increase of the yield. In the light of this result, we reasoned that the use of additive that prevents formation of the chelate would reverse the selectivity. Indeed, the use of HMPA additive produced the diastereomeric **13b** (with 1:8 selectivity) as the major product in overall 94% yield.

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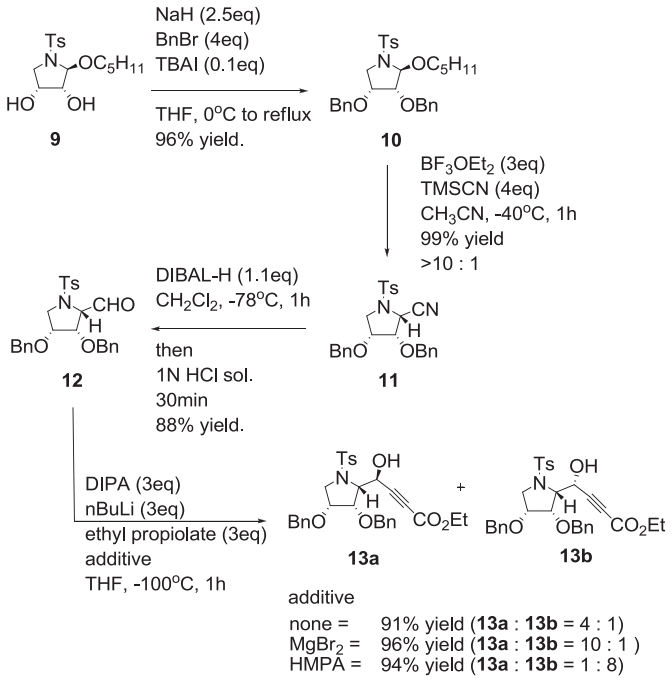
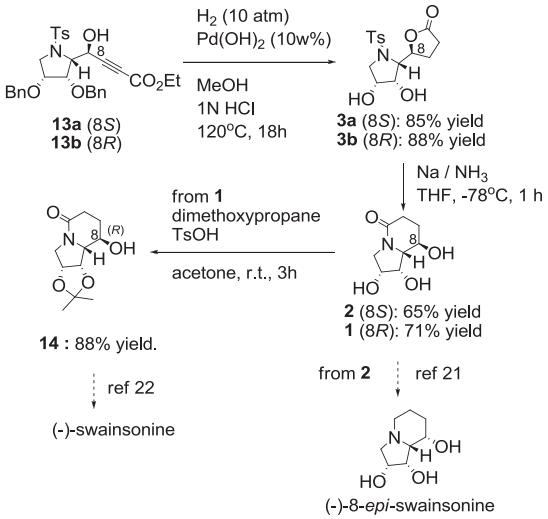


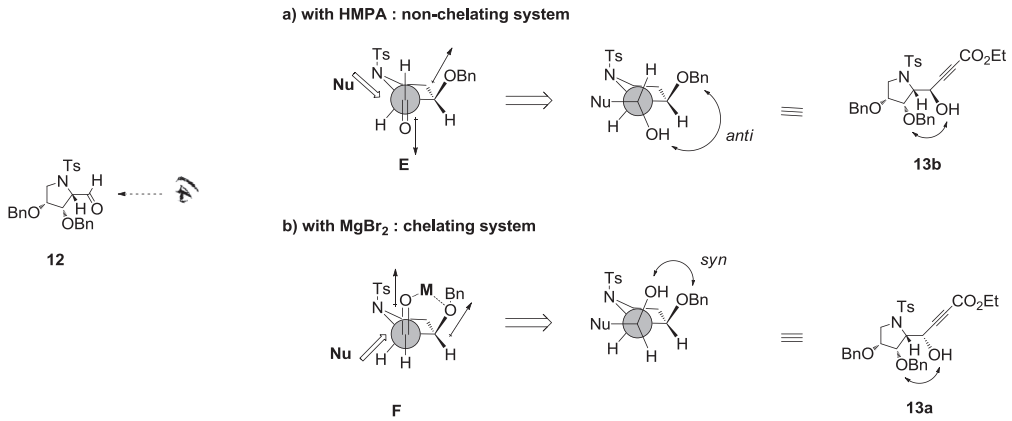
Scheme 3. Synthesis of alcohol **13a** and **13b**.

