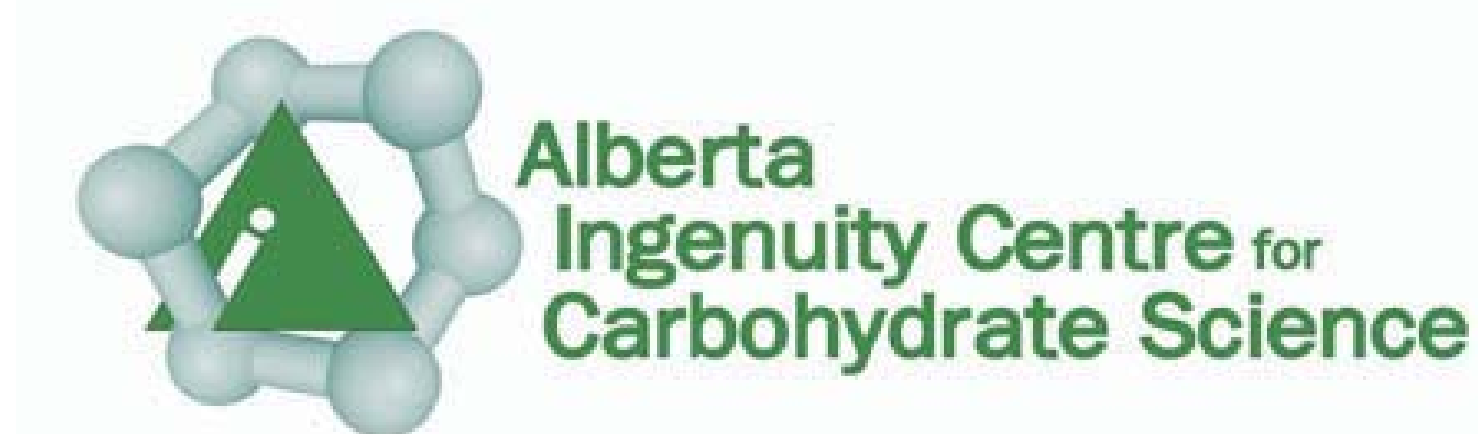




An efficient route to sphinganine, phytosphingosine and their analogs

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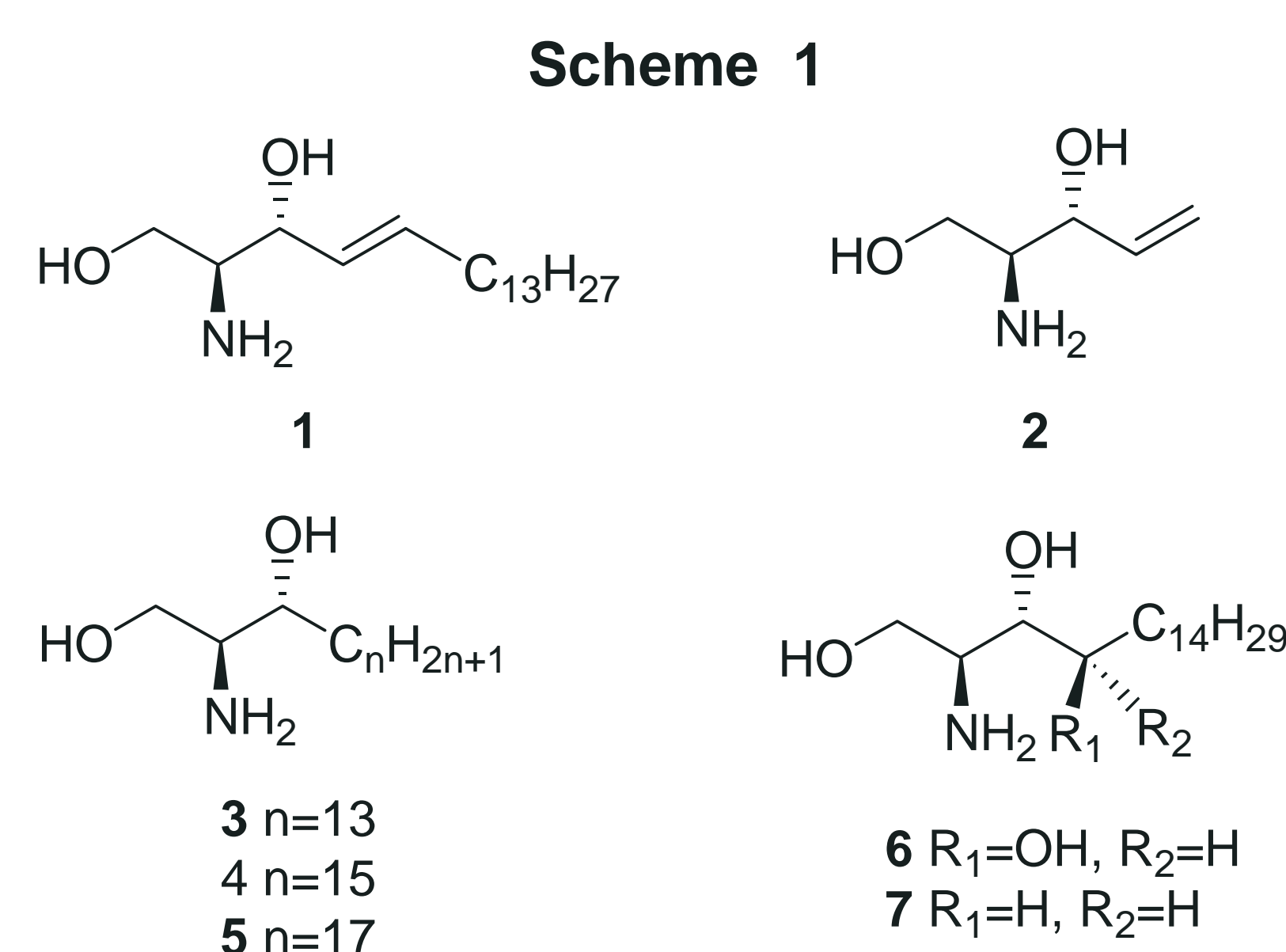
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Introduction

