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A Stereoselective Approach to Polyhydroxylated Quinolizidine Alkaloids

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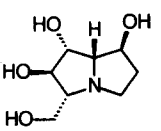
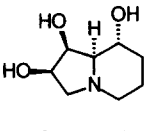
Abstract: Both 1,2,9-trihydroxylated and 1,2,3,9-tetrahydroxylated quinolizidines have been stereoselectively prepared in few steps and high overall yields from the readily available γ-oxygenated-α,β-unsaturated sulfones **1** and **2**. © 1997 Elsevier Science Ltd.

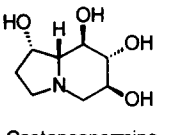
Many classes of alkaloids have either a pyrrolizidine[1] or an indolizidine[2] skeleton as a key structural element. Particularly, polyhydroxylated indolizidine and pyrrolizidine alkaloids, such as swainsonine, castanospermine and alexine (figure 1) have attracted considerable interest due to their high activity as glycosidase inhibitors and, probably as a consequence of this, they show a wide range of biological activities, including anti-viral, anti-cancer and anti-feedant properties.[3] In order to undertake the study of structure-activity relationships, considerable efforts have been made in recent years on the synthesis of this type of alkaloids as well as stereoisomers and analogues.[4] By contrast, studies dealing to the synthesis and biological activity of polyhydroxylated quinolizidines are scarce,[5] although these compounds represent the formal homologation of the indolizidine structure. As part of our current interest on the use of the readily available γ-oxygenated-α,β-unsaturated sulfones[6] as versatile starting materials in the stereoselective synthesis of important structures,[7] we describe herein a new approach to the stereoselective preparation of 1,2,9-trihydroxylated- and 1,2,3,9-tetrahydroxylated quinolizidines (homo-castanospermine stereoisomers).



Alexine



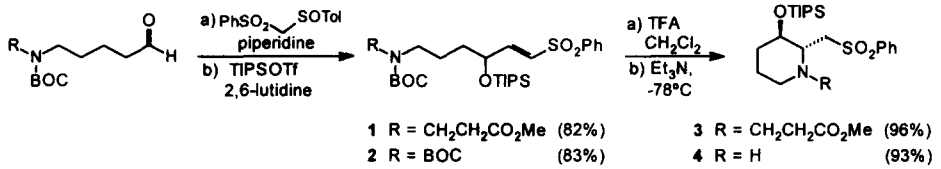
Swainsonine



Castanospermine

Figure 1

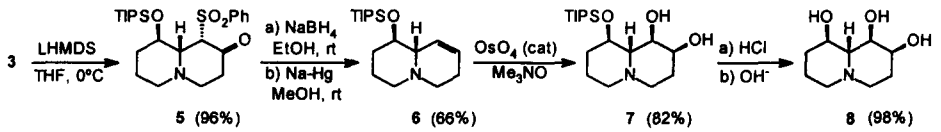
As we previously reported, the required highly functionalyzed γ-oxygenated-α,β-unsaturated sulfones **1** and **2** were readily prepared by condensation of phenylsulfonyl *p*-tolylsulfinyl methane with the corresponding aldehydes and subsequent protection as TIPS derivatives.[8] After cleavage of the BOC group (TFA, CH_2Cl_2) and addition of Et_3N to generate the free amine, its intramolecular addition to the α,β-unsaturated sulfone occurred rapidly at -78°C in a highly *trans*-stereoselective manner.[8] The *trans* piperidines **3** and **4** were isolated in excellent yields after chromatographic purification (scheme 1).



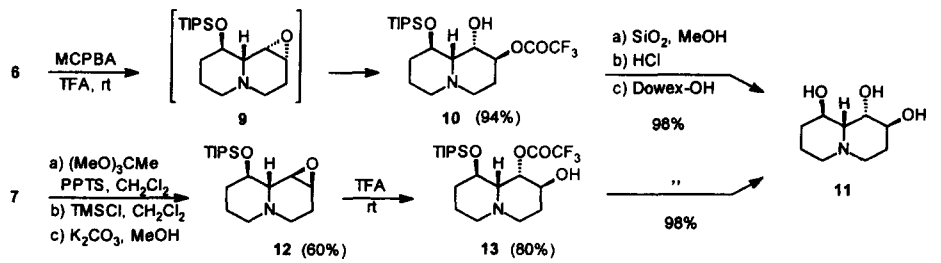
Scheme 1

The stereoselective synthesis of a pair of 1,2-*cis* and 1,2-*trans* 1,2,9-trihydroxylated quinolizidines from piperidine **3** is depicted in schemes 2 and 3. Deprotonation of **3** with LHMDS (2 equiv.) in THF led to the α-sulfonyl carbanion, which evolved by intramolecular acylation to furnish stereoselectively the quinolizidine **5** (96% yield). Carbonyl reduction of **5** with $NaBH_4$ gave exclusively the equatorial alcohol, whose Julia reaction with Na-Hg afforded the olefin **6**[9] (66% yield from **5**). *Syn*-dihydroxylation of **6** with OsO_4(cat)/Me_3NO (in a 8:1 mixture of acetone/water at rt) occurred also with complete stereocontrol to give the diol **7**. Subsequent deprotection of the TIPS group (HCl 5M) and neutralization with a basic ion-exchange resin (Dowex-OH) afforded the trihydroxylated quinolizidine **8**[10] (51% yield from piperidine **3**).

