ORGANIC LETTERS

2006
Vol. 8, No. 21
4739−4742

# Asymmetric [2 + 2] Cycloaddition: Total Synthesis of (−)-Swainsonine and (+)-6-Epicastanospermine†

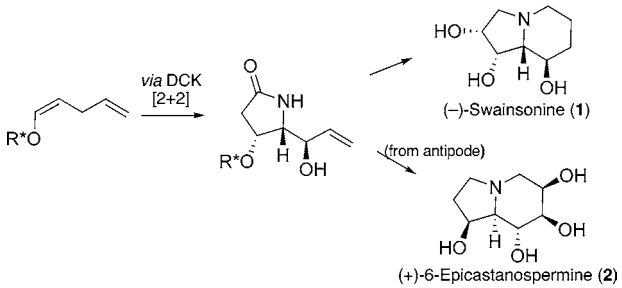
**Julien Ceccon, Andrew E. Greene, and Jean-François Poisson***

*Chimie Recherche (LEDSS), Université Joseph Fourier, 38041 Grenoble, France*

*jean-francois.poisson@ujf-grenoble.fr*

**Received July 19, 2006**

## ABSTRACT




**An asymmetric total synthesis of (−)-swainsonine and (+)-6-epicastanospermine is described from a common intermediate, which is obtained through diastereoselective [2 + 2] cycloaddition of dichloroketene to a chiral enol ether.**

The [2 + 2] cycloaddition of dichloroketene (DCK) to chiral enol ethers provides an efficient enantioselective approach to substituted 4-hydroxypyrrolidinones.[1] This methodology, which has already been used successfully for the synthesis of various relatively simple natural alkaloids,[1b−h] appeared also to offer possible access to complex polyhydroxylated indolizidines, such as (−)-swainsonine (**1**), (+)-6-epicastanospermine (**2**), and (+)-castanospermine (**3**) (Figure 1). These naturally occurring azasugars, which are efficient glycosidase inhibitors,[2] have received considerable attention due to their biological activities and the challenge inherent in their total synthesis.[3]

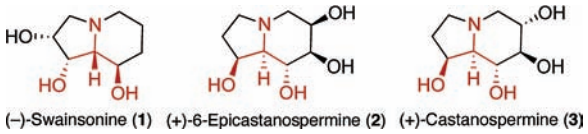



**Figure 1.** Polyhydroxylated indolizidines.

Since a cis−trans aminodiol core is shared by many of the polyhydroxylated indolizidines, (e.g., **1**−**3**, highlighted in red, Figure 1), it seemed a unified route to several of these important compounds might be possible from a single

† Dedicated to the memory of an outstanding person, Dr. Pierre Potier (deceased February 3, 2006).

(1) (a) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210−5211. (b) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660−4663. (c) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383−1386. (d) Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. (e) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443. (f) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741−1744. (g) Muniz, M. N.; Kanazawa, A.; Greene, A. E. *Synlett* **2005**, 1328−1330. (h) Ceccon, J.; Poisson, J. F.; Greene, A. E. *Synlett* **2005**, 1413−1416. (i) Roche, C.; Kadlecikova, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E.; Flot, D.; Burghammer, M. *J. Org. Chem.* **2005**, *70*, 8352−8363.

(2) (a) Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182−190. (b) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750−770. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300−2324. (d) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265−295. (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515−553. (f) Nash, R. *Chem. World* **2004**, *1*, 42−44.

(3) For reviews on the indolizidines, see: (a) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579−8629. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680. (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603−626. (d) Pyne, S. G. *Curr. Org. Synth.* **2005**, *2*, 39−57 and references cited therein.

10.1021/ol0617751 CCC: $33.50 
**Published on Web 09/13/2006**

intermediate. We now describe the synthesis of (−)-swainsonine and (+)-6-epicastanospermine from a common intermediate.