The above result on the stereodivergent addition reaction can be reasonably explained by the models shown in Scheme 4.[18,19] In the presence of HMPA, which prevents the chelation-controlled addition, **E** seems to be the reactive conformer in which the formyl group moves away from the polar −OBn group. In this case, the nucleophile should approach the aldehyde from the *re*-face, which leads to the formation of diastereomer **13b**. In the presence of $MgBr_2$, intermediate **F** is formed invoking chelation between the formyl and OBn group. The subsequent addition reaction should generate **13a** as the major product.



Scheme 5. Synthesis of lactam **1** and **2**.

without harming various functional groups that are present in the starting material. In this case, migration of the lactone moiety to the lactam also occurred to provide a desired indolizidine compound **2** in 65% yield. Using the same protocol, the epimeric lactam **1** was obtained in 71% yield from **3b**. Based upon the known procedure for the synthesis of **2** and its conversion into (−)-8-*epi*-swainsonine, the above result represents a formal total synthesis of (−)-8-*epi*-swainsonine.[21] Our final task was to convert the compound **1** into the known dimethylacetal analog **14**, which was previously used for the total synthesis of (−)-swainsonine. This transformation was successfully accomplished in 88% yield by the reaction of **1** with dimethoxypropane in the presence of catalytic *p*-TsOH. Thus, this result represents a formal synthesis of (−)-swainsonine. In addition, the spectral data of compound **14** are in full accordance with the literature value,[22] thus unambiguously verifying the structural



Scheme 4. Rationlization of this selectivity in the synthesis of **13a** and **13b**.

With the both diastereomeric alcohols **13a** and **13b** in hand, we moved to the final stage of the synthesis (Scheme 5). Debenzylation of **13a** and **13b** with concomitant hydrogenation proceeded well with $Pd(OH)_2/C$ under 10 atm of H_2 atmosphere in the presence of HCl. The resulting saturated ester slowly cyclized to furnish the alcohol **3a** and **3b** in 85% and 88% yield, respectively. Initial efforts towards the removal of the *p*-toluenesulfonyl group in **13a** employing Tomooka protocol[20] ($KPPh_2$ then HCl) showed extensive decomposition of the starting material. To our delight, using classical dissolving-metal method (Na/NH_3) smoothly proceeded assignment suggested for the alcohol **13a** and **13b**. It should be finally pointed out that the lactam **1** and **2** could be obtained in 11 steps over 23–27% yield from commercially available starting material n-pentanol (6 steps from known intermediate **9** in 37–41% yield).

3. Conclusions

In conclusion, we have accomplished a concise formal synthesis of (−)-swainsonine. The signature step features Pd-catalyzed

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asymmetric hydroalkoxylation of alkoxyallene, which can be performed on a multi-gram scale. Noteworthy is the flexible nature of the synthesis that gives access to both (−)-swainsonine and its 8-epimer with comparable synthetic efficiency. Synthesis of other nitrogen heterocycle natural products using the cyclic *N*,*O*-acetal **9** (and its piperidine analog) as the key building block are actively ongoing in our laboratory.

4. Experimental section

4.1. General information

Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of nitrogen. Similarly all solvents were dried and distilled according to the standard methods before use, then were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. $Pd_2(dba)_3$ was purchased from Aldrich Chemical. The Grubbs' catalysts and chiral Trost ligands were purchased form Strem Chemical Inc, and stored in glove box. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and acidic *p*-anisaldehyde and heat as developing agent. Flash chromatography was carried out on Merck 60 silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Bruker (300 MHz, 500 MHz) spectrometer. ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), and reported as follows; chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, aps=apparent singlet, apd=apparent of doublet, apt=apparent triplet, m=multiplet, br=broad). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.23 ppm). Infrared spectra were recorded on a Shimadzu IR-470 spectrometer. Specific rotation data were measured on JASCO P-1020 Polarimeter. HPLC was performed with an Agilent Technologies 1220 infinity LC system. Melting points were measured on Electrothermal 9100. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer (EI and FAB).

