JOC The Journal of Organic Chemistry

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α,β-Unsaturated Diazoketones as Platforms in the Asymmetric Synthesis of Hydroxylated Alkaloids. Total Synthesis of 1-Deoxy-8,8a-diepicastanospermine and 1,6-Dideoxyepicastanospermine and Formal Synthesis of Pumiliotoxin 251D

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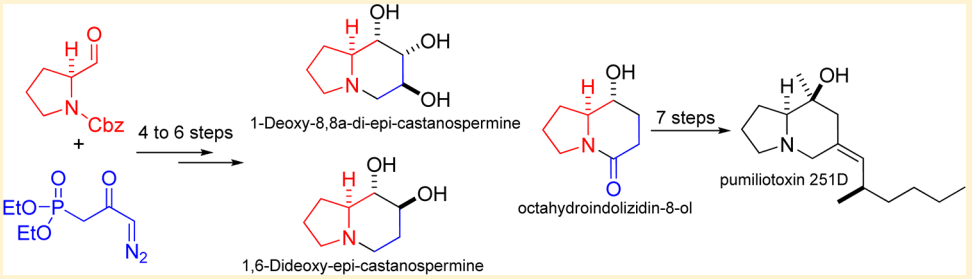
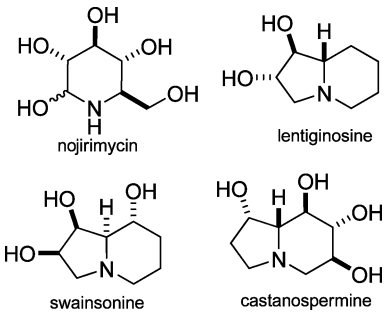
Supporting Information



ABSTRACT: A versatile and concise approach for the stereoselective synthesis of mono-, di-, and trihydroxylated indolizidines is presented in four to six steps from Cbz-prolinal and a diazophosphonate. The key steps involved a Wolff rearrangement, followed by a stereoselective dihydroxylation/epoxidation reaction, from an α,β-unsaturated diazoketone. The strategy also permits extension to the synthesis of many natural hydroxylated indolizidine alkaloids as demonstrated in the formal synthesis of pumiliotoxin 251D.

Hydroxylated nitrogen heterocycles are well-known for their ability to act as potent α and β-glycosidase inhibitors.[1] Many of these heterocycles are widespread in nature, some examples being nojirimycin,[2] lentiginosine,[3] swainsonine,[4] and castanospermine[5] (Chart 1). Castanospermine,[5] for example, is isolated from the trees *Castanospermum australe* and *Alexa leiopetale* and possesses a plethora of interesting biological activities such as the inhibition of HIV infectivity, angiogenesis, and thyroglobulin secretion.[6] Castanospermine has also been demonstrated to act as an antitumor agent.[7] These wide ranges of biological effects in vivo and in vitro are produced mainly due to the strong inhibition of some types of α and β-glycosidases. Interestingly, modification of the five castanospermine stereocenters has been proven to cause significant changes in these biological activities.[8] For example, 1-deoxycastanospermine inhibits *N*-acetyl-β-D-glucosaminidase, whereas castanospermine itself does not. In the same way, 1-deoxy-6,8a-diepicastanospermine and 1-deoxy-6-epicastanospermine exhibit much stronger α-mannosidades and α-fucosidade inhibition than castanospermine.[8] As a result, plenty of castanospermine analogues, as well as other hydroxylated cyclic systems, have been developed in the last few decades to be employed in glycoscience.[9] Considering that, concise and versatile approaches to these compounds, especially diversity-oriented ones, are of tremendous potential value.