(−)-Swainsonine was first isolated in 1973 from the fungus *Rhizoctonia leguminicolain*.[4] It has been identified as the major toxin in the Australian legume *Swainsona canescens*[5] and shown to be responsible for the "peastruck disease" in sheep. It has also been found in *Astragalus* and *Oxytropis* species (commonly called locoweed) and is currently extracted in gram quantities from the latter.[6] Swainsonine is a potent inhibitor of α-D-mannosidase and thus exhibits notable biological properties, such as alteration of virus proliferation and antimetastatic activity.[7] It has been tested in many countries as an adjunct to chemotherapy and is currently in phase II clinical trials in the United States for the treatment of cancer.[8] Due to these exciting biological activities, as well as its interesting structure, (−)-swainsonine has been a particularly popular target for total synthesis.[3,9] Most of the approaches to date, however, parlay carbohydrate chirality.

(−)-Swainsonine, it seemed, would be obtainable by dihydroxylation of dehydroindolizidine **V**,[10] which could arise through ring-closing metathesis (RCM) of **IV** (Figure 2). Despite the obviousness of forming the indolizidine skeleton through the use of RCM to close the six-membered ring, no total synthesis of (−)-swainsonine has so far been reported using this strategy.[11] The substrate for the metathesis reaction, in turn, could originate from allylic alcohol **III**, the envisioned pivotal intermediate for the preparation of several of the polyhydroxylated indolizidines. This aminodiol,[12] secured by allylic oxidation of the Beckmann ring-expanded product **II**, has recently been used in the synthesis of the unusual amino acid (−)-detoxinine[1h] and in a preparation of (+)-retronecine.[1i]

Pyrrolidinone **9a** was synthesized starting from the *S* enantiomer of 1-(2,4,6-triisopropylphenyl)ethanol (Scheme 1).[13] The potassium alkoxide of this alcohol (**4**, R*OH) reacted with trichloroethylene to give dichloroenol ether **5** in high yield. Treatment of the latter with 2 equiv of *n*-butyllithium produced an ynol ether acetylide, which was alkylated in situ with allyl iodide to yield ynol ether **6a**. The selective partial reduction of the triple bond in **6a** with diisobutylaluminum hydride in toluene[14] at 50 °C then afforded enol ether **6b**, free of the allyl-reduced product partially formed under catalytic hydrogenation conditions.[15]

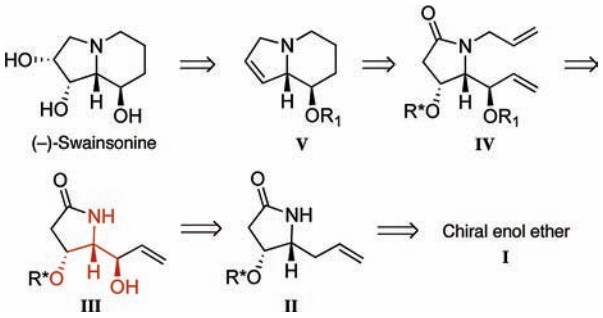
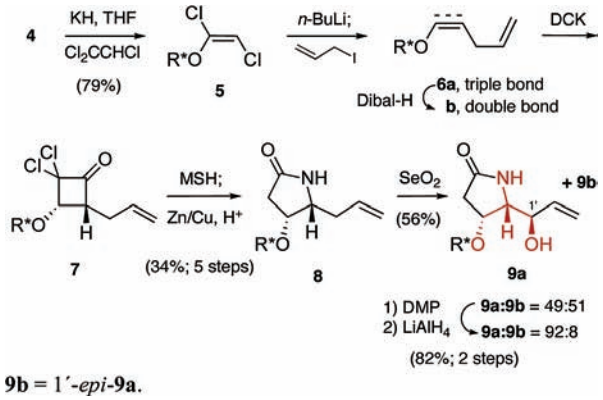



**Figure 2.** Retrosynthetic approach to (−)-swainsonine.

**Scheme 1.** Synthesis of the Key Intermediate




The [2 + 2] cycloaddition of dichloroketene (DCK) to enol ether **6b** generated with excellent diastereoselectivity (ca. 95%, $^1$H NMR) dichlorocylobutanone **7**, which was directly subjected to Beckmann ring expansion using Tamura's reagent (MSH).[16] Dechlorination of the uniquely formed regioisomer with zinc−copper couple in acidic methanol then afforded pyrrolidinone **8** in 34% overall yield for the 5 steps (80%/step). It should be noted that this sequence was routinely performed on a multigram scale with only a final

(4) (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, 29−32.