4.2. (2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(pentyloxy)-1-tosylpyrrolidine (10)

To a cold (0 °C) slurry of NaH (1.5 g, 37.5 mmol, 60 w% in mineral oil) in THF (50 ml) was added a solution of diol (6.61 g, 15 mmol) in THF (100 ml) and stirred for 1 h at 0 °C. The solution of BnBr (10.2 g, 7.13 ml, 60 mmol) in THF (50 ml) and TBAI (554 mg, 1.5 mmol) was added and the reaction temperature was increased to reflux condition. After 12 h, the reaction was quenched with satd NH_4Cl sol (10 ml) and H_2O (150 ml) and the THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH2Cl2 (150 ml) twice. Combined organic layer was dried with Na_2SO_4 and solvent was removed. The obtained crude oil was purified by flash column chromatography eluted with (hexane/EtOAc=80:20) to give the product **10** as white solid. R_f 0.55 (Hexane:EtOAc=70:30); mp: 60–62 °C; $[\alpha]_D^{20}$ +15.592 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.3 Hz, 2H), 7.37–7.20 (m, 8H), 7.19–7.04 (m, 4H), 5.02 (s, 1H), 4.54–4.35 (m, 4H), 4.31 (ddd, *J*=8.9, 7.4, 3.7 Hz, 1H), 3.90–3.72 (m, 2H), 3.65 (dd, *J*=8.4, 7.4 Hz, 1H), 3.49 (dt, *J*=9.6, 6.5 Hz, 1H), 3.16 (t, *J*=8.8 Hz, 1H), 2.28 (s, 3H), 1.61–1.47 (m, 2H), 1.40–1.20 (m, 4H), 0.91 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.57, 137.75, 137.66, 135.08, 129.52, 128.62, 128.43, 128.10, 127.93, 127.86, 127.69, 91.69, 79.46, 77.50, 72.58, 72.04, 68.51, 48.67, 29.30, 28.46, 22.66, 21.67, 14.27. IR (NaCl) ν 3089, 3065, 2953, 2871, 1650, 1598, 1497, 1455, 1351, 1209, 1168, 1098, 1063, 1029, 1002 cm^{-1}; HRMS (EI+) calcd for $C_{30}H_{37}NO_5S$ (M+) 523.2392, found 523.2389.

4.3. (2*R*,3*S*,4*R*)- 3,4-Bis(Benzyloxy)-1-tosylpyrrolidine-2-carbonitrile (11) and (2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)-1-tosylpyrrolidine-2-carbonitrile (11′)

To a cold solution of compound **10** (6.99 g, 13 mmol) in CH_3CN (100 ml) at −40 °C was added a solution of trimethylsilyl cyanide (5.16 g, 6.51 ml, 52 mmol) and $BF_3{\bullet}OEt_2$(5.54 g, 4.82 ml, 39 mmol) in CH_3CN (160 ml), respectively. The resulting solution was stirred for 1 h at −40 °C, and then warmed up to room temperature. The reaction was monitored by TLC. When the reaction was completed, the solution was quenched by satd $NaHCO_3$ (100 ml). The reaction solution was concentrated under reduced pressure and aqueous residue was extracted with CH_2Cl_2 (3×30 ml). The organic layers were combined and dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=80:20) to give the product mixture **11** (major isomer, 5.40 g, 11.7 mmol, 90%) and **11′** (minor isomer, 541 mg, 1.17 mmol, 9%).