Chart 1. Examples of Some Hydroxylated Alkaloids

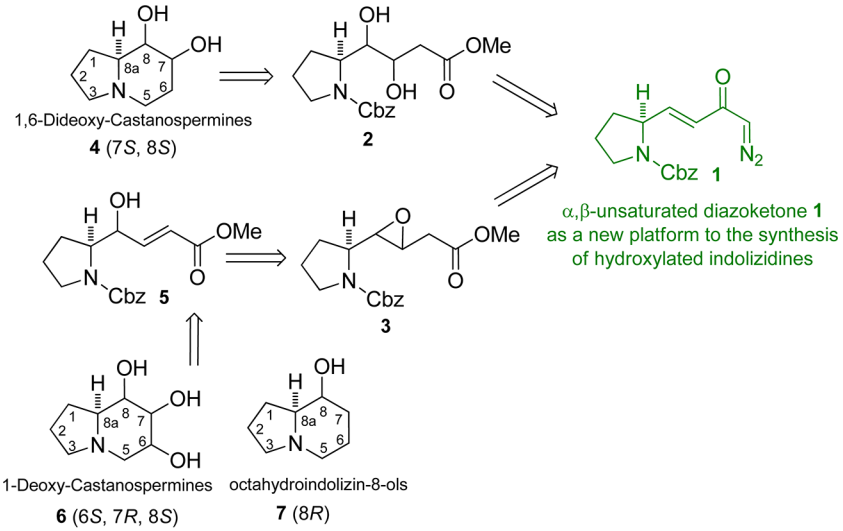


As a part of our ongoing studies to use α,β-unsaturated diazoketones as multifunctional platforms/building blocks,[10,11] we envisioned that hydroxylated indolizidines could be easily prepared in just four to five steps in a diversity-oriented fashion, starting from proline-derived diazoketone **1** (Scheme 1). Compound **1** possesses all of the carbons necessary to construct an indolizidine system as well as all the desired functionalities to provide mono-, di-, and trihydroxylated indolizidines. For example, Wolff rearrangement[12] from **1**, followed by dihydroxylation or epoxidation reactions, could provide oxygen-functionalized esters **2** or **3**, respectively. Ester **2** could lead to dihydroxylated indolizidines[13] in two steps after

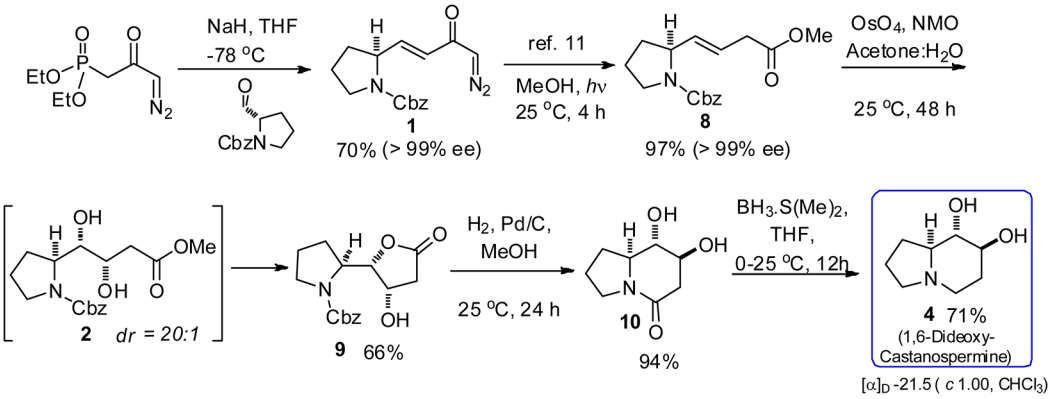
Received: September 13, 2012
Published: October 15, 2012

dx.doi.org/10.1021/jo301967w | J. Org. Chem. 2012, 77, 9926−9931

Scheme 1. Strategy for the Syntheses of Hydroxylated Indolizidines from α,β-Unsaturated Diazoketone 1



Scheme 2. Synthesis of 1,6-Dideoxycastanospermine (4), a Dihydroxylated Indolizidine



Cbz removal/cyclization and lactam reduction. On the other hand, the β-elimination of compound **3** could provide γ-hydroxylated α,β-unsaturated ester **5** to furnish, after two or three steps, mono- and trihydroxylated indolizidines,[13] respectively. Herein, to evaluate the usefulness of α,β-unsaturated diazoketones as common platforms to the synthesis of tri-, di- and monohydroxylated indolizidines, we focused on the total synthesis of 1-deoxy-8,8a-diepicastanospermine **6**, 1,6-dideoxyepicastanospermine **4**, and the formal synthesis of octahydroindolizidin-8-ol **7** (as well as pumiliotoxin 251D), respectively.

To evaluate our proposal, we first prepared 1,6-dideoxyepicastanospermine, a dihydroxylated indolizidine previously synthesized by Koskinen.[14] We started our work from proline-derived α,β-unsaturated diazoketone **1** (Scheme 2). Compound **1** (70% yield; >99% ee; single *E* isomer) can be prepared from L-prolinal and 3-diazo-2-oxopropylphosphonate, employing our recently described methodology.[10] Next, prior to the conversion of **1** into key dihydroxylated ester **2**, Wolff rearrangement in the presence of MeOH was carried out as described by us during the total synthesis of the alkaloid indolizidine 167B.[11] For this transformation, photochemical conditions were applied, furnishing the desired β,γ-unsaturated ester **8** (Scheme 2) in an almost quantitative yield after 4 h at 25 °C using a Xenon arc lamp with IR filter and with no need for purification.[15] As an alternative, thermal Wolff rearrangement from diazoketone **1** can also be carried out, although in a lower 76% yield and with a cost of 50 mol % of the expensive silver triflate catalyst.[16] As an extension of the photochemical Wolff rearrangement from unsaturated diazoketones, we also synthesized new β,γ-unsaturated esters **11**–**13** (Figure 1) in

