Efficient Stereoselective Access to Polyhydroxylated Indolizidine Compounds Based on γ-Hydroxy-α,β-unsaturated Sulfones

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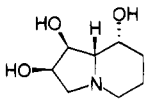
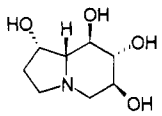
Received May 16, 1995

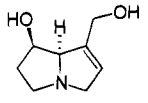
Naturally occurring polyhydroxylated indolizidine and pyrrolizidine alkaloids, such as castanospermine, swainsonine, or retronecine (necine subunit), exhibit very diverse and important physiological properties, which explain the intense efforts made in order to develop efficient syntheses of these compounds, as well as their stereoisomers and derivatives.[1] By far, most of the reported syntheses of polyhydroxylated indolizidine alkaloids require carbohydrates as starting materials, which limits their flexibility for the preparation of stereoisomers and analogues.



Swainsonine



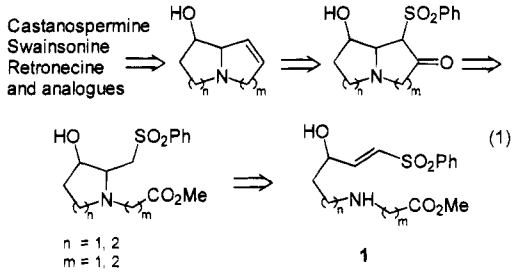
Castanospermine

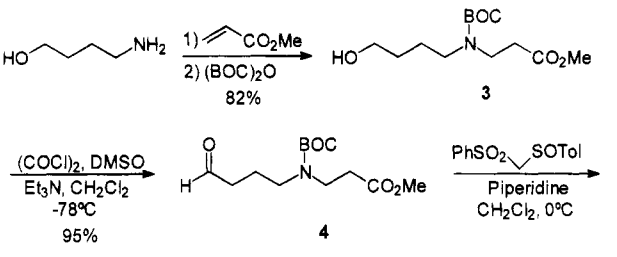


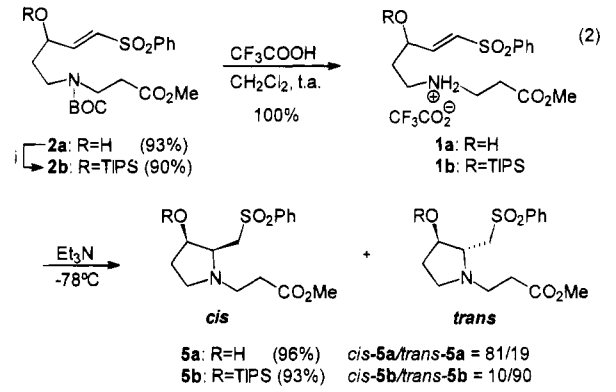
Retronecine

As a part of our current interest concerning the use of γ-hydroxy-α,β-unsaturated sulfones as versatile intermediates in stereoselective synthesis,[2] we planned that the monohydroxylated bicyclic skeleton of these alkaloids could be readily prepared by intramolecular conjugate addition of the N-substituted γ-hydroxy-α,β-unsaturated sulfone **1**, followed by intramolecular condensation between the α-sulfonyl carbanion and the ester moiety. Further elimination of the sulfonyl group by Julia reaction would lead to a C=C bond suitable for dihydroxylation reactions (eq 1).

The BOC derivatives **2** of the unstable substrates **1** were readily prepared in four steps from 4-amino-1-butanol (72% overall yield) by applying the synthetic sequence shown in eq 2. The conjugate addition of 4-amino-1-butanol to methyl acrylate (EtOH, 0 °C) followed by reaction of the resulting amine with BOC_2O (CH_2Cl_2, rt) furnished carbamate **3**. Oxidation of **3** (DMSO, oxalyl chloride, Et_3N) yielded aldehyde **4**, the







(i) TIPS-triflate, 2,6-lutidine, CH_2Cl_2

condensation of which with (phenylsulfonyl)(*p*-tolylsulfinyl)methane in the presence of piperidine (CH_2Cl_2, 0 °C, 10 h) gave the key γ-hydroxy-α,β-unsaturated sulfone[3] **2a**.

