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An Efficient and Stereoselective Synthesis of Enantiopure 1,2,7-Trihydroxylated Pyrrolizidines

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Abstract. An efficient approach to the stereoselective synthesis of enantiopure 1,2,7-trihydroxylated pyrrolizidines from the readily available optically pure γ–hydroxy-α,β-unsaturated sulfone **2a** is described.

Keywords: pyrrolizidines, stereoselective synthesis, α,β-unsaturated sulfones, lipases.

Natural products having the 1-azabicyclo[3.3.0]octane skeleton (pyrrolizidine alkaloids) are widespread in nature, occurring in various plant species (especially those belonging to Compositae, Leguminosae, Gramineae and Boraginaceae families) and in insects (mainly species from Lepidoptera).[1] Their structural and stereochemical complexity, coupled with their diverse and potent biological activities, make these alkaloids very attractive synthetic targets.[2] These naturally occurring pyrrolizidines can be classified into two main groups: the wide family of the necines (for instance the rosmarinecine and crotanecine as common necine bases), and the more recently discovered family of the polyhydroxylated pyrrolizidines,[3,4] such as alexine or casuarine (figure 1). From a structural point of view, all these compounds have in common the presence of several hydroxyl groups (at C1, C2, C6 or C7) and one hydroxymethyl group (at C1 in the necine bases and at C3 in the polyhydroxylated pyrrolizidines) as substituents of the 1-azabicyclo[3.3.0]octane skeleton.

Recently we described a stereoselective method for the preparation of racemic polyhydroxylated indolizidines from readily available ω-nitrogenated-γ-hydroxy-α,β-unsaturated sulfones.[5] By using similar functionalized α,β–unsaturated sulfones, but in optically pure form, herein we describe a highly efficient and general approach to the stereoselective synthesis of enantiopure 1,2,7-trihydroxylated pyrrolizidines.

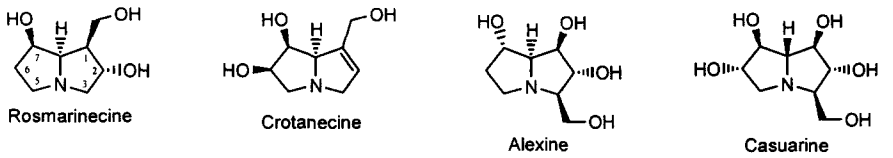

Figure 1

Some years ago we reported a practical lipase-catalyzed kinetic resolution of (±)-γ-hydroxy-α,β-unsaturated phenyl sulfones based on their highly enantioselective acetylation with vinyl acetate in the presence of lipase PCL (*Pseudomonas cepacia* lipase, Amano) and *i*-Pr_2O as solvent.[6] Under these conditions, regardless of the nature of the chain at the γ-position, only the (*R*) alcohol was acetylated. However, when these conditions were applied to the substrate (±)-**1**[5] no reaction took place even after 10 days. In an attempt to improve the reactivity of the substrate by reducing the size of the γ-chain, one of the BOC groups was selectively deprotected (1.5 equiv of TFA, CH_2Cl_2, rt) to give the carbamate **2a** (95%).

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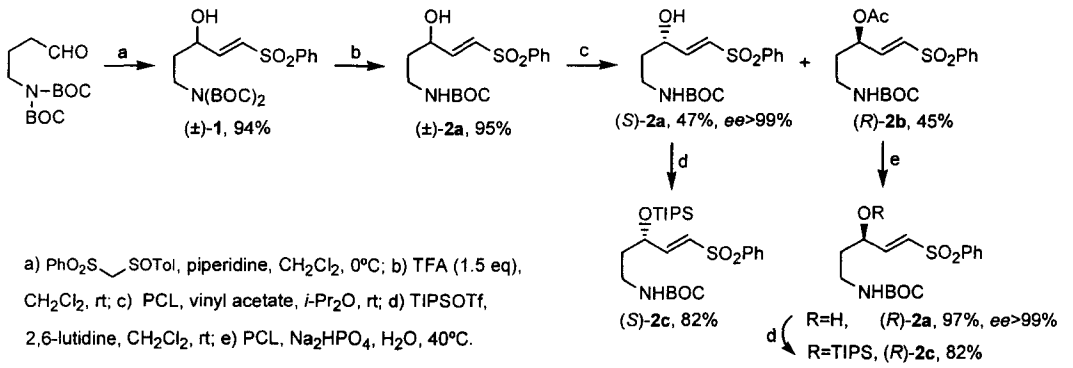
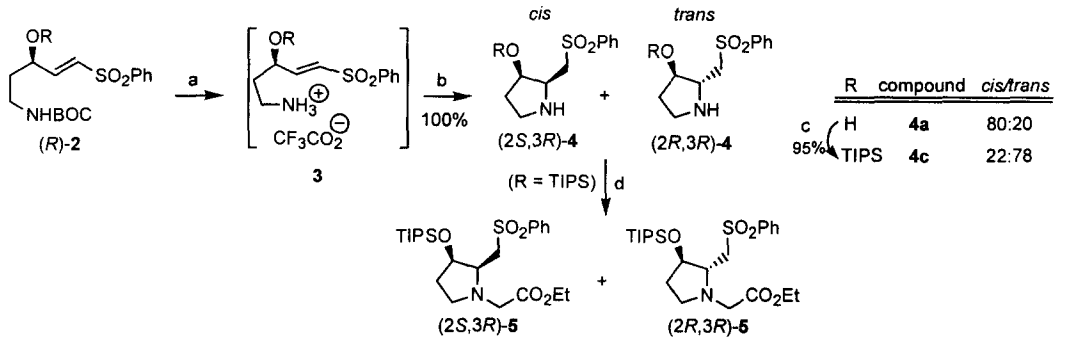
Pleasingly, the reaction of **2a** with PCL and vinyl acetate (*i*-Pr_2O, molecular sieves, rt) stopped at 50% conversion after 74 h, affording 47% of alcohol (*S*)-**2a** and 45% of acetate (*R*)-**2b** after flash chromatography. To end the resolution procedure, the enzymatic hydrolysis of the acetate (*R*)-**2b** (PCL, 0.1M Na_2HPO_4, 40°C, 48h) gave quantitatively the alcohol (*R*)-**2a**. The optical purities of (*R*)-**2a** and (*S*)-**2a**, determined by chiral HPLC,[7] were in both cases very high (>99% *ee*).