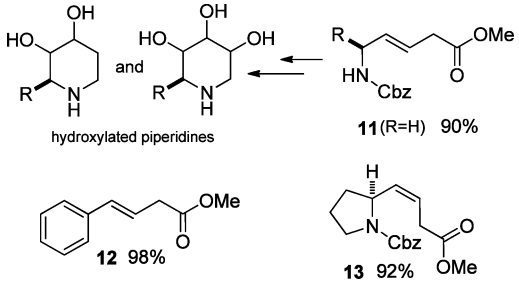
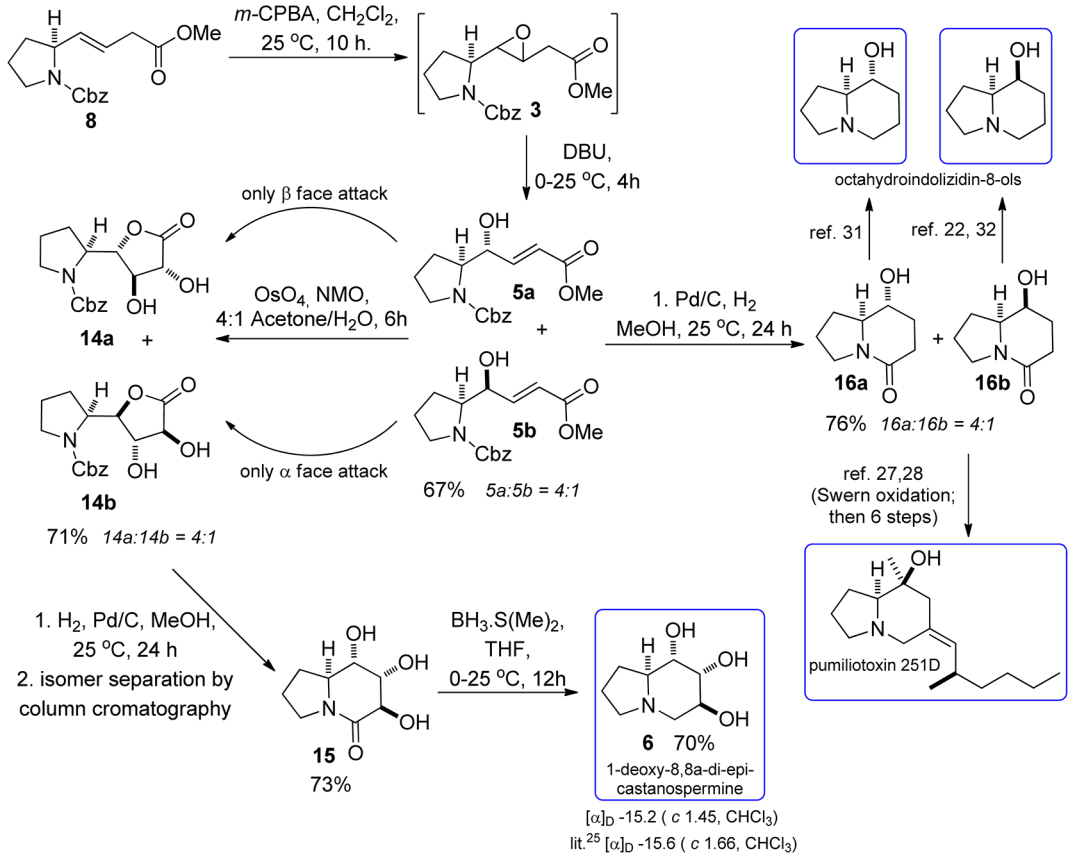


Figure 1. Synthesized β,γ-unsaturated esters to be applied in other types of hydroxylated alkaloids.

quantitative yields. Ester **11**, for example, may be applied in the synthesis of polyhydroxylated piperidines applying a similar strategy to the one depicted in scheme 1. On the other hand, *Z*-β,γ-unsaturated ester **13**[17] can be applied to the same sequence described for compound **4** (scheme 2), leading to all *cis* 1,6-dideoxycastanospermine. Finally, ester **12** could lead to pyrrolidines after a few transformations.[18]

dx.doi.org/10.1021/jo301967w | J. Org. Chem. 2012, 77, 9926–9931

Scheme 3. Total Synthesis of 1-Deoxy-8,8a-diepicastanospermine (6) and Formal Synthesis of Pumiliotoxin 251D



To accomplish the synthesis of 1,6-dideoxycastanospermine, compound **8** was then submitted to a highly selective dihydroxylation reaction in the presence of OsO_4/NMO[19] (dr = 20:1)[20] to provide lactone **9** in 66% yield after column chromatography and diastereomer separation. Diol **2** could not be detected after the dihydroxylation reaction and suffered lactonization upon its formation. Completion of the synthesis was then straightforward. The exposure of lactone **9** in the presence of H_2/Pd removed the Cbz protecting group, with subsequent lactone ring-opening by the free amino group, to afford lactam **10** in a 94% yield. The reduction of **10** using the classical $LiAlH_4$ reductive protocols[21] was somewhat tedious initially, furnishing many byproducts. In this case, amide reduction in the presence of $BH_3{\cdot}SMe_2$ seemed to be the best choice,[22] furnishing 1,6-dideoxyepicastanospermine **4** in a 71% yield. All of the spectroscopic data for **4** are in complete accordance with those published by Koskinen.[14]