The treatment of carbamates **2** with CF_3CO_2H (excess) in CH_2Cl_2 at rt yielded quantitatively the ammonium salts **1**, which after isolation were redissolved and treated with Et_3N (excess). The cyclizations were complete in less than 30 min, giving almost quantitatively a mixture of *cis*- and *trans*-pyrrolidines **5**.[4] Interestingly, whereas the cyclization of **1a** in toluene at 0 °C afforded the *cis*-pyrrolidine as the major isomer (*cis*-**5a**/*trans*-**5a** = 81/19), the cyclization of the TIPS derivative **1b** in THF at −78 °C was highly stereoselective in favor of the *trans* isomer (cis-**5b**/*trans*-**5b** = 10/90).[5]

The overall transformation of *cis* pyrrolidines **5** into a trihydroxylated indolizidine with *cis*-stereochemistry at C1−C8 is shown in eq 3. The construction of the second ring was readily accomplished by intramolecular Claisen-like condensation of the TBDMS derivative *cis*-**5c** (prepared in 71% overall yield from **2a** by standard silylation of the mixture *cis*-**5a** + *trans*-**5a** and further chromatographic purification) by using LHDMS (2.2 equiv) as the base, in THF at 0 °C.[6] The resulting bicyclic α-sulfonyl

(1) For a review on synthetic approaches to castanospermine and analogues, see: (a) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. For some very recent references, see: (b) Jadhav, P. K.; Woerner, F. J. *Tetrahedron Lett.* **1994**, *35*, 8973. (c) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487. (d) Kim, N.-S.; Kang, C. H.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3489. (e) Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1994**, *35*, 3143. (f) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358. (g) Denmark, S. E.; Thorarensen, A. *J. Org. Chem* **1994**, *59*, 5672. (h) Pandey, G.; Lakshamaiah, G. *Synlett.* **1994**, 278. (i) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949. (j) Martín-López, M. J.; Bermejo-González, *Tetrahedron Lett.* **1994**, *35*, 8843. (k) Herczegh, P.; Kovács, I.; Szilágyi, L.; Sztaricska, F. *Tetahedron* **1994**, *50*, 13671. (l) Martin, S. F.; Chen, H.-J., Lynch, V. N. *J. Org. Chem.* **1995**, *60*, 276. (m) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (n) Oishi, T.; Iwakuma, T.; Hirama, M.; Itô, S. *Synlett.* **1995**, 404. (o) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501. (p) Zhou, W.-S.; Xie, Z.-H.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291. (q) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2335.

(2) (a) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1994**, *50*, 7557. (b) Blas, J.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1994**, *35*, 4603. (c) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1993**, *58*, 1596.

(3) (a) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867. (b) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197.

(4) The *cis*/*trans* configuration of pyrrolidines **5** was determined by ^{1}H-NMR (in *cis* isomers, $J_{3,2} \approx J_{3,4a} \approx J_{3,4b} \approx 6.4$ Hz and in *trans* isomers $J_{3,2} \approx 2.8$ Hz and $J_{3,4a} \approx J_{3,4b} \approx 1$ Hz; see: Gallina, C.; Paci, M.; Viglino, P. *Org. Magn. Reson.* **1972**, *4*, 31) and by straightforward chemical correlation between unprotected **5a** and protected pyrrolidines **5b**.

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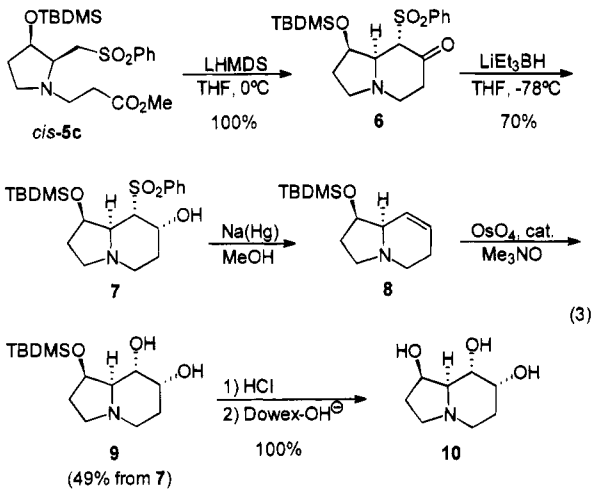

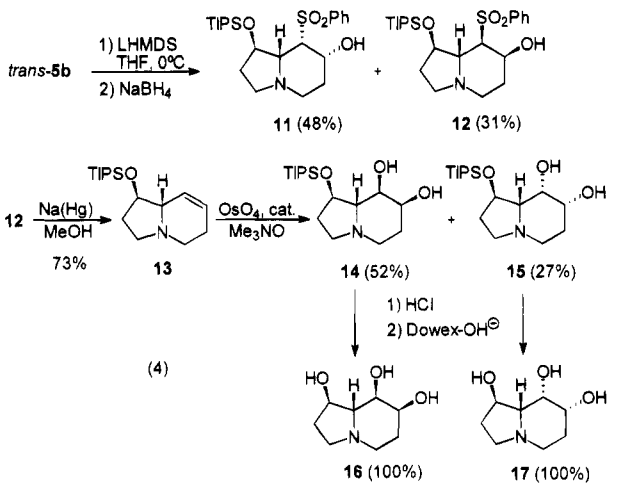

ketone **6** was obtained in quantitative yield as a single stereoisomer,[7] the further reduction of which with $LiEt_3BH$[8,9] (1 equiv) in THF at −78 °C was completely stereoselective affording the alcohol **7** in 70% overall yield (from *cis*-**5c**) after chromatography.[7] The β-hydroxy sulfone **7** underwent the Julia elimination by treatment with Na(Hg) in MeOH (Na_2HPO_4), giving the olefin **8** as the main product. Due to its moderate stability, crude **8** was immediately dihydroxylated under standard conditions (OsO_4 cat., Me_3NO) to afford a single diol **9**[7] (49% overall yield from **7** after chromatography). Finally, deprotection of the TBDMS group (5 N HCl) and neutralization with a basic ion-exchange resin (Dowex-OH) furnished quantitatively the trihydroxylated indolizidine **10**.