For (2*R*,3 *S*,4*R*)- 3,4-bis(benzyloxy)-1-tosylpyrrolidine-2-carbonitrile (**11**); R_f 0.34 (Hexane:EtOAc=70:30); $[\alpha]_D^{20}$ −4.18 (*c* 5.12, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.31 Hz, 2H), 7.31 (m, 12H), 4.71 (m, 4H), 4.57 (d, *J*=12.19 Hz, 1H), 4.05 (dt, *J*=2.21 Hz, 4.11 Hz, 1H), 3.96 (dd, *J*=3.75 Hz, 7.10 Hz, 1H), 3.47 (dd, *J*=4.38 Hz, 10.73 Hz, 1H), 3.39 (dd, *J*=2.13 Hz, 10.74 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 137.6, 136.5, 134.5, 130.2, 128.9, 128.6, 128.6, 128.2, 127.9, 127.8, 127.7, 115.3, 78.7, 76.0, 73.4, 72.5, 50.7, 49.5.; IR (NaCl) ν 2876, 1597, 1497, 1455, 1352, 1212, 1165, 1045, 816, 739 cm^{-1}; HRMS (FAB+) calcd for $C_{26}H_{27}N_2O_4S^+$ $(M+H)^+$ 463.1692, found 463.1688.

For (2*S*,3*S*,4*R*)-3,4-bis(benzyloxy)-1-tosylpyrrolidine-2-carbonitrile (**11′**); R_f 0.40 (Hexane:EtOAc=70:30); $[\alpha]_D^{20}$ +30.348 (*c* 1.12, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.26 Hz, 2H), 7.28 (m, 12H), 4.52 (m, 2H), 4.40 (m, 2H), 4.33 (d, *J*=4.72 Hz, 1H), 4.17 (m, 1H), 4.04 (m, 1H), 3.54 (dd, *J*=5.09 Hz, 10.32 Hz, 1H), 3.45 (dd, *J*=5.41 Hz, 10.33 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 137.0, 136.4, 133.5, 130.1, 128.8, 128.7, 128.6, 128.4, 128.0, 128.0, 127.9, 81.1, 77.5, 77.2, 77.0, 75.8, 73.0, 72.3; IR (NaCl) ν 2924, 1597, 1497, 1455, 1354, 1215, 1167, 1091, 1028, 815, 740, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{26}H_{27}N_2O_4S^+$ $(M+H)^+$ 463.1692, found 463.1690.

4.4. (2*S*,3*S*,4*R*)-3,4-Bis(Benzyloxy)-1-tosylpyrrolidine-2-carbaldehyde (12)

To a cold solution of **11** (230 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) at −78 °C was dropwisely added a solution of DIBAL-H (85 mg, 0.4 ml, 0.55 mmol, 1.5 M solution in toluene). The resulting solution was stirred for 1 h at −78 °C (monitored by TLC). Solution of aq 0.5 N HCl (1 ml) and H_2O (4 ml) was added and the solution was stirred for 1 h at 0 °C. The precipitate was filtered and filtrate was extracted with CH_2Cl_2 (3×10 ml). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=80:20) to give the desired aldehyde **12** (204 mg, 0.44 mmol, 88% yield). R_f 0.40 (Hexane:EtOAc=70:30); $[\alpha]_D^{20}$ −33.193 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (dd, *J*=0.71 Hz, 2.75 Hz, 1H), 7.68 (m, 2H), 7.30 (m, 12H), 4.60 (m, 4H), 4.01 (m, 2H), 3.84 (dd, *J*=3.20 Hz, 7.46 Hz, 1H), 3.71 (dd, *J*=3.38 Hz, 10.75 Hz, 1H), 3.31 (dd, *J*=4.59 Hz, 10.73 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 144.4, 137.5, 137.1, 134.4, 130.2, 128.7, 128.2, 128.2, 128.0, 127.9, 127.6, 81.2, 76.5, 73.0, 72.5, 65.8, 50.7, 21.8.; IR (NaCl) ν 2869, 1732, 1597, 1496, 1454, 1349, 1213, 1164, 1093, 1048, 1027, 816, 738 cm^{-1}; HRMS (FAB+) calcd for $C_{26}H_{28}NO_5S^+$ $(M+H)^+$ 466.1688, found 466.1685.