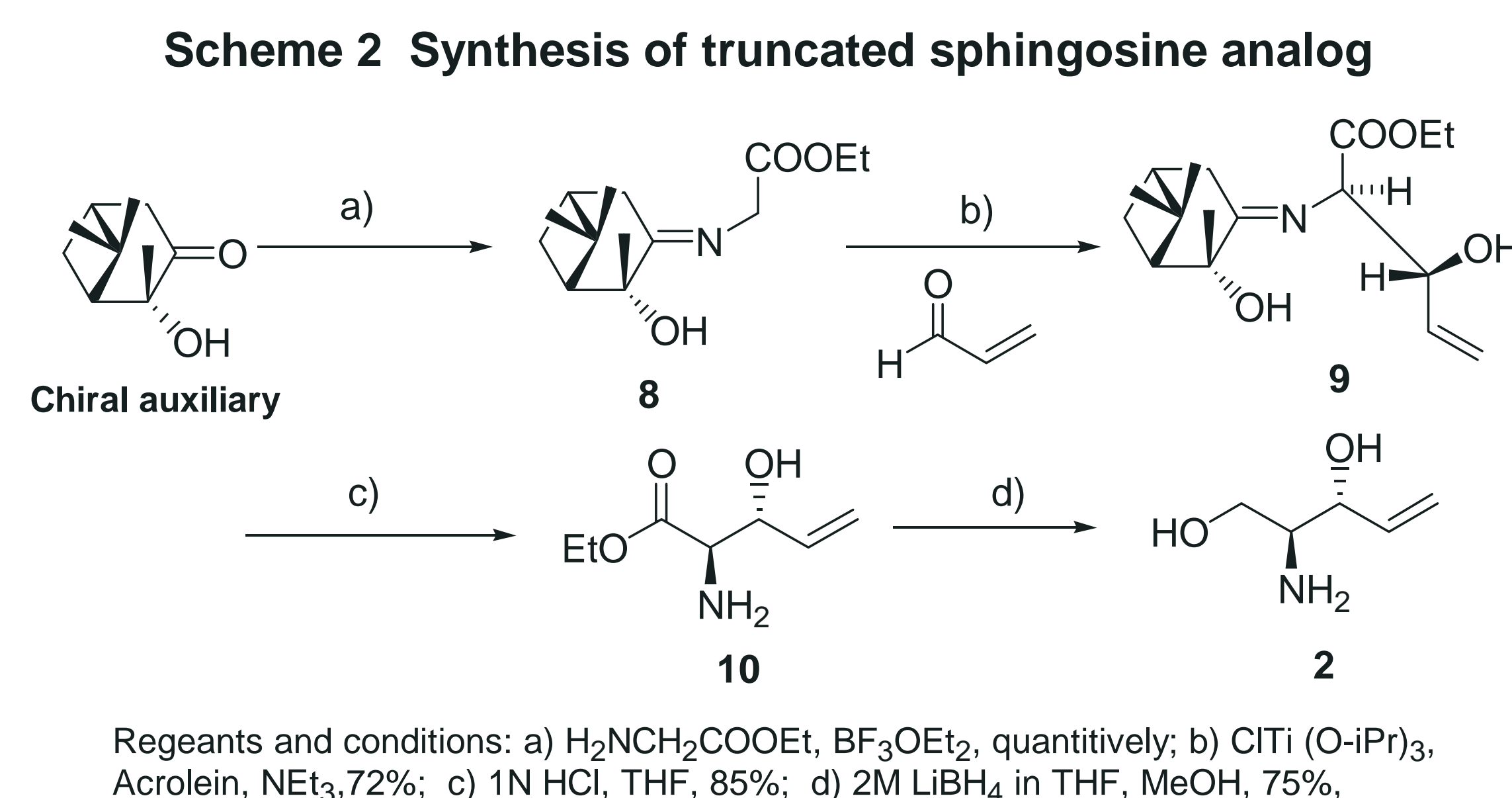
Sphingolipids, such as sphingosine, sphinganine and phytosphingosine, are important structural components of cellular membranes. They play a critical role in many physiological process, including modulation of immune response, signaling and cellular recognition¹. Due to their biological significance, as well as the complication of isolation from natural sources in homogeneous form, a great deal of effort have been devoted to synthetic studies of this class of compounds².

Here we describe an efficient route to synthesize several sphingolipid family members through an enantioselective aldol condensation. This method employs (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone as a chiral auxiliary and was developed by Soladie-Cavallo *et al* to prepare the natural sphingosine **1**³. We report here an extension of this method in the preparation of a number of sphingolipids, including a truncated analog of natural sphingosine **2**, sphinganines **3-5**, phytosphingosine **6** and its 4-epimer.

