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Synthesis of penaresidins and sphingolipids from Glucose

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Other posters of the group

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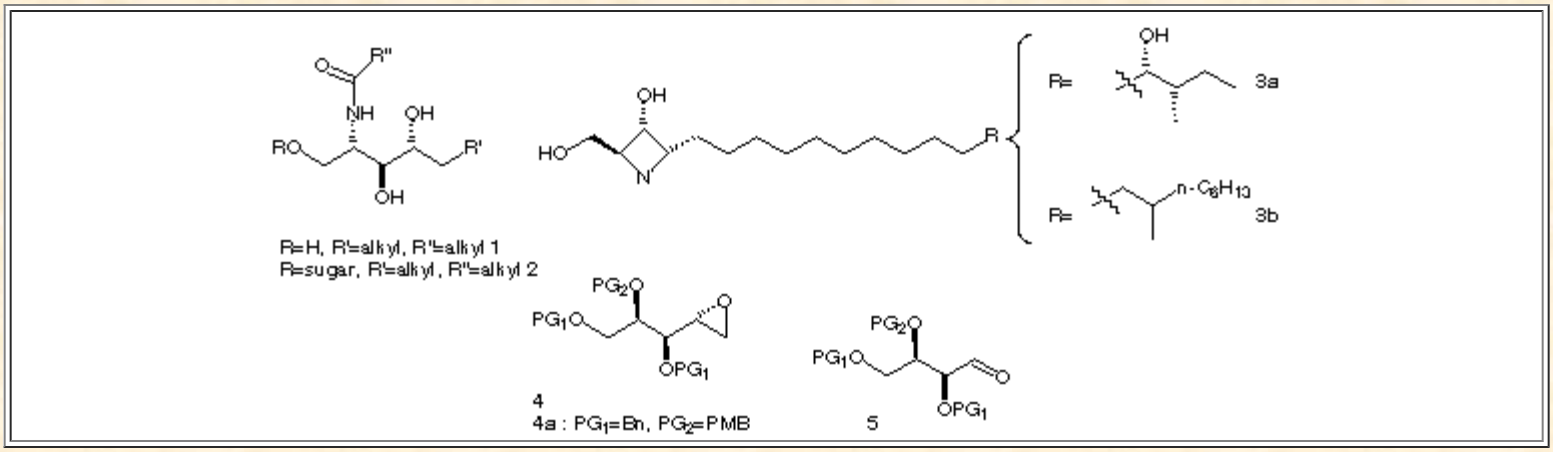
Introduction :



The scientific interest of the immunological properties of sphingolipids **1**1-6 and related glycosphingolipids **2 7** has recently increased on account of the role that they could play as therapeutic agents. Their antifongic properties have been the first studied 8. For number of them, immunomodulating activity as well as in vivo antitumoral activities have been reported 9-12. Some other compounds with original chemical structure have also been recently isolated from sponges 13-14

On the other hand, the original chemical structure and the promising protein kinase C inhibitor activity of penarezidines **3a** and penazetidines **3b** type of alkaloïds15-17 make them attracting molecules in a therapeutic screening as well as in studies of other biological phenomena including plant diseases involving cell growth disorders.

Although some syntheses18-28 of these products have already been described in the litterature, the fact that all these molecules were presenting a very similar feature consisting in a terminal tetraheterosubstituted butyl subunit prompted us to design a unifiying strategy involving a same synthetic versatile intermediate for all these compounds elaborated from a carbohydrate synthon.

The more appropriate starting material, according to the well defined configurations of the stereogenic centers of these natural products was D-Glucose (Scheme 1a).

In all cases, the aliphatic side chain could be introduced in the final steps of the synthesis by condensation of an appropriate organometallic species on an epoxyde ring, the nitrogen atom beeing then introduce at C-4 or C-2 (for sphingolipids) with inversion of configuration of this carbon atom. For penazeridine and penazetidine synthesis, the azetidine ring closure would be achieved by standart methodologies with inversion of configuration at carbon C-2.
According to this retrosynthetic analysis, the target intermediate of our strategy is thus epoxide **4** 18 with the appropriate protecting groups for the three remaining hydroxy groups. A closely related strategy for the synthesis of penarezidine has been reported earlier in the litterature and involves the use of the corresponding trihydroxy butanal synthon **5**27 ; nevertheless, the drawback of this strategy is that it requires, after condensation of the organometallic species on the carbonyl group, an oxidation-reduction sequence to obtain a good diastereomeric control of the configuration of the hydroxy group formed during the alkylation step.

In rder to complmete the synthesis of the penaresidines from epoxide **4**, three main routes can be used. First of all, route A described on Scheme 1b, which is the most similar to the works already described in the literature and which consists in the protection of the hydroxy group at C-2 before the introduction of the side chain through organometallic epoxide openning; the amino group is thereafter introduced at C-4 through substitution of a tosyl or mesyl group derived from the hydroxy group at C-4 generated during the epoxide openning. Nevertheless, in order to reduce the protection deprotection sequence of hydroxy or amino groups involved in the formation of the azetidine ring, one should consider the possibility of either introducing a leaving group at C-2 before the epoxide openning (Route A') or of keeping the hydroxy group at C-2 unprotected during this reaction and to manage the rest of the synthesis according to the presence of two free hydroxy groups in the molecule (Route B)

This poster deals with a new methodology for the synthesis of the polyhydroxylated azetidinic alkaloids encountered in the penaresidin and penazetidin family through route B described on Scheme 1b. The main feature of this synthesis lies in the absence of amine and/or hydroxyl protection/deprotection sequences usually encountered in the last steps of the synthesis devoted to the heterocycle ring closure.

Previous publications :

Beauhaire, J. ; Ducrot, P.-H. *C. R. Acad. Sci. IIc* **1999**, 477-482.
Beauhaire, J. ; Ducrot, P.-H. *Synth. Commun.* **1998**, *28*, 2443-2456.

Results :

- Synthesis of epoxide **4** from Glucose
- Synthesis of the appropriate side chain for penaresidine synthesis 29
- Azetidine formation : the final steps 30-35
- Synthesis of modified penarezidine

References : follow this link

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