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4.5. (*S*)-Ethyl 4-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-1-tosylpyrrolidin-2-yl)-4-hydroxybut-2-ynoate (13a)

To a cold solution of diisopropylamine (152 mg, 0.21 ml, 1.5 mmol) in THF (2 ml) was added *n*-BuLi (102 mg, 0.94 ml, 1.5 mmol, 1.6 M solution in hexane) at −78 °C and the resulting solution was stirred for 30 min at 25 °C. The temperature was decreased to −100 °C and ethyl propiolate (147 mg, 0.15 ml, 1.5 mmol) in THF (1 ml) was added to the reaction mixture via syringe, and the solution was stirred for 30 min. To the resulting solution was added a solution of **12** (233 mg, 0.5 mmol) in THF (2 ml) and finally $MgBr_2$ (184 mg, 1 mmol) in THF (2 ml). The resulting solution was stirred at −100 °C for 1 h. The reaction mixture was quenched by aq NH_4Cl solution (10 ml) and THF was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=80:20) to give the desired product **13a** (248 mg, 0.44 mmol) and **13b** (24 mg, 0.04 mmol) in 96% yield.

For **13a**; R_f 0.40 (Hexane:EtOAc=70:30); $[\alpha]_D^{20}$ −21.580 (*c* 2.52, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.30 (m, 12H), 4.95 (dd, *J*=4.36 Hz, 6.97 Hz, 1H), 4.63 (m, 4H), 4.20 (m, 2H), 4.10 (d, *J*=4.34 Hz, 1H), 4.02 (m, 1H), 3.93 (m, 1H), 3.55 (m, 3H), 2.42 (s, 3H), 1.28 (t, *J*=7.07 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 153.5, 141.6, 137.5, 137.2, 134.1, 130.2, 128.8, 128.6, 128.3, 128.1, 128.0, 127.8, 86.5, 78.4, 76.6, 74.0, 72.7, 64.3, 62.2, 62.0, 51.2, 21.8, 14.2; IR (NaCl) ν 3447, 3032, 2926, 2240, 1709, 1597, 1497, 1455, 1344, 1250, 1160, 1090, 1026, 941 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{34}NO_7S^+$ $(M+H)^+$ 564.2056, found 564.2060.

For **13b**; R_f 0.31 (Hexane:EtOAc=70:30); $[\alpha]_D^{20}$ −45.841 (*c* 6.25, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.18 Hz, 2H), 7.31 (m, 12H), 4.98 (dd, *J*=3.58 Hz, 10.75 Hz, 1H), 4.80 (d, *J*=10.43 Hz, 1H), 4.64 (d, *J*=10.44 Hz, 1H), 4.55 (q, *J*=12.01 Hz, 2H), 4.23 (m, 4H), 4.02 (dd, *J*=3.66 Hz, 6.31 Hz, 1H), 3.59 (m, 2H), 3.44 (m, 1H), 2.42 (s, 3H), 1.30 (t, *J*=7.14 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 144.3, 137.0, 136.9, 134.5, 130.1, 130.1, 128.7, 128.6, 128.5, 128.3, 127.8, 127.5, 86.4, 79.7, 77.6, 76.5, 74.7, 72.6; IR (NaCl) ν 3473, 3064, 3032, 2983, 2938, 2874, 2234, 1709, 1497, 1455, 1402, 1249, 1159, 1092, 1026, 913 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{34}NO_7S^+$ $(M+H)^+$ 564.2056, found 564.2054.