Having succeeded in preparing 1,6-dideoxycastanospermine **4**, we then turned our attention to preparing the more complex 1-deoxy-8,8a-diepicastanospermine **6** (Scheme 3) via epoxy ester **3**. 1-Deoxy-8,8a-diepicastanospermine has already been synthesized, and important contributions were provided by Chan,[23] Martin,[24] Koskinen,[25] and Fisera.[26] Epoxy ester **3**, also prepared from *α,β*-unsaturated diazoketone **1**, could be applied not only in the synthesis of **6** but also in the formal synthesis of pumiliotoxin 251D.[27,28] Pumiliotoxins are well-known for their cardiotonic activities since they are positive modulators of sodium chanels.[29] To accomplish that, epoxidation of *β,γ*-unsaturated ester **8** with *m*-chloroperbenzoic acid furnished epoxide **3**. The addition of base (DBU) to the same reaction flask provided *γ*-hydroxylated *α,β*-unsaturated esters **5a** and **5b** in a 67% yield (4:1 inseparable mixture)[20,30] after a *β*-elimination/epoxide-opening reaction. Interestingly, osmium tetraoxide-catalyzed dihydroxylation of this diastereomeric mixture proved to be completely face-selective in each isomer, furnishing **14a** and **14b** in a 71% yield[20,30] (Scheme 3). Submission of **14a** and **14b** to a one-pot Cbz deprotection/cyclization in the presence of H_2/Pd furnished pure lactam **15** in 73% yield after column chromatography and isomer separation. Borane reduction of **15** led to 1-deoxy-8,8a-diepicastanospermine **6** in a 70% yield. Once again, all of the spectroscopic data for **6** are in accordance with those published in the literature.[24,25]

The formal syntheses of monohydroxylated indolizidines were also achieved in a single step from advanced intermediates **5a** and **5b** as illustrated in Scheme 3 (formal synthesis of pumiliotoxin 251D and octahydroindolizidin-8-ols). One-pot reduction, Cbz-deprotection, and lactamization of this mixture afforded known hydroxy lactams **16a** and **16b** in 76% yield. This mixture can be converted to pumiliotoxin 251D after a Swern oxidation reaction, followed by a sequence of six steps as described by Sudau.[27,28] Octahydroindolizidin-8-ols can also be easily achieved from **16a** and **16b** as described by Huang,[31] Lee,[32] and Wee.[22] In this later case, benzoate derivatization is necessary for complete diastereomeric mixture separation.

In conclusion, we have demonstrated that *α,β*-unsaturated diazoketones are powerful platforms to be applied in a number of diverse approaches to mono-, di-, and trihydroxylated indolizidines. The straightforward syntheses of 1,6-dideoxycastanospermine and 1-deoxy-8,8a-diepicastanospermine from diazoketone **1** in just four to five steps, employing simple and mild transformations, exemplifies that. To the best of our

dx.doi.org/10.1021/jo301967w | J. Org. Chem. 2012, 77, 9926−9931

knowledge, the strategy presented here also constitutes the shortest approach for the preparation of these types of hydroxylated indolizidines, taking into consideration equivalent starting materials with respect to price and accessibility. Moreover, the possibility of using different α,β-unsaturated diazoketones along with this strategy, as well as diazoketones like **1** with a *Z* geometry, also offers flexibility for the preparation of other alkaloids such as quinolizidines, piperidines, pyrrolidines, and even new indolizidines.

EXPERIMENTAL SECTION

General Procedures. All solvents were dried and distilled prior to use by standard procedures. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm silica gel plates using UV light as visualizing agent and potassium permanganate in aqueous KOH for staining. Column chromatography was performed using silica gel 60 (particle size 0.063−0.210 mm). Unless stated otherwise, all of the yields refer to isolated products after flash column chromatography. The solvent mixtures employed in TLC analysis and in flash column chromatography purifications are reported as volume by volume and in percentages. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using 200, 400, or 600 MHz equipment. For ^{1}H NMR spectra, chemical shifts (δ) are referenced from TMS (0.00 ppm). Coupling constants (J) are reported in Hz. For multiplicities the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; bs; broad singlet; dt, double triplet. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using an NMR spectrometer at 50, 100, or 150 MHz. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm) or MeOH (49.0 ppm). Photochemical reactions were carried out using UV light generated by an Osram 150 Xenon lamp accommodated in an Oriel Model 8500 Universal arc lamp source with focusing quartz lens, a water-filled infrared filter, and a thermostated cell holder. Infrared spectra were obtained using FTIR at 4.0 cm-1 resolution and are reported in wavenumbers. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (hybrid linear ion trap−orbitrap FT-MS and QqTOF/MS−Microtof−QII model).