On the other hand, the *anti*-dihydroxylation at C_1-C_2 was accomplished either from olefin **6** or from diol **7** (scheme 3). In order to minimize the N-oxide formation, epoxidation of **6** with MCPBA (1 equiv.) was performed in TFA as solvent.[11] The reaction was again highly stereoselective but with opposite stereoselectivity to that observed in the dihydroxylation reaction.[12] The resulting unstable epoxide **9** could be detected by ^{1}H-NMR, but it evolved rapidly by *trans*-diaxial opening in the trifluroacetic medium to give the 1,2-*trans* trifluoracetate **10**. Hydrolysis of **10** with silica gel in MeOH, followed by cleavage of the TIPS group (HCl 5M) and neutralization with Dowex-OH afforded the trihydroxylated quinolizidine **11**[10] (91% overall yield from **6**). Alternatively, **11** was prepared from *cis*-diol **7** in 47% overall yield as follows: formal dehydratation of diol **7** to the diastereomeric epoxide **12** following the Sharpless procedure,[13] trifluoroacetolysis of the epoxide to give the *trans*-diaxial derivative[14] **13** and hydrolysis of the silyl ether and trifluoroacetate protecting groups.

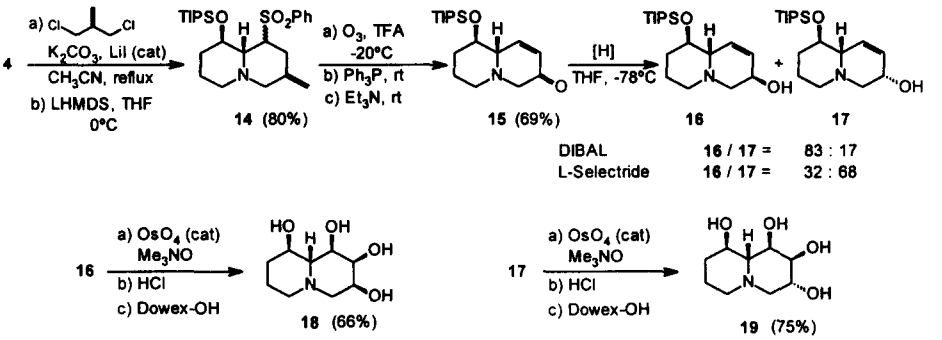


Scheme 2



Scheme 3

For the preparation of homo-castanospermine stereoisomers (1,2,3,9-tetrahydroxylated quinolizidines) we developed the synthetic approach shown in scheme 4. N-alkylation of piperidine **4** with 3-chloro-2-chloromethylpropene (K_2CO_3, cat LiI, THF, rt), followed by C-alkylation (LHMDS, THF, 0°C) furnished the methylene quinolizidine **14** as a mixture of both epimers at C-1 (80% yield).[15] Ozonolysis of **14** in TFA as solvent,[16] subsequent reductive work-up (PPh_3), and final addition of Et_3N to promote the basic elimination of the sulfonyl group gave the key enone **15** (69% yield). We were pleased to find that the stereoselectivity observed in the carbonyl reduction of **15** was very dependent on the hydride used. Thus, whereas the reduction with DIBAL (THF, -78°C) was highly stereoselective in favour of the equatorial alcohol **16** (**16:17**= 83:17), the reaction with L-Selectride (THF, -78°C) led predominantly to the axial alcohol **17** (**16:17**=32:68). Both epimers, **16** and **17**, were separated by flash chromatography and regardless of the stereochemistry at C-3 the *syn*-dihydroxylation (cat. OsO_4, Me_3NO, 8:1 mixture of acetone/water, rt) occurred in both cases with complete stereocontrol from the same face of the olefin (*syn* to the hydrogen at C-9a),[17] as it was previously observed in the dihydroxylation of the C-3 unsubstituted quinolizidine **6** (scheme 2). After quantitative hydrolysis of the silyl ether (HCl 5M), the resulting tetrahydroxylated quinolizidines **18** (from **16**) and **19** (from **17**) were obtained in good overall yields, 66% and 75% respectively.[10]



Scheme 4

In summary, a short and stereoselective synthesis of 1,2,9-trihydroxylated and 1,2,3,9-tetrahydroxylated quinolizidines based on readily available functionalyzed γ–hydroxyvinyl sulfones has been described. Stereoselective synthesis of other isomers as well as the preparation of enantiopure compounds are currently under investigation in our laboratory. The biological activity of these compounds will be reported in due course.