4.6. (*R*)-Ethyl 4-((2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-1-tosylpyrrolidin-2-yl)-4-hydroxybut-2-ynoate (13b)

To a cold solution of diisopropylamine (152 mg, 0.21 ml, 1.5 mmol) in THF (2 ml) was added *n*-BuLi (102 mg, 0.94 ml, 1.5 mmol, 1.6 M solution in hexane) at −78 °C and the resulting solution was stirred for 30 min at 25 °C. The temperature was decreased to −100 °C and ethyl propiolate (147 mg, 0.15 ml, 1.5 mmol) in THF (1 ml) was added to the reaction mixture. After 30 min, hexamethylphosphoramide was added to generate (269 mg, 0.26 ml, 1.5 mmol) pale red solution. To this solution was added a solution of **12** (233 mg, 0.5 mmol) in THF (2 ml), and the resulting solution was stirred for 1 h. The reaction mixture was quenched by aq NH_4Cl solution (10 ml) and THF was removed under reduced pressure. The mixed residue was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed with water (3×10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=80:20) to give the desired product **13a** (28 mg, 0.05 mmol) and **13b** (237 mg, 0.42 mmol) in 94% yield.

4.7. Large scale preparation of (*R*)-ethyl 4-((2*R*,3 *S*,4*R*)-3,4-bis(benzyloxy)-1-tosylpyrrolidin-2-yl)-4-hydroxybut-2-ynoate (13b)

To a cold solution of **11** (5.56 g, 12 mmol) in CH_2Cl_2 (100 ml) at −78 °C was added a solution of DIBAL-H (2.05 g, 9.6 ml, 14.4 mmol, 1.5 M solution in toluene). The reaction solution was stirred for 1 h at −78 °C (monitored by TLC) and hydrolyzed by aq 0.5N HCl solution (24 ml) and H_2O (80 ml) for 1 h at 0 °C. The precipitate was filtered and filtrate was extracted with CH_2Cl_2 and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil of **12** was filtered through a pad of silica eluted with EtOAc 80% in Hexane. The solvent was removed under reduced pressure, and the crude oil employed next reaction without further purification.

To a cold solution of diisopropylamine (3.64 g, 5.04 ml, 36 mmol) was added *n*-BuLi (2.31 g, 22.5 ml, 36 mmol, 1.6 M solution in hexane) at −78 °C and stirred for 30 min at 25 °C. The temperature was decreased to −100 °C and ethyl propiolate (3.53 g, 3.65 ml, 36 mmol) was added to the reaction mixture. After 30 min, hexamethylphosphoramide (6.45 g, 6.26 ml, 36 mmol) was added to this solution, and the resulting solution was stirred for 30 min.

To this solution was added the solution of crude **12** generated above in THF (50 ml) slowly at −100 °C and the resulting solution was stirred for 1 h. The reaction mixture was quenched by aq NH_4Cl solution (100 ml) and THF was removed under reduced pressure. The mixed residue was extracted with CH_2Cl_2 (100 ml×3). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=80: 20) to give the desired product **13a** (549 mg, 0.97 mmol) and **13b** (4.39 g, 7.78 mmol) in 73% yield over two step.

4.8. (*S*)-5-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-tosylpyrrolidin-2-yl)dihydrofuran-2(3*H*)-one (3b)