(5) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257−2264.

(6) Gardner, D. R.; Lee, S. T.; Molyneux, R. J.; Edgar, J. A. *Phytochem. Anal.* **2003**, *14*, 259−266.

(7) (a) Olden, K.; Breton, P.; Grzegorzewski, K.; Yasuda, Y.; Gause, B. L.; Oredipe, O. A.; Newton, S. A.; White, S. L. *Pharmacol. Ther.* **1991**, *50*, 285−290. (b) Galustian, C.; Foulds, S.; Dye, J. F.; Guillou, P. J. *Immunopharmacology* **1994**, *27*, 165−172.

(8) (a) Klein, J.-L. D.; Roberts, J. D.; George, M. D.; Kurtzberg, J.; Breton, P.; Chermann, J.-C.; Olden, K. *Br. J. Cancer* **1999**, *80*, 87−95. (b) Shaheen, P.; Stadler, W.; Elson, P.; Knox, J.; Winquist, E.; Bukowski, R. *Invest. New Drugs* **2005**, *23*, 577−581.

(9) For recent syntheses, see: (a) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325−2328. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609−1612 and references cited therein.

(10) (a) Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287. (b) de Vicente, J.; Arrayas, R. G.; Canada, J.; Carretero, J. C. *Synlett* **2000**, 53−56. (c) Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (d) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774−7780.

(11) See, however, ref 9a. For the application of RCM to form the 6-membered ring in the preparation of other indolizidines, see: (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251−7264. (b) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621−2624. (c) El-Nezhawy, A. O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137−4142. (d) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630−4633.

(12) With R* = (*S*)-1-(2,4,6-triisopropylphenyl)ethyl.

(13) This chiral alcohol was obtained by resolution of the racemic material. See: Delair, P.; Kanazawa, A. M.; M. B. de Azevedo, M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710.

(14) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178−6195.

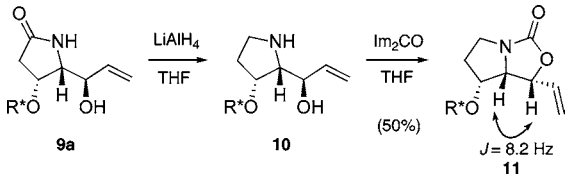
(15) There is usually ca. 10% reduction of the terminal double bond under catalytic hydrogenation conditions.

(16) MSH = *O*-mesitylenesulfonylhydroxylamine. See: Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1−17.

purification. The assignment of the indicated stereochemistry to the major diastereomer was initially based on considerable precedent[1] and was subsequently confirmed by the realization of the synthesis of (−)-swainsonine. The minor lactam diastereoisomer (ca. 5%), conveniently, filtered out over the course of the synthesis.

Allylic oxidation of **8** under Sharpless conditions ($SeO_2$, *t*-BuOOH, $ClCH_2CH_2Cl$, reflux, 3.3 h) afforded the corresponding allylic alcohols **9a**,**b** in 56% yield as a difficult to separate 1:1 mixture, together with 25% of recovered starting material. These conditions were found to be optimal, as the over-oxidized enone product was unstable under the reaction conditions. Certain variations in the starting material, for example, replacing the chiral auxiliary with a benzoyl group, did afford the allylic alcohols in a better ratio, but at the expense of the yield (2:1 ratio and 36% yield for benzoyl). The allylic alcohols were therefore oxidized with the Dess−Martin periodinane to the corresponding sensitive enone, which was then directly reduced using $LiAlH_4$ in THF at −25 °C. The desired cis−anti isomer **9a** was obtained as the major product (92:8 diastereoisomeric ratio) in 82% yield for the two steps. The assignment of the relative stereochemistry in the major diastereoisomer was made through $^1H$ NMR analysis of the oxazolidinone derivative **11** ($LiAlH_4$; carbonyldiimidazole, Scheme 2): a coupling constant of 8.2