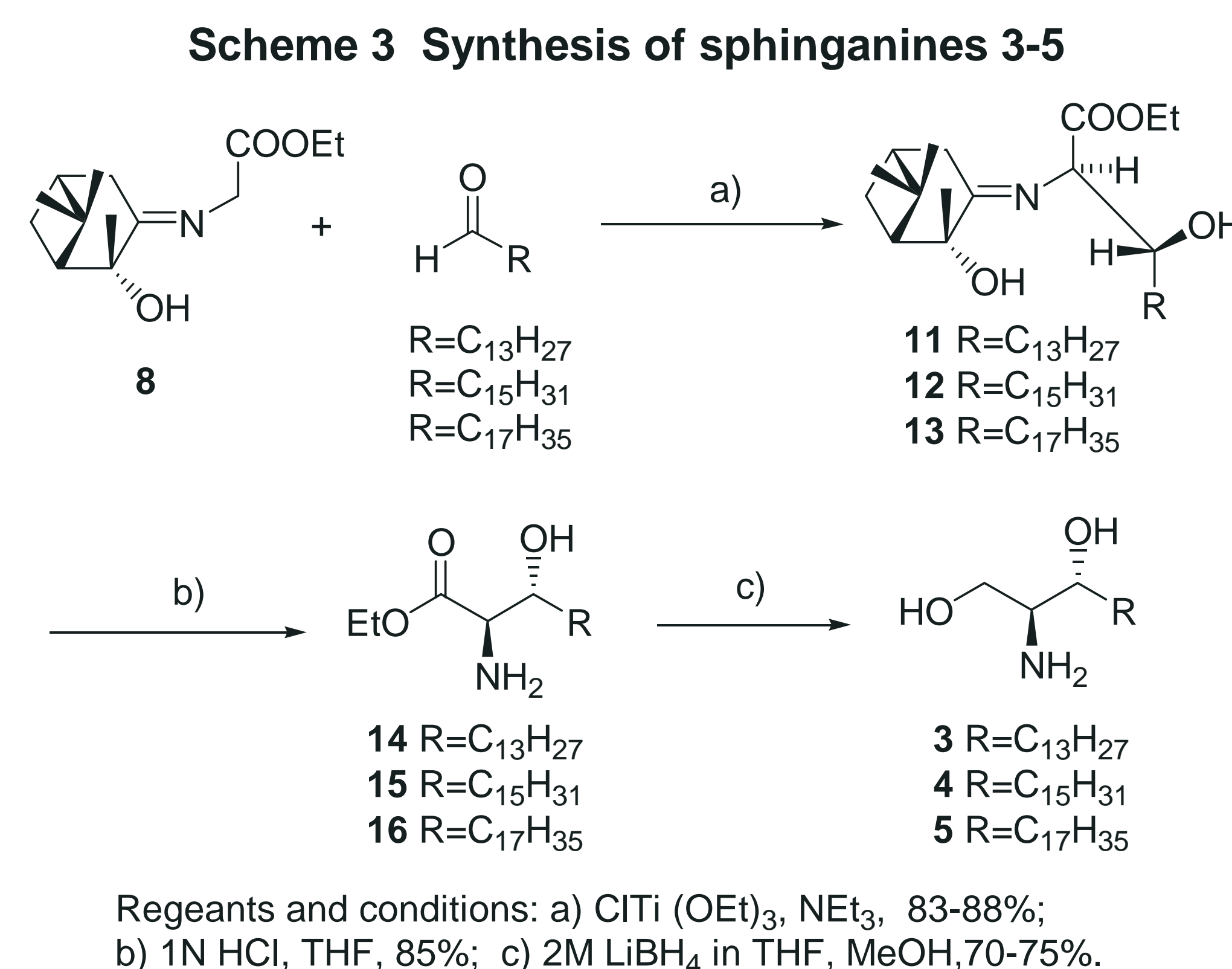


Results and discussion

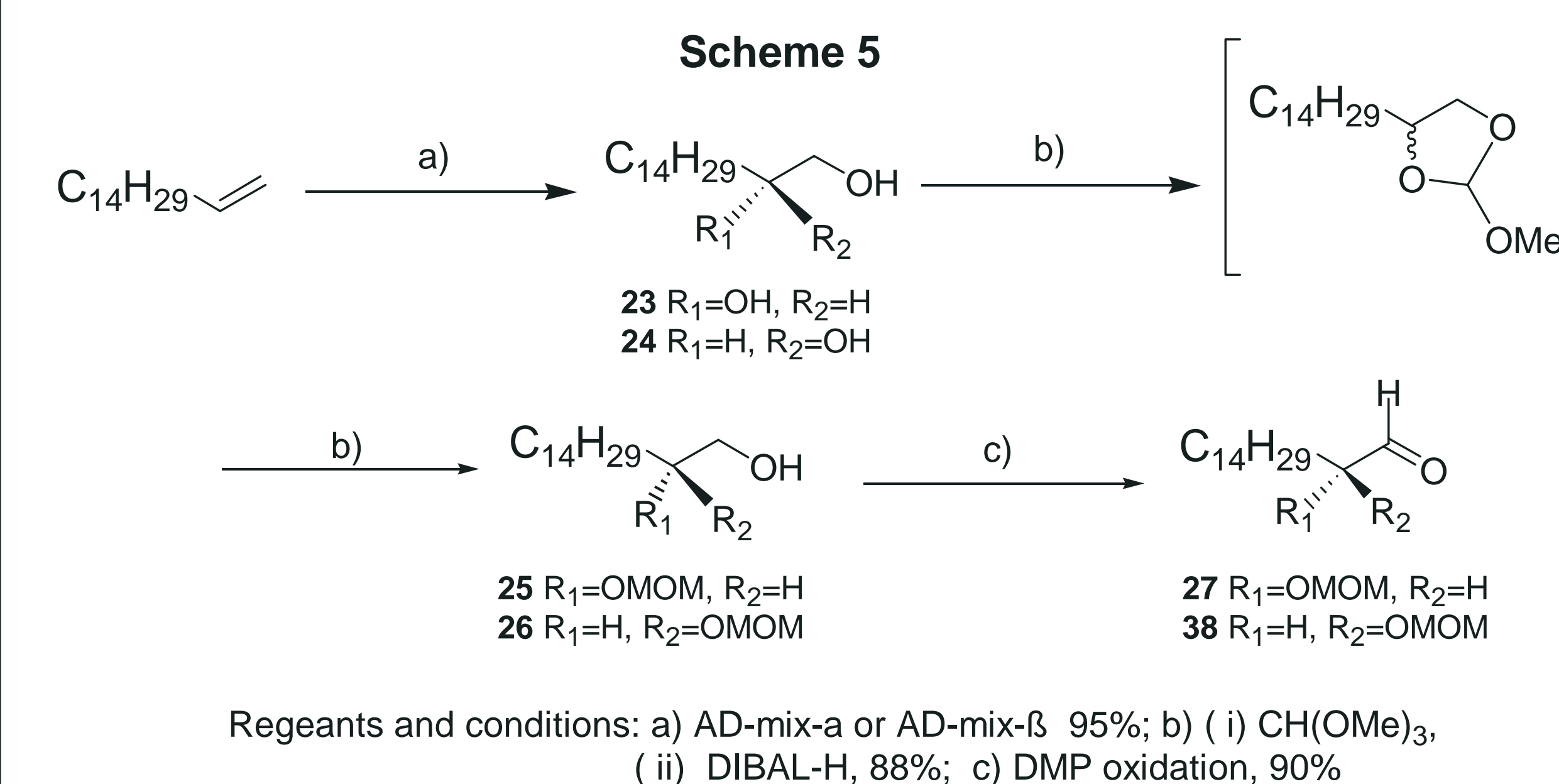
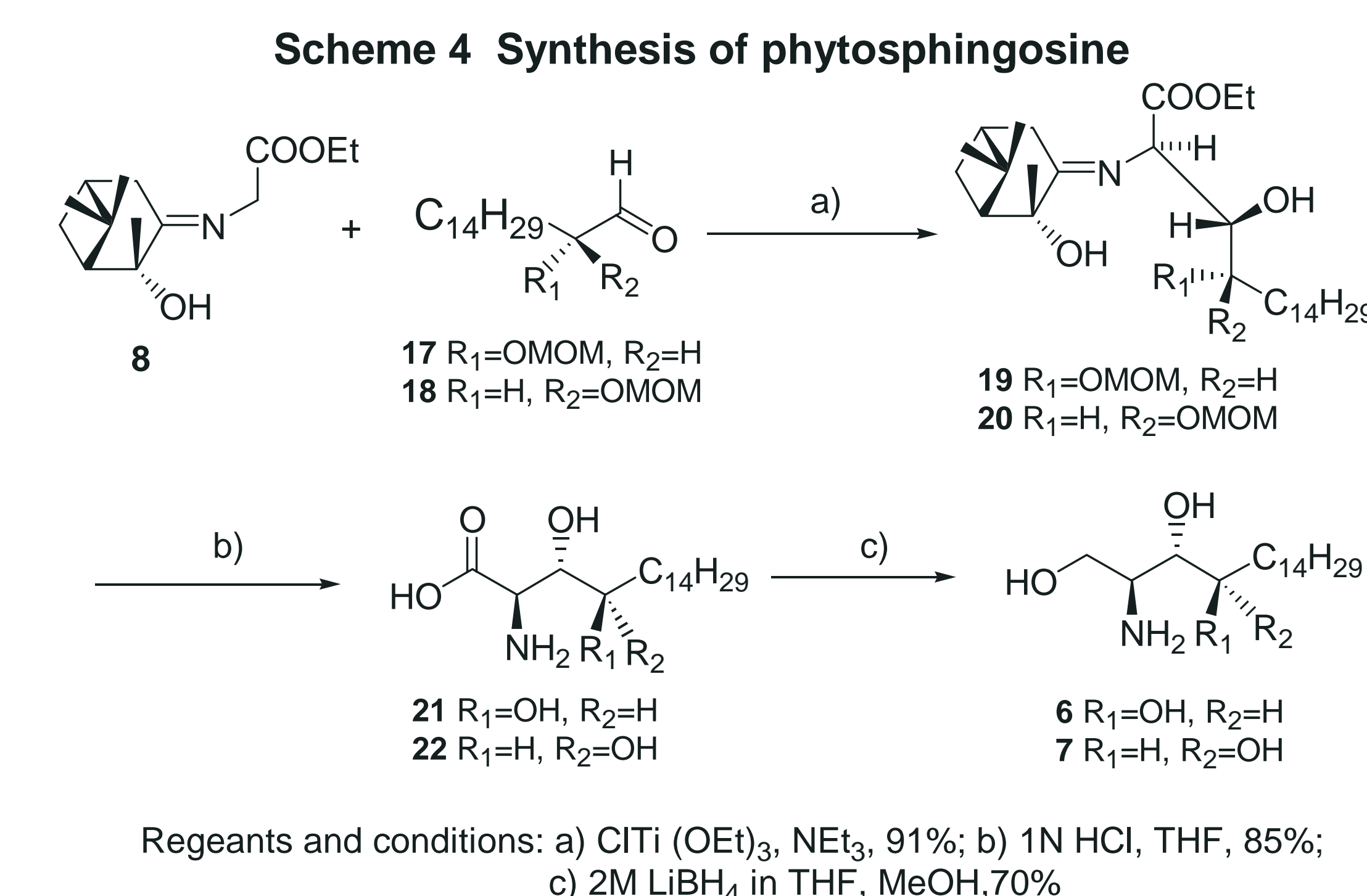
Imine **8** was used as a common starting material for all the syntheses. When reacted with acrolein in the presence of CITi(O-*i*Pr)₃ (scheme 2), the corresponding aldol condensation product **9** was obtained in good yield with excellent diastereofacial selectivity. The imine intermediate (**9**) was hydrolyzed under acidic conditions followed by reduction with LiBH₄ to give the truncated sphingosine analog (**2**).