(*S*)-Benzyl 2-(4-Diazo-3-oxobut-1-enyl)pyrrolidine-1-carboxylate (1).[10,11] To a suspension of NaH (60% in mineral oil) (272.0 mg, 6.80 mmol, 2.2 equiv) in dry THF (10 mL), under argon atmosphere and at 0 °C, was added a 0.15 M solution of diethyl 3-diazo-2- oxopropylphosphonate (1.36 g, 6.20 mmol, 2.0 equiv) in dry THF. After the mixture was stirred for 15 min at this temperature, the system was cooled to −78 °C and then a 0.1 M solution of (*S*)-prolinal (719.0 mg, 3.10 mmol, 1.0 equiv) in dry THF was added dropwise. After 1 h, the temperature was allowed to rise naturally to −30 °C, when a saturated aqueous NH_4Cl solution (25 mL) was added to the reaction vessel. Next, the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in rotary evaporator. Purification by flash column chromatography (30% AcOEt/hexanes) afforded diazoketone **1** (646.0 mg, 2.20 mmol, 70%) as a stable yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$, mixture of rotamers) δ 7.36−7.32 (m, 5H), 6.69 (dd, J = 15.3, 5.7 Hz, 1 H), 6.0−5.8 (2d (rotamers), J = 15.3 Hz, 1H), 5.32−5.01 (m, 3H), 4.54−4.51 (m, 1H), 3.50−3.47(m, 2H), 2.09−1.76 (m, 4H); ^{13}CNMR (50 MHz, $CDCl_3$, mixture of rotamers) δ 184.2, 154.7, 143.7, 143.1, 136.5, 128.4, 127.9, 126.2, 66.8, 58.1, 57.7, 55.8, 46.8, 46.4, 31.6, 30.9, 23.6, 22.7; FT-IR (neat, cm^{-1}) 3085, 2973, 2879, 2102, 1701, 1656, 1606, 1448, 1413, 1357, 1186, 1107; HRMS (ESI) calcd for $C_{16}H_{17}N_3NaO_3$ [M + Na]$^+$ 322.1162, found 322.1159; $[\alpha]^{20}_D$ −93.3 (*c* 2.25, CH_2Cl_2); R_f 0.15 (40% EtOAc/hexanes).

(*S*,*E*)-Benzyl 2-(4-Methoxy-4-oxobut-1-enyl)pyrrolidine-1-carboxylate (8).[11] A solution of diazoketone **1** (269.0 mg, 0.90 mmol) in dry methanol (3.0 mL), in a 1 cm optical path quartz cell was irradiated with a Osram 150 Xenon arc lamp (IR filter) for 4 h under magnetic stirring (nitrogen gas evolution observed). Next, the solvent was evaporated in rotary evaporator to furnish ester **8** (265.0 mg, 0,87 mmol, 97%) with no need for purification: $[\alpha]^{20}_D$ −30.0 (*c* 4.0 CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$, mixture of rotamers) δ 7.30 (bs, 5H), 5.79−5.44 (m, 1H,), 5.18 (d, J = 12.0 Hz, 1H), 5.08 (d, J = 12.0 Hz, 1H), 4.50−4.31 (m, 1H), 3.66 (s, 3H), 3.53−3.41 (m, 2H), 3.16−2.96 (m, 2H), 2.08−1.68 (m, 4H); ^{13}CNMR (50 MHz, $CDCl_3$, mixture of rotames) δ 172.0, 155.0, 137.0, 134.3, 134.0, 128.4, 127.8, 122.0, 66.6, 58.4, 51.8, 46.6, 46.4, 37.3, 32.2, 31.3, 29.7, 23.5, 22.8; FT-IR (neat, cm^{-1}) 2954, 2927, 1737, 1701, 1452, 1411, 1353, 1270, 1189, 1170; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_4$ [M + Na]$^+$ 326.1363, found 326.1364; R_f: 0.40 (40% EtOAc/hexanes).

(*E*)-Methyl 5-(benzyloxycarbonylamino)pent-3-enoate (11): 88.0 mg, 0.33 mmol, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 5.76−5.70 (m, 1H), 5.65−5.58 (m, 1H), 5.11 (s, 2H), 4.81 (s, 1H), 3.82 (m, 2H), 3.69 (s, 3H), 3.08 (d, J = 6.6 Hz, 2H); ^{13}CNMR (150 MHz, $CDCl_3$) δ 171.9, 156.2, 136.5, 130.3, 128.5, 128.1, 124.2, 66.8, 51.9, 42.6, 37.4; HRMS (ESI) calcd for $C_{14}H_{17}NNaO_4$ [M + Na]$^+$ 286.1049, found 286.1084.

(*E*)-Methyl 4-Phenylbut-3-enoate (12). All of the data are in accordance with those described in the literature[33] (17.5 mg, 0.10 mmol, 98%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.50 (d, J = 15.6 Hz, 1H), 6.29 (dt, J = 15.6, 7.0 Hz, 1H), 3.72 (s, 3H), 3.26 (m, 2H).

(*S*,*Z*)-Benzyl 2-(4-methoxy-4-oxobut-1-enyl)pyrrolidine-1-carboxylate (13): 76.0 mg, 0.25 mmol, 92%; ^{1}HNMR (200 MHz,$CDCl_3$, mixture of rotamers) δ 7.32 (bs, 5H), 5.82−5.32 (m, 2H), 5.24−4.94 (m, 2H), 4.51 (bs, 1H), 3.89−2.64 (m, 7H), 2.26−1.54 (m, 4H); ^{13} CNMR (50 MHz, $CDCl_3$, mixture of rotamers) δ 171.9, 154.8, 133.4, 128.4, 127.8, 122.1, 121.1, 66.9, 66.5, 54.5, 54.0, 51.8, 46.7, 46.3, 32.9, 32.7, 32.4, 32.1, 29.6, 24.2, 23.5; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_4$ [M + Na]$^+$ 326.1368, found 326.1402.