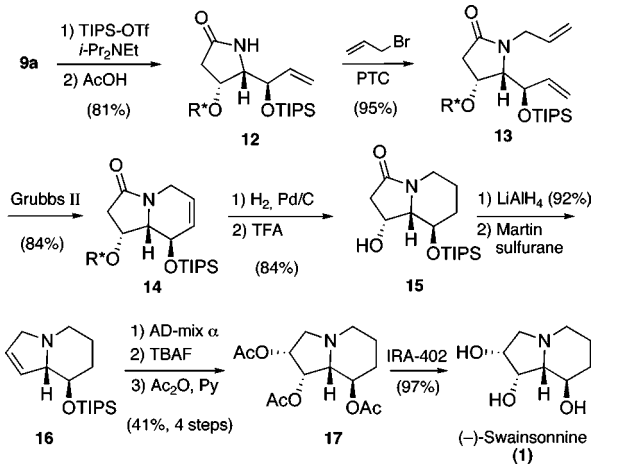
**Scheme 2.** Assignment of Relative Stereochemistry




Hz was observed for the oxazolidinone protons, which indicated a cis relationship[17] and thus cis−anti stereochemistry in **9a**.

With this central intermediate in hand, the synthesis of (−)-swainsonine was pursued (Scheme 3). The allylic alcohol was converted into its triisopropylsilyl ether **12** through disilylation, followed by selective hydrolysis of the silyl imidate with acetic acid (81%). *N*-Allylation of the lactam was next achieved in 95% yield under phase-transfer conditions (PTC).[18] Ring-closing metathesis of **13** using the Grubbs II catalyst could be efficiently achieved in refluxing dichloromethane to provide bicyclic **14** in 84% yield. Hydrogenation of the double bond over palladium on charcoal was followed by selective cleavage of the chiral auxiliary using TFA to furnish indolizidinone **15** (84% yield). Reduction of the lactam with $LiAlH_4$ and subsequent

**Scheme 3.** Synthesis of (−)-Swainsonine




elimination of the secondary hydroxyl group by using the Martin sulfurane in ether then afforded the dehydroindolizidine **16**, which was used without purification.[19] This dehydration was particularly difficult, and numerous alternative conditions and procedures proved unsuccessful. The sulfurane in dichloromethane or acetonitrile, instead of ether, for example, failed to effect the elimination.

Dihydroxylation of **16** furnished the diol as a 20:1 mixture of diastereoisomers, in favor of the desired endo isomer. The observed selectivity in this reaction, which is concordant with previously reported results with similar indolizidines, is undoubtedly due to steric hindrance on the exo face by the large silyloxy group and the pseudoaxial allylic protons.[10] To facilate purification, the mixture was desilylated with TBAF and the resulting triol peracetylated with acetic anhydride in pyridine, which gave, after $SiO_2$ chromatography, pure triacetate **17** (41% over the last four steps, 80%/step). This highly stereocontrolled total synthesis of (−)-swainsonine was completed by treatment of **17** with the ion-exchange resin IRA-402 ($OH^-$ form). (−)-Swainsonine ($[\alpha]^{20}_D$ −86.2 (*c* 1.0, MeOH), mp 143−144 °C) so obtained was spectroscopically and chromatographically identical with an authentic sample of the natural product ($[\alpha]^{20}_D$ −87.2 (*c* 2.1, MeOH), mp 144−145 °C).[4b,20]

Indolizidinone **14**, the product of ring-closing metathesis, also seemed to be an ideal intermediate for a straightforward synthesis of (+)-6-epicastanospermine;[21,22] however, the absolute configuration required for this natural product is opposite to that for (−)-swainsonine. The synthesis was thus repeated starting now from the antipodal *R* enantiomer of alcohol **4**, which produced ***ent*-14** in 10.4% overall yield.

(17) (a) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308−3310. (b) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A.; Varchi, G. *J. Org. Chem.* **1999**, *64*, 8008−8013. (c) Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560.

(18) At this stage, the minor diastereomer derived from **9b** could be completely removed chromatographically.

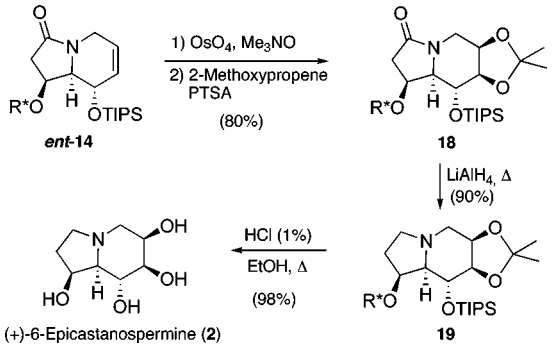
(19) Compound **16** was contaminated with a byproduct from the Martin sulfurane, but this impurity did not affect the outcome of the next step.