The deprotection of carbamate (*R*)-**2** (TFA, rt) afforded the corresponding ammonium salts (*R*)-**3**, which were redissolved in THF and treated with Et_3N (10 equiv) at –78°C. The *in situ* formed free amines evolved by rapid cyclization to give quantitatively the pyrrolidines **4** as unseparable *cis*+*trans* mixtures of isomers. Interestingly, whereas the cyclization of **3a** (R= H) was *cis*-stereoselective (*cis/trans*= 80:20), those of **3b** (R= Ac) and **3c** (R= TIPS) were *trans*-stereoselective (*cis/trans*= 28:72 and 22:78, respectively).[8] The required *N*-alkylated pyrrolidines (2*S*, 3*R*)-**5** and (2*R*, 3*R*)-**5** were readily separated by flash chromatography of the isomer mixtures obtained after treatment of the *cis*+*trans* pyrrolidines **4c** with ethyl bromoacetate (K_2CO_3, LiI cat, CH_3CN, reflux). By this way, (2*R*, 3*R*)-**5** was isolated in 73% overall yield from (*R*)-**2c**, and (2*S*, 3*R*)-**5** in 71% yield by cyclization of (*R*)-**2a** and further silylation of *cis*+*trans* **4a** (scheme 2).



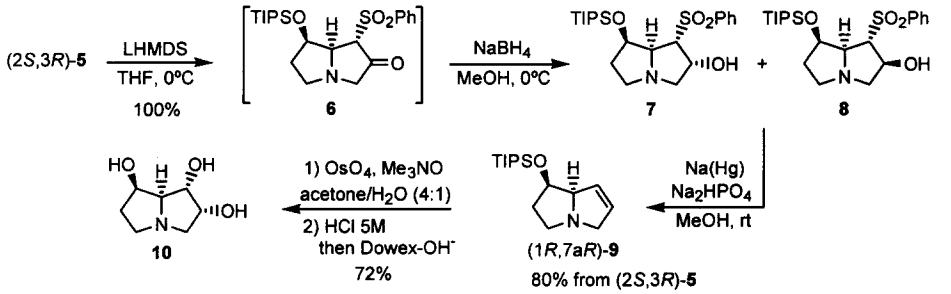
Scheme 1



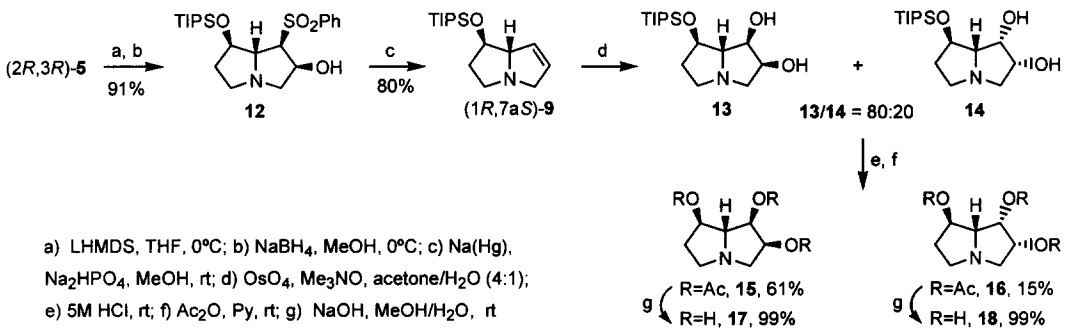
Scheme 2

The highly efficient and completely stereoselective five-step transformation of (2*S*, 3*R*)-**5** into the 1,2,7-trihydroxylated pyrrolizidine **10** (59% overall yield) is shown in scheme 3. Claisen-like intramolecular acylation of (2*S*, 3*R*)-**5** (LHDMS, THF, 0°C) afforded quantitatively a single and somewhat unstable