(*S*)-Benzyl 2-((2*S*,3*S*)-3-Hydroxy-5-oxotetrahydrofuran-2-yl)-pyrrolidine-1-carboxylate (9). To a solution of olefin **8** (157.0 mg, 0.52 mmol) in 20 mL of 4:1 acetone/H_2O were added, in succession, *N*-methylmorpholine *N*-oxide (243.0 mg, 4.0 equiv, 2.10 mmol) and a 0.15 M aqueous solution of OsO_4 (0.26 mL, 0.075 equiv, 0.039 mmol). The solution was stirred for 48 h at room temperature. Next, after addition of Na_2SO_3 (1.40 g), the mixture was poured into a saturated aqueous solution of NaCl and extracted with AcOEt (4 × 15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The diastereoisomers (dr = 20:1) were separated by column chromatography (70% AcOEt/hexanes) to furnish pure lactone **9** (104.0 mg, 0.34 mmol, 66%) as a white solid: mp 150−153 °C; $[\alpha]^{20}_D$ −90.4 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H), 5.76 (t, J = 2.1 Hz, 1H), 5.18 (d, J = 12.3 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H), 4.38−4.34 (m, 2H), 3.95 (dd, J = 10.3, 2.6 Hz, 1H), 3.53−3.42 (m, 2H), 2.67 (dd, J = 4.7, 2.2 Hz, 1H), 2.63 (s, 1H), 2.29−2.22 (m, 1H), 2.11−1.91 (m, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 175.3, 157.1, 135.9, 128.6, 128.3, 128.0, 83.2, 67.8, 67.4, 54.9, 47.2, 38.6, 28.2, 23.0; FT-IR (neat, cm^{-1}) 3301, 2962, 2887, 1774, 1676, 1419, 1359, 1178, 1122, 1027, 767, 734; HRMS (ESI) calcd for $C_{16}H_{19}NNaO_5$ [M + Na]$^+$ 328.1155, found 328.1167; R_f 0.50 (AcOEt/hexanes 70%).

(7*S*,8*S*,8a*S*)-7,8-Dihydroxyhexahydroindolizin-5(1*H*)-one (10). To a solution of lactone **9** (42.0 mg, 0.14 mmol) in dry MeOH (1.75 mL) was added 10% Pd on charcoal (8.4 mg, 7.9 μmol, 0.06 equiv). The reaction was stirred under hydrogen atmosphere for 12 h, and then the solution was filtered over filter paper. Solvent evaporation in rotatory evaporator furnished lactam **10** (22.2 mg, 0.13 mmol) as a white solid in 94% yield: mp 142−145 °C; $[\alpha]^{20}_D$ −29.3 (*c* 1.27, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 3.85−3.76 (m, 1H), 3.52−3.36 (m, 2H), 3.34−3.24 (m, 2H), 2.80 (dd, J = 17.7, 7.0 Hz, 1H), 2.34−2.26 (m, 1H), 2.27 (dd, J = 17.6, 9.4 Hz, 1H), 2.06−1.96 (m, 1H), 1.90−1.76 (m, 1H), 1.68−1.55 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 77.0, 70.8, 62.4, 46.7, 40.1, 32.4, 23.5; FT-IR (neat, cm^{-1}) 3394, 1608, 1485, 1415, 1288, 1058; HRMS (ESI) calcd for $C_8H_{14}NO_3$ [M + H]$^+$ 172.09682, found 172.09724; R_f 0.23 (MeOH/CH_2Cl_2 20%).

(7*S*,8*S*,8a*S*)-Octahydroindolizine-7,8-diol (4). Lactam **10** (20.0 mg, 0,12 mmol) was dissolved in dry THF (2.20 mL) and cooled to 0

dx.doi.org/10.1021/jo301967w | J. Org. Chem. 2012, 77, 9926−9931

°C. A 2 M solution of BH_3·SMe_2 in toluene (0.95 mL) was added dropwise to the solution, and the mixture was stirred at 0 °C for 30 min and then at rt for 12 h. The reaction mixture was then cooled to 0 °C, and EtOH (4 mL) was carefully added. The reaction mixture was concentrated and the resulting white solid redissolved in EtOH (8 mL). After the mixture was refluxed for 24 h, the solvent was evaporated and the residue purified in an ion-exchange resin (Dowex 50WX8-100, eluent water and then 5% NH_4OH solution) to furnish 1,6-dideoxycastanospermine **4** as a clear oil (13 mg, 0.08 mmol, 71%): $[\alpha]^{20}_D$ −21.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 2H), 3.44 (ddd, *J* = 11.3, 8.6, 5.1 Hz, 1H), 3.30 (t, *J* = 8.8 Hz, 1H), 3.09 (dt, *J* = 8.7, 2.3 Hz, 1H), 3.04 (ddd, *J* = 11.4, 4.6, 2.3 Hz, 1H), 2.30−1.53 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8, 74.5, 67.7, 53.6, 49.5, 32.2, 28.1, 21.9; FT-IR (neat, cm^{-1}) 3371, 2933, 2802, 1458, 1446, 1369, 1325, 1259, 1162, 1114, 1089, 1051, 987; HRMS (ESI) calcd for $C_8H_{16}NO_2$ $[M + H]^+$ 158.11756, found 158.11747; R_f 0.45 (MeOH/$CHCl_3$ 50%).