Acknowledgement. Financial support from the DGICYT (Grant No. PB93-244 and PB96-0021) is gratefully acknowledged.

References and Notes

1. For a recent review, see: Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413.
2. For a recent review, see: Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535.
3. For a review, see: Elbein, A. D.; Molyneux, R. J. *In Alkaloids: Chemical and Biological Perspectives;* Pelletier, S. W.; Ed. Wiley: New York, 1987; Vol. 5, Chapter 1.

4. For a review on synthesis of castanopermine and analogues, see: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. For some recent references, see: Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547. b) Mootoo, D. R.; Zhao, H. *J. Org. Chem.* **1996**, *61*, 6762. c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7219.
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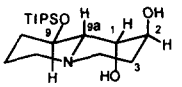
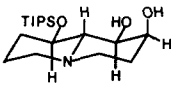
6. For the synthesis of racemic and enantiomerically pure γ-hydroxy-α,β-unsaturated phenyl sulfones see: a) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867. b) Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1991**, *56*, 5159. c) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197
7. a) Synthesis of [3.3.0] and [4.3.0] bicyclic compounds: Adrio, J.; Carretero, J. C.; Gómez Arrayás, R. *Synlett* **1996**, 640. b) Synthesis of indolizidines: Carretero, J. C.; Gómez Arrayás, R. *J. Org. Chem.* **1995**, *60*, 6000. c) Synthesis of polypropionate chains: Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1993**, *58*, 1596.
8. Carretero, J. C.; Gómez Arrayás, R.; Storch de Gracia, I. *Tetrahedron Lett.* **1996**, *37*, 3379.
9. It is interesting to note that although in this cyclic β-hydroxysulfone the OH group is in equatorial position, its reaction with Na(Hg) occurred with formation of the C-C double bond (Julia olefination) instead of the reductive elimination of the sulfone. So, it is not required its previous activation as acetate or mesylate derivative. For the Julia olefination in cycles, see: Kocienski, P. J. *Chem. Ind. (London)* **1981**, 548.
10. The stereochemical assignment of the polyhydroxylated quinolizidines reported here has been unequivocally established by ^{1}H-NMR, mainly by analysis of their vecinal coupling constants (see figures below).

TIPS-11



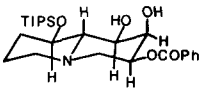
$J_{9,9a}$ = 10.3 Hz
$J_{1,9a}$ = 3.0 Hz
$J_{1,2}$ = 3.0 Hz
$J_{2,3eq}$ = 3.0 Hz
$J_{2,3ax}$ = 3.0 Hz

TIPS-8



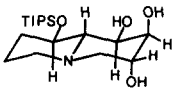
$J_{9,9a}$ = 8.9 Hz
$J_{1,9a}$ = 8.9 Hz
$J_{1,2}$ = 3.2 Hz
$J_{2,3eq}$ = 3.1 Hz
$J_{2,3ax}$ = 3.1 Hz

TIPS,BzO-18



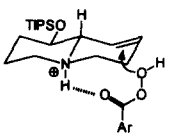
$J_{9,9a}$ = 8.6Hz
$J_{1,9a}$ = 8.6 Hz
$J_{1,2}$ = 3.0 Hz
$J_{2,3}$ = 3.0 Hz
$J_{3,4eq}$ = 4.6 Hz
$J_{3,4ax}$ = 10.9 Hz

TIPS-19



$J_{9,9a}$ = 8.3Hz
$J_{1,9a}$ = 8.3 Hz
$J_{1,2}$ = 2.9 Hz
$J_{2,3}$ = 3.2 Hz

11. In other solvents (like CH_2Cl_2) a complex mixture of products was obtained.
12. The opposite stereoselectivity observed in the epoxidation of **6** (compared with its dihydroxylation) could be due to the association of the peracid with the ammonium salt, likely by hydrogen bonding, which would direct the approach of the peracid from the lower face of the olefin (see figure).



13. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
14. In this case a minor amount of the *trans*-diequatorial product was also formed (15% yield).
15. For direct dialkylations of β–nitrogenated sulfones to form six member rings, see: a) Alonso, D. A.; Costa, A.; Mancheño, B.; Nájera, C. *Tetrahedron* **1997**, *53*, 4791. b) Caturla, F.; Nájera, C. *Tetrahedron Lett.* **1997**, *38*, 3789.
16. When the ozonolysis was performed in other solvents (MeOH or CH_2Cl_2) the desired ketone **15** was obtained in very low yields.
17. Likely, steric effects are determinant in the origin of this high stereoselectivity, being the face of the olefin *syn* to H_{9a} much less hindered. Accondingly, only in the case of the benzoate derivative of **16**, where the bulky benzoate is in *syn* relationship with regard to H_{9a}, the dihydroxylation was not highly stereoselective, being observed as minor product the diol resulting of the dihydroxylation from the face *anti* to H_{9a} (70:30 ratio of isomers).

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