pyrrolizidinic α-sulfonylketone **6**, which was immediately reduced with $NaBH_4$ (MeOH, rt) to give cleanly a 70:30 mixture of the hydroxysulfones **7** and **8**, epimers at C2.[9] Although both compounds can be purified by chromatography and transformed independently, it is synthetically more efficient to treat the crude mixture **7**+**8** with sodium amalgam (Na_2HPO_4, MeOH, rt) to afford the unsaturated pyrrolizidine (1*R*, 7a*R*)-**9** [80% yield from (2*S*, 3*R*)-**5**]. Finally, the *syn*-dihydroxylation of (1*R*, 7a*R*)-**9** (OsO_4 cat, Me_3NO, acetone, water, rt) occurred with complete stereocontrol from its less hindered face (*syn* to H7a and *anti* with regard to the bulky oxygenated substituent at C1) to provide the corresponding diol (72% yield), which after acid hydrolysis (HCl 5M, rt) and neutralization through a basic-ion exchange resin furnished the trihydroxylated pyrrolizidine **10**.[9]



Scheme 3



Scheme 4

Following a similar reaction sequence, enantiopure trihydroxylated pyrrolizidines with *trans* stereochemistry at C7-C7a were obtained from the pyrrolidine (2*R*, 3*R*)-**5** (scheme 4). Both the intramolecular acylation of (2*R*, 3*R*)-**5** and the reduction of the resulting ketone ($NaBH_4$) were completely stereoselective, affording a single hydroxysulfone **12**[9] (91% overall yield). Julia olefination of **12** (Na-Hg, MeOH) led to the unsaturated pyrrolizidine (1*R*, 7a*S*)-**9** (80% yield), which was dihydroxylated under the usual conditions (cat OsO_4, Me_3NO). However, unlike the stereochemical behavior of the isomer (1*R*, 7a*R*)-**9**, the reaction of (1*R*, 7a*S*)-**9** was less stereoselective, leading to an unseparable 80:20 mixture of diols **13** (dihydroxylation *syn* to H7a) and **14** (*anti* approach of the oxidant with regard to the substituent at C1), respectively. In order to separate the isomeric pyrrolizidines, the **13**+**14** mixture was desilylated (HCl 5M), fully acetylated (Ac_2O, pyridine, rt) and purified by flash chromatography to provide the corresponding triacetates **15** (61%) and **16** (15%), which led quantitatively to the trihydroxylated pyrrolizidines **17** and **18** after basic deacetylation

(NaOH, MeOH, rt). The spectroscopic data and optical rotation of the trihydroxylated pyrrolizidine **18** were quite similar to those reported in the literature for this compound,[10] confirming otherwise its absolute configuration and, hence, that of its synthetic precursors [(*R*)-**2a**, (2*R*, 3*R*)-**5**, (1*R*, 7a*S*)-**9** and **14**].

In summary, a short, efficient and stereochemically flexible approach to the synthesis of enantiopure 1,2,7-trihydroxylated pyrrolizidines from non carbohydrate precursors has been described. Key steps are the lipase-mediated kinetic resolution of the vinyl sulfone (±)-**2a**, the stereoselective construction of the pyrrolizidine skeleton by an intramolecular conjugate addition of the amine derived from **2a** or **2c**, followed by a Claisen-like cyclization of the pyrrolidines **5**, and the stereoselective *syn*-dihydroxylation of the diastereomeric unsaturated pyrrolizidines **9**. The extension of this methodology to the synthesis of alexines and the evaluation of the biological activity of polyhydroxylated pyrrolizidines as glycoside inhibitors are in progress in our laboratory.

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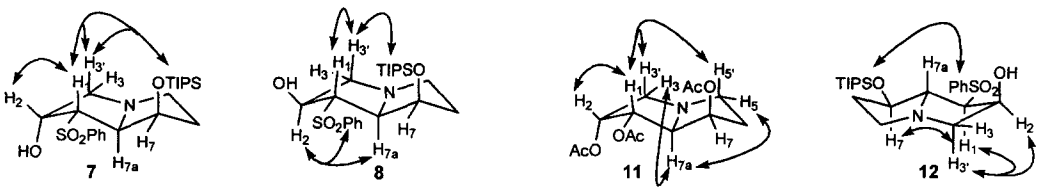

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