This strategy was also applied to the synthesis of sphinganines (scheme 3). Similar aldol condensations using CITi(OEt)₃ instead of CITi(O-*i*Pr)₃ gave compounds **11-13** in excellent yield with high diastereoselectivity. Sphinganines **3-5** were obtained following a similar reaction sequence to scheme 2.



Furthermore, the above strategy was extended to prepare phytosphingosine (scheme 4). When imine **8** was reacted with aldehyde **17** or **18**, the corresponding imine intermediates **19** or **20** were obtained. The initial studies showed that treatment of compounds **19** or **20** with 1N HCl hydrolyzed both the imine and ester linkage, and by treating the acid with LiAlH₄, the desired phytosphingosine **6** and its 4-epimer were obtained in good yield. The aldehyde **17** and **18** were prepared according to scheme 5.



References

- 1 Susanne Brodesser, Peter Sawatzki, and Thomas Kolter, *Eur. J. Org. Chem.* **2003**, 2021-2034
- 2 Koskinen, P. M.; Koskinen, A. M.P. *Synthesis* **1998**, 1075-1091
- 3 A. Solladie-Cavallo and J. L. Koessler, *J. Org. Chem.*, 1994, **59**, 3240-3242

Acknowledgements

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Conclusions

We have demonstrated that using (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone as a chiral auxiliary offers a good opportunity in the construction of (2*S*,3*R*)-*D*-erythro structures through aldol condensations. This method has been proven to be highly practical and enantioselective. It should allow us to prepare structurally more elaborate compounds related to sphingolipids.