(20) The spectral data and chromatographic behavior were compared with those of a sample of (−)-swainsonine purchased from Sigma.

(21) (+)-6-Epicastanospermine has been isolated from *Castanospermum australe* and is a potent inhibitor of amyloglucosidase. See: (a) Molyneux, R. J.; Roitman, J. N.; Dunnheim, G.; Szumilo, T.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**, *251*, 450−457. (b) Nash, R. J.; Fellows, L. E.; Girdhar, A.; Fleet, G. W. J.; Peach, J. M.; Watkin, D. J.; Hegarty, M. P. *Phytochemistry* **1990**, *29*, 1356−1358.

Dihydroxylation of the double bond with osmium tetroxide[23] led selectively (>20:1) to the corresponding diol, which was directly converted into its acetonide derivative **18**, isolated as a single isomer in 80% yield (two steps, Scheme 4). In the most stable conformation of the olefin (AM1

**Scheme 4.** Synthesis of (+)-6-Epicastanospermine




calculations), the six-membered ring is quite flat and α-face-protected by the bulky silyloxy group, which could explain the observed face selectivity (Figure 3). The lactam was reduced with $LiAlH_4$ in THF to give amine **19**, and then all of the protecting groups were simultaneously removed with acidic ethanol to afford (+)-6-epicastanospermine in excellent yield. The spectroscopic data for **2** ($[\alpha]^{20}_D$ +2.3 (*c* 0.7, MeOH)) were in complete agreement with the reported data for the naturally derived product.[24]

(22) For a review on syntheses of **2** through 1992, see: (a) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045−4066. For subsequent syntheses, see: (b) Kang, S. H.; Kim, J. S. *J. Chem. Soc., Chem. Commun.* **1998**, 1353−1354. (c) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056. (d) Zhang, H.-X.; Xia, P.; Zhou, W.-S. *Tetrahedron* **2003**, *59*, 2015−2020. (e) Kim, J. H.; Seo, W. D.; Lee, J. H.; Lee, B. W.; Park, K. H. *Synthesis* **2003**, 2473−2478.

(23) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976. (b) Chevallier, F.; Le Grognec, E.; Beaudet, I.; Fliegel, F.; Evain, M.; Quintard, J.-P. *Org. Biomol. Chem.* **2004**, *2*, 3128−3133.

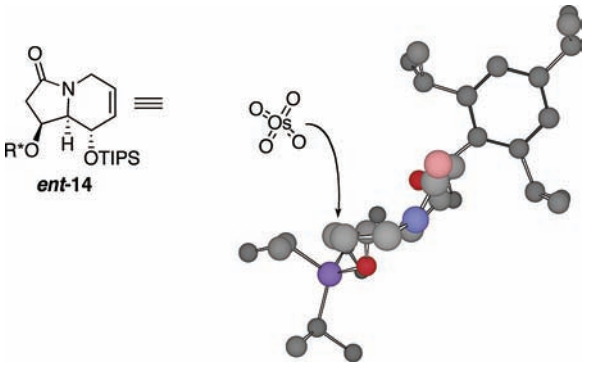



**Figure 3.** Attack on the less hindered face of *ent*-**14**.

In summary, the total synthesis of two natural polyhydroxylated indolizidines has been achieved in a highly stereoselective manner from a common intermediate, obtained by asymmetric [2 + 2] cycloaddition. To underscore the general nature of our approach, we are currently applying a similar strategy from this same intermediate for the synthesis of (+)-castanospermine.

**Acknowledgment.** We thank Professor P. Dumy (UJF) for his interest in our work. Financial support from the CNRS and the Université Joseph Fourier (UMR 5616, FR 2607) and a fellowship award (to J.C.) from the Research Ministry (MENRT) are gratefully acknowledged.

**Supporting Information Available:** Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0617751

(24) Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700−3706.