(2*S*)-Benzyl 2-((*E*)-1-Hydroxy-4-methoxy-4-oxobut-2-enyl)-pyrrolidine-1-carboxylate (5a) and (5b). To a solution of olefin **8** (310.0, 1.0 mmol) in 17 mL of dry dichloromethane under magnetic stirring was added 453 mg (1.8 mmol, 1.8 equiv) of *m*-chloroperoxybenzoic acid. The mixture was stirred for 10 h. After that time, the solution was cooled to 0 °C, and 760 mg (5.0 mmol, 5 equiv) of DBU was carefully added. After addition, the mixture was allowed to reach to room temperature and stirred for 4 h. After this period, the volatiles were evaporated in rotary evaporator. Purification by flash column chromatography (40% AcOEt/hexanes) afforded allylic alcohols **5a** and **5b** (dr = 4:1) (214 mg, 0.67 mmol, 67%) as a stable colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ ppm 7.38−7.31 (m, 5H), 6.91 (dd, *J* = 15.47, 5.20 Hz, 1H), 6.20 (d, *J* = 15.47 Hz, 1H), 5.16 (s, 2H), 5.02 (bs, 1H), 4.30 (m, 1H), 3.94 (m, 1H), 3.76 (s, 3H), 3.65−3.56 (m, 1H), 3.44−3.38 (m, 1H), 2.02−1.72 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of diastereomers) δ 166.8, 157.1, 146.0, 136.3, 128.5, 128.1, 127.8, 122.2, 73.6, 67.4, 63.0, 51.6, 47.9, 27.9, 24.1; FT-IR (neat, cm^{-1}) 3425, 2952, 2883, 1722, 1701, 1419, 1089, 611; HRMS (ESI) calcd for $C_{17}H_{22}NO_5$ $[M + H]^+$ 320.14925, found 320.14914; R_f 0.35 (50% EtOAc/hexanes).

(*R*)-Benzyl 2-((2*S*,3*R*,4*S*)-3,4-Dihydroxy-5-oxotetrahydrofuran-2-yl)pyrrolidine-1-carboxylate (14). To a solution of allylic alcohols (140.0 mg, 0.45 mmol) in 15 mL of 4:1 acetone/H_2O were added, in succession, *N*-methyl-morpholine-*N*-oxide (205.0 mg, 1.75 mmol, 4.0 equiv), and OsO_4 (0.15 M in H_2O, 0.22 mL, 0.033 mmol). The solution was stirred for 6 h at room temperature. After addition of Na_2SO_3 (800 mg), the mixture was poured into a saturated aqueous solution of NaCl and extracted with AcOEt (4 × 15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave the lactones **14a** and **14b** (102.7 mg, 0.32 mmol, 71%) as a mixture of diastereomers (dr =4:1). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 7.43−7.29 (m, 5H), 5.22−5.04 (m, 2H), 5.02−4.61 (2bs, 1H), 4.58−4.43 (m, 1H), 4.41−4.27 (m, 2H), 4.27−4.13 (m, 1H), 3.58−3.38 (m, 2H), 2.39 (s, 1H), 2.22−1.76 (m, 4H); ^{13} C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 173.7, 156.1, 136.2, 128.5, 128.1, 127.8, 79.9, 74.1, 67.7, 67.4, 58.7, 47.1, 26.3, 23.8; FT-IR (neat, cm^{-1}) 3407, 2952, 2885, 1793, 1672, 1423, 1118; HRMS (ESI) calcd for $C_{16}H_{19}NNaO_6$ $[M + Na]^+$ 344.1105, found 344.1099; R_f 0.50 (10% MeOH/CH_2Cl_2).

(6*S*,7*R*,8*S*,8a*S*)-6,7,8-Trihydroxyhexahydroindolizin-5(1*H*)-one (15). To a solution of lactones **14** (40.0 mg, 0.12 mmol) in MeOH (13 mL) was added 10% Pd on charcoal (25.0 mg, 0.024 mmol, 0.2 equiv). Next, the reaction was stirred under hydrogen atmosphere for 16 h and the solution filtered over filter paper. The solvent was then evaporated in a rotary evaporator, and the diastereoisomers were separated by flash column chromatography (15% MeOH/DCM) to afford pure lactam **15** (15.0 mg, 0.087 mmol) in 73% yield: $[\alpha]^{20}_D$ −16.4 (*c* 9.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.95 (d, *J* = 3.1 Hz, 1H), 3.90 (t, *J* = 2.8 Hz, 1H), 3.68 (dd, *J* = 8.99, 2.73 Hz,1H), 3.63 (td, *J* = 10.00, 4.70 Hz, 1H), 3.57−3.37 (m, 2H), 2.34−2.26 (m, 1H), 2.08−1.98 (m, 1H), 1.92−1.78 (m, 1H), 1.66−1.54 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 170.4, 74.4, 73.8, 71.3, 59.4, 46.7, 32.3, 23.3; FT-IR (neat, cm^{-1}) 3390, 2925, 1625, 1471, 1083; HRMS (ESI) calcd for $C_8H_{14}NO_4$ $[M + H]^+$ 188.09173, found 188.09208; R_f 0.30 (15% MeOH/CH_2Cl_2).