Following a similar reaction sequence, trihydroxylated indolizidine compounds with *trans* stereochemistry at C1−C8a were obtained from *trans*-**5b** (eq 4). Unlike the behavior of *cis*-**5c**, the intramolecular Claisen condensation of *trans*-**5b** (2.2 equiv of LHDMS, THF, 0 °C) occurred with low stereoselectivity, yielding quantitatively a 3:2 mixture of the corresponding bicyclic α-sulfonyl ketones. This crude mixture of ketones was stereoselectively reduced with $NaBH_4$[9] (EtOH, CH_2Cl_2, rt) to give a 58:42 mixture of alcohols **11** and **12**, which were separated by silica gel chromatography.[7] Only the alcohol **12**, having the hydroxyl group in axial position,[10] afforded the olefin **13** in good yield (73%) after Julia elimination of the sulfonyl group (Na−Hg, MeOH, rt). Unlike the behavior of olefin **8**, the dihydroxylation of **13** (OsO_4 cat., Me_3NO in a 5:1 mixture of acetone/water at rt) was not as selective, leading in 79% yield to a 67:33 mixture of diols **14** and **15**, which were readily separated by flash chromatography.[7] The quantitative deprotection of the TIPS group by treatment with 5 N HCl and further neutralization (Dowex 1-X8 ion-exchange chromatography) furnished the trihydroxylated indolizidines **16** and **17**.

In summary, a new and stereoselective access to polyhydroxylated indolizidine alkaloids has been described. This procedure requires few steps from the readily available γ-hydroxy vinyl sulfones **2** and shows a great stereochemical flexibility. Further studies oriented to the preparation of all possible stereoisomers of polyhydroxylated indolizidines and the synthesis of pyrrolizidine or quinolizidine compounds by appropiate choice of the carbon chains in the starting γ-hydroxy vinyl sulfone **1** are in progress in our laboratory.

Acknowledgment. Financial support from the DGICYT (Grant No. PB-93-0244) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and compound characterization data (6 pages).

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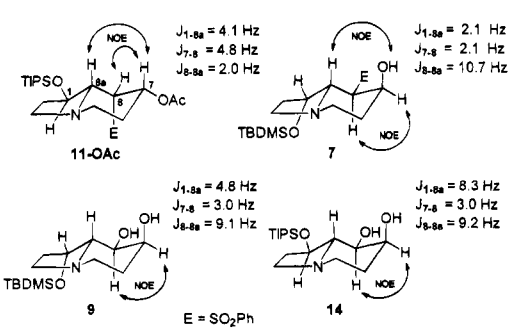
(5) The cyclization of other hydroxyl-protected derivatives of **2a** such as acetate, MOM, and TBDMS derivatives was also studied, but the *trans*-stereoselectivity of the cyclization was lower than in the case of **2b**. For the effect of the γ-substitution on the stereoselectivity of the intramolecular conjugate addition of alkoxides to γ-oxygenated-α,β-unsaturated esters, see: Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177.

(6) Very low yields of **6** were obtained by using LDA instead of LHDMS. For other examples of intramolecular condensations between esters and α-sulfonyl carbanions see: Grimm, E. L.; Coutu, M. L.; Trimble, L. A. *Tetrahedron Lett.* **1993**, *34*, 7017. See also: William, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 35. Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1995**, 249.

(7) The stereochemical assignment of all compounds was unequivocally established by ^{1}H-NMR by analysis of the coupling constants and the NOE's. For instance, in the shown below are the most significant data of **7**, **9**, **11**, and **14**.



(8) The reduction of **6** with DIBAL (CH_2Cl_2, −78 °C) was also completely stereoselective but favored the other stereoisomeric alcohol (**18**).

(9) For a general study on the stereoselectivity of the hydride reduction of 2-sulfonylcyclohexanones, see: Carreño, M. C.; Domínguez, E.; García Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619.

(10) For the Julia elimination in cyclic β-hydroxy sulfones it is required the hydroxyl group to be in an axial position as in **7** and **12** (see: Kocienski, P. J. *Chem. Ind. (London)* **1981**, 548). Thus, from **11** and **18**, which have the OH in equatorial position, the alcohols **19** and **20** were obtained, respectively, as the main products after reaction with Na(Hg).