To a stainless steel autoclave equipped with a stirring bar, the catalyst $Pd(OH)_2/C$ (130 mg, 10 w%) and **13b** (1.30 g, 2.31 mmol) in MeOH and aqueous 1N HCl (20 ml, 1: one ratio by volume) were placed. The autoclave was evacuated and filled with a hydrogen gas three times (hydrogen was introduced until pressure gauge indicates 10 atm). The reaction temperature was increased to 120 °C and the resulting solution was stirred for 24 h. When the reaction was completed, an reaction mixture was neutralized with aq 1N NaOH solution until pH seven was reached. The reaction mixture was extracted with CH_2Cl_2 (3×50 ml). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=20:80) to give the desired diol **3b** (690 mg, 2.03 mmol, 88% yield). R_f 0.32 (Hexane:EtOAc=40:60); $[\alpha]_D^{20}$ −112.15 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J*=8.28 Hz, 2H), 7.35 (d, *J*=8.00 Hz, 2H), 4.99 (m, 1H), 3.96 (dd, *J*=5.11 Hz, 6.74 Hz, 1H), 3.87 (dd, *J*=5.33 Hz, 8.48 Hz, 1H), 3.71 (dd, *J*=5.50 Hz, 5.46 Hz, 1H), 3.55 (dd, *J*=6.10 Hz, 12.29 Hz, 1H), 3.34 (m, 1H), 2.75 (br s, 2H), 2.58 (m, 3H), 2.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 144.8, 134.1, 130.5, 130.4, 127.8, 127.5, 79.8, 72.3, 70.4, 63.6, 52.9, 28.2, 25.5, 21.8; IR (NaCl) ν 3487, 3446, 3005, 2944, 2938, 1764, 1344, 1162, 667, 575 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{20}NO_6S^+$ $(M+H)^+$ 342.1011, found 342.1012.

4.9. (1*S*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyhexahydroindolizin-5(1*H*)-one (1)

To a deep blue solution of sodium (300 mg) in liq. NH_3 (45 mL) at −78 °C was added compound **3b** (66 mg, 0.2 mmol) in THF (5 mL)

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and the solution was stirred at −78 °C for 90 min. The reaction was quenched by addition of solid NH_4Cl (200 mg). The solvent was neutralized with aq 1N HCl solution until the pH reached seven and the solvent was removed under reduced pressure. The resulting crude product was dissolved in H_2O and applied to ion-exchange chromatography (Dowex 50WX8-100, H+ form, 100–200 mesh) eluting with H_2O (100 ml) and 5% aq ammonium hydroxide solution (100 ml). Removal of water in vacuo provided **1** (27 mg, 0.14 mmol, 71% yield). R_f 0.25 ($CHCl_3$:MeOH=80:20); $[\alpha]_D^{20}$ −24.755 (*c* 1.01, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 4.44 (m, 1H), 4.26 (m, 1H), 4.00 (m, 1H), 3.72 (m, 1H), 3.53 (m, 1H), 3.19 (m, 1H), 2.43 (m, 2H), 2.09 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 177.3, 144.8, 134.1, 130.5, 130.4, 127.8, 127.5, 79.8; IR (NaCl) ν 3343, 2919, 2850, 1570, 1456, 1418, 1033, 469 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{13}NO_4Na^+$ $(M+Na)^+$ 210.0742, found 210.0740.

4.10. (1*R*,2*R*,8*R*,8a*S*)-1,2,8,8a-Tetrahydroxyhexahydroindolizin-5(1*H*)-one (14)

To a solution of **1** (6 mg, 0.03 mmol) in acetone (1 ml) was added dimethoxypropane (0.040 ml, 0.3 mmol) and *p*-toluenesulfonic acid (3 mg, 0.017 mmol). The reaction solution was stirred for 3 h at room temperature. When the reaction was complete, the reaction solution was extracted with CH_2Cl_2 and water. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=70: 30) to give the desired product **14** (5 mg, 0.026 mmol, 88% yield). R_f 0.36 (Hexane:EtOAc=70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (t, *J*=5.4 Hz, 1H), 4.75 (t, *J*=5.3 Hz, 1H), 4.15 (m, 2H), 3.33 (dd, *J*=8.1 Hz, 4.3 Hz, 1H), 3.13 (dd, *J*=13.7 Hz, 5.0 Hz, 1H), 2.48 (m, 2H), 2.13 (m, 1H), 1.87 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 122.2, 79.8, 66.1, 65.6, 50.6, 29.7, 29.69, 26.3, 24.6; IR (NaCl) 3290, 2919, 1609, 1412, 1115 cm^{-1}. Spectral data are in full agreement with the literature data.[22]