(6*S*,7*R*,8*S*,8a*S*)-Octahydroindolizine-6,7,8-triol (6). A solution of lactam **15** (15.0 mg 0.08 mmol) in THF (1.5 mL) at 0 °C was added dropwise to BH_3·SMe_2 in toluene (0.70 mL, 2 M, 16 equiv). The mixture was stirred at 0 °C for 30 min and then at rt temperature overnight. The reaction mixture was cooled to 0 °C and then slowly quenched with ethanol (4 mL). The solvent was removed under reduced pressure, to the residue was added 95% ethanol (8 mL), and the mixture was refluxed for 24 h, after which time the less polar borane complex was completely converted to a polar compound. The reaction mixture was cooled to room temperature and then treated with concentrated HCl (12 drops). Ethanol was evaporated off, and the white solid was dissolved in distilled water (15 mL). The solution was concentrated under reduced pressure, and the residue was subjected to ion-exchange chromatography (Dowex 50 × 2−400 ion-exchange resin, 200−400 mesh) eluting with water and then 5% NH_4OH solution as eluent. The fractions were combined and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL), dried, filtered, and evaporated to afford **6** (9.0 mg, 0.05 mmol, 70% yield): $[\alpha]^{20}_D$ −15.2 (*c* 1.45, $CHCl_3$); $[\alpha]^{20}_D$ −14.5 (*c* 7.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 4.00−3.96 (m, 1H), 3.89 (t, *J* = 3.2 Hz, 1H), 3.85 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.49−3.39 (m, 1H), 3.28−3.00 (m, 3H), 2.99−2.88 (m, 1H), 2.34−2.21 (m, 1H), 2.09−1.95 (m, 2H), 1.88−1.69 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 71.4, 70.5, 69.9, 64.7, 54.5, 53.4, 27.6, 20.8.; FT-IR (neat, cm^{-1}) 3377, 2941, 2923, 1571, 1436, 1108; HRMS (ESI) calcd for $C_8H_{16}NO_3$ $[M + H]^+$ 174.11247, found 174.11251; R_f 0.38 (50% MeOH/$CHCl_3$).

(8a*S*)-8-Hydroxyhexahydroindolizin-5(1*H*)-one (16). To a solution of esters **5a** and **5b** (374.0 mg, 1.2 mmol) in MeOH (150 mL) was added 249 mg of 10% Pd on charcoal (0.23 mmol, 0.2 equiv). Next, the reaction was stirred under hydrogen atmosphere for 16 h and the solution filtered over Celite. The solvent was then evaporated in a rotary evaporator and the residue purified by flash column chromatography (10% MeOH/EtOAc) to afford lactams **16a** and **16b** (dr = 4:1) (138.0 mg, 0.89 mmol) in 76% yield as a colorless oil. All of the spectroscopic data are in accordance with the ones described in the literature.[22,31,32] **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63−3.38 (m, 3H), 3.32−3.23 (m, 1H), 2.90 (bs, 1H), 2.59−2.50 (m, 1H), 2.49−2.28 (m, 2H), 2.12−2.04 (m, 1H), 2.02−1.86 (m, 1H), 1.84−1.69 (m, 2H), 1.60−1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 71.8, 64.0, 45.6, 31.7, 30.3, 30.1, 22.4; FT-IR (neat, cm^{-1}): 3360, 2945, 2877, 1614, 1467, 1415, 1321, 1415, 1338, 1321, 1267, 1224, 1142, 1089, 993, 964, 842, 771; HRMS (ESI) calcd for $C_8H_{14}NO_2$ $[M + H]^+$ 156.10191, found 156.10194; R_f 0.20 (10% MeOH/EtOAc).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new and final known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank FAPESP (Research Supporting Foundation of the State of Sao Paulo) for financial support (2012/04685-5) and a fellowship to V.D.P. (2008/09653-9). We also thank CNPq for a research fellowship to A.C.B.B. (307905/2009-8) and a

student fellowship to B.B. (160428/2011-4). We also thank IQSC-USP for facilities, Professor Timothy Brocksom (UFSCar) and Carlos R. D. Correia (UNICAMP) for optical rotation analysis, Professor Daniel Cardoso for help with the photochemical system, Eduardo Sanches Pereira do nascimento for NMR and HRMS (FAPESP 2009/54040-8) acquisitions, Guilherme Miola Titato for HRMS acquisitions, and DQO-UFSCar for some NMR analyses.

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