4.11. (*S*)-5-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-tosylpyrrolidin-2-yl) dihydrofuran-2(3*H*)-one (3a)

To a stainless steel autoclave equipped with a stirring bar, the catalyst $Pd(OH)_2$/C (100 mg, 10 w%) and **13a** (1.0 g, 1.77 mmol) in MeOH and aqueous 1N HCl (10 ml, 1: one ratio by volume) were placed. The autoclave was evacuated and filled with a hydrogen gas three times (hydrogen was introduced until pressure gauge indicates 10 atm). The reaction temperature was increased to 120 °C and the solution was stirred for 24 h. When the reaction was completed, an acidic reaction solvent was neutralized with aq 1 N NaOH solution until the pH reached 7. The reaction mixture was extracted with CH_2Cl_2 (3×30 ml). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (hexane/EtOAc=20:80) to give the desired diol **3a** (514 mg, 1.51 mmol, 85% yield). R_f 0.34 (Hexane:EtOAc=40:60); $[\alpha]_D^{20}$ −21.580 (*c* 2.52, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.29 Hz, 2H), 7.34 (d, *J*=8.01 Hz, 2H), 4.98 (ddd, *J*=1.91 Hz, 6.29 Hz, 7.82 Hz, 1H), 3.97 (dd, *J*=1.96 Hz, 8.01 Hz, 1H), 3.84 (m, 2H), 3.59 (m, 1H), 3.34 (m, 1H), 3.23 (m, 1H), 3.03 (m, 1H), 2.76 (m, 2H), 2.56 (m, 1H), 2.45 (s, 3H), 2.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 144.9, 134.1, 130.4, 127.5, 77.0, 70.9, 69.6, 63.8, 55.2, 28.1, 24.1, 21.8; IR (NaCl) ν 3492, 2919, 2849, 1761, 1343, 1162, 668, 576, 549 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{20}NO_6S^+$ $(M+H)^+$ 342.1011, found 342.1010.

4.12. (1*S*,2*R*,8*S*,8a*R*)-1,2,8-Trihydroxyhexahydroindolizin-5(1*H*)-one (2)

To a deep blue solution of Na (400 mg) in liq. NH_3 (55 ml) at −78 °C was added compound **3a** (67 mg, 0.2 mmol) in THF (5 mL) and the solution was stirred at −78 °C for 90 min. The reaction was quenched by addition of solid NH_4Cl (200 mg). The solvent was neutralized with aq 1N HCl solution until the pH reached seven and the solvent was removed under reduced pressure. The resulting crude product was dissolved in H_2O and applied to ion-exchange chromatography (Dowex 50WX8-100, H+ form, 100–200 mesh) eluting with H_2O (100 ml) and 5% aq ammonium hydroxide solution (100 ml). Removal of water in vacuo provided **2** (25 mg, 0.13 mmol, 65% yield). R_f 0.27 ($CHCl_3$:MeOH=80:20); $[\alpha]_D^{20}$ −0.807 (*c* 2.60, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 4.51 (td, *J*=2.06 Hz, 3.87 Hz, 1H), 4.47 (t, *J*=3.93 Hz, 1H), 4.35 (dt, *J*=3.92 Hz, 7.87 Hz, 1H), 3.78 (d, *J*=1.62 Hz, 1H), 3.71 (dd, *J*=7.65 Hz, 11.91 Hz, 1H), 3.36 (dd, *J*=7.32 Hz, 10.93 Hz, 1H), 2.42 (m, 2H), 1.94 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 172.3, 73.2, 69.0, 63.8, 61.3, 48.3, 26.6, 25.5; IR (NaCl) ν 3355, 2919, 2849, 1609, 1470, 1412, 1327, 1115, 1033, 810 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{14}NO_4S^+$ $(M+H)^+$ 188.0923, found 188.0923.

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Supplementary data

Supplementary data (Supplementary data (Electronic Supplementary Data available: ^{1}H and ^{13}C NMR spectra of the new compounds)) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.034.

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