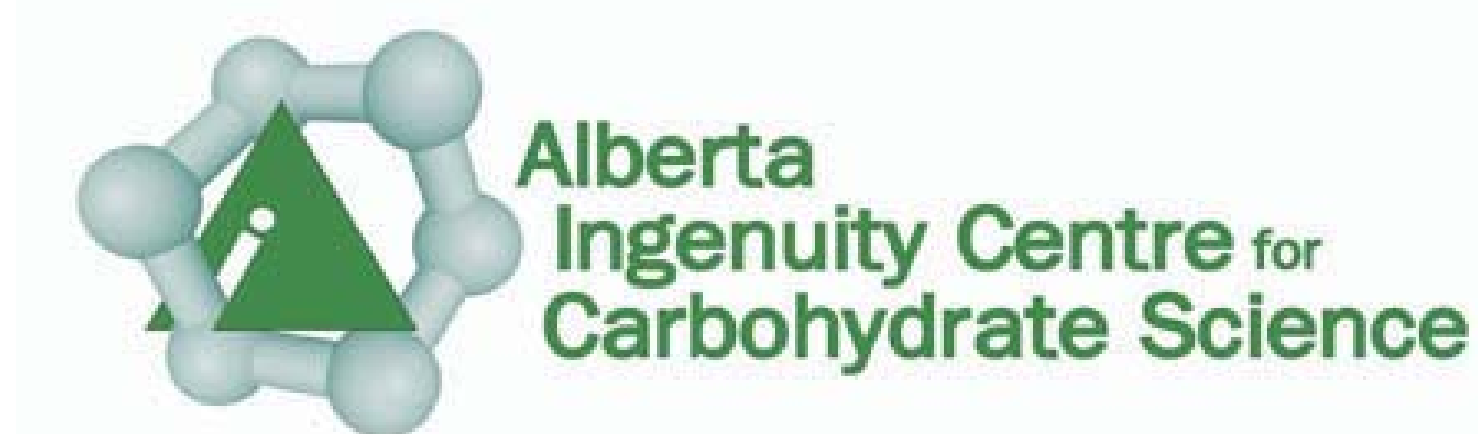




# An efficient route to sphinganine, phytosphingosine and their analogs

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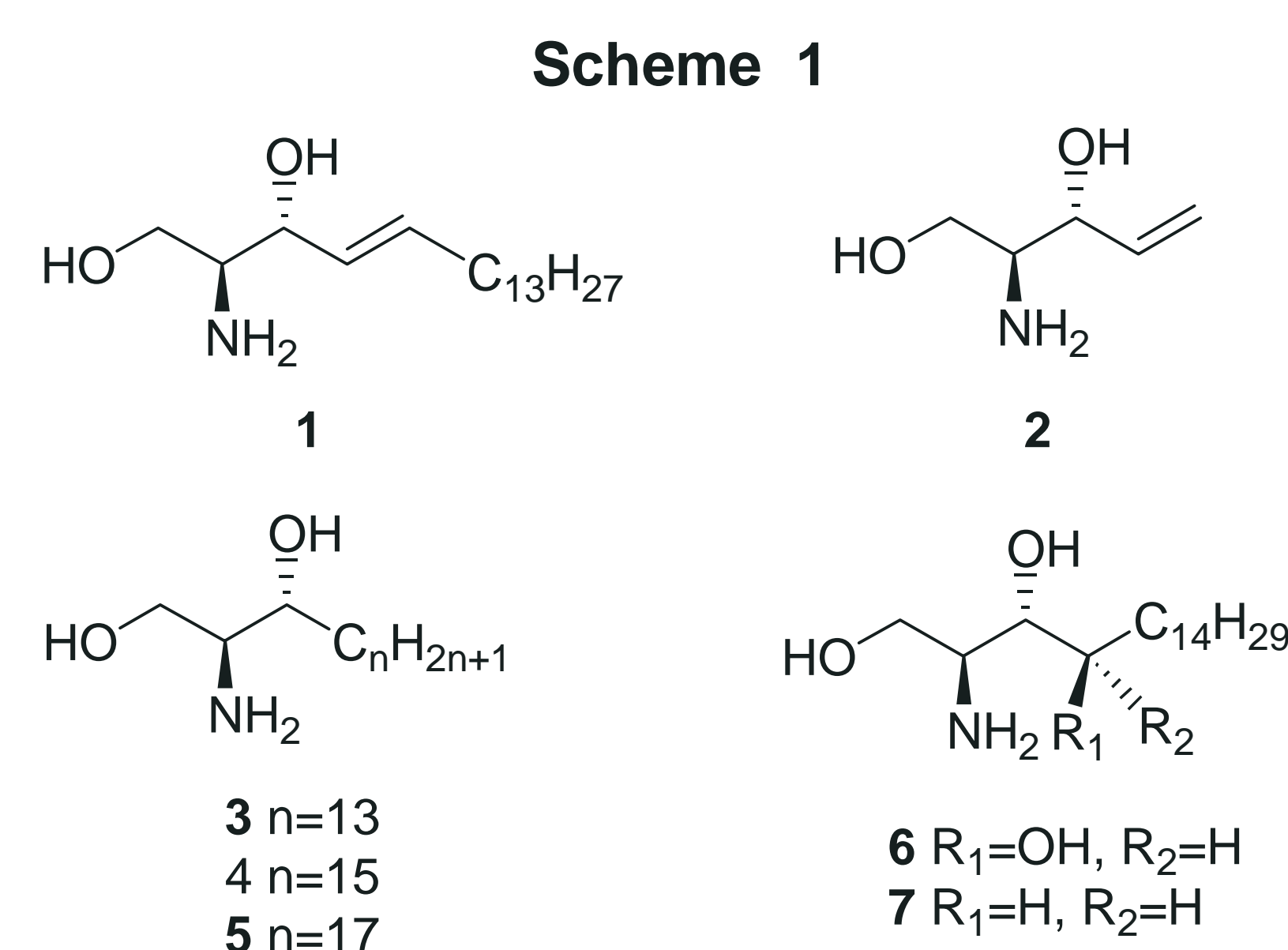
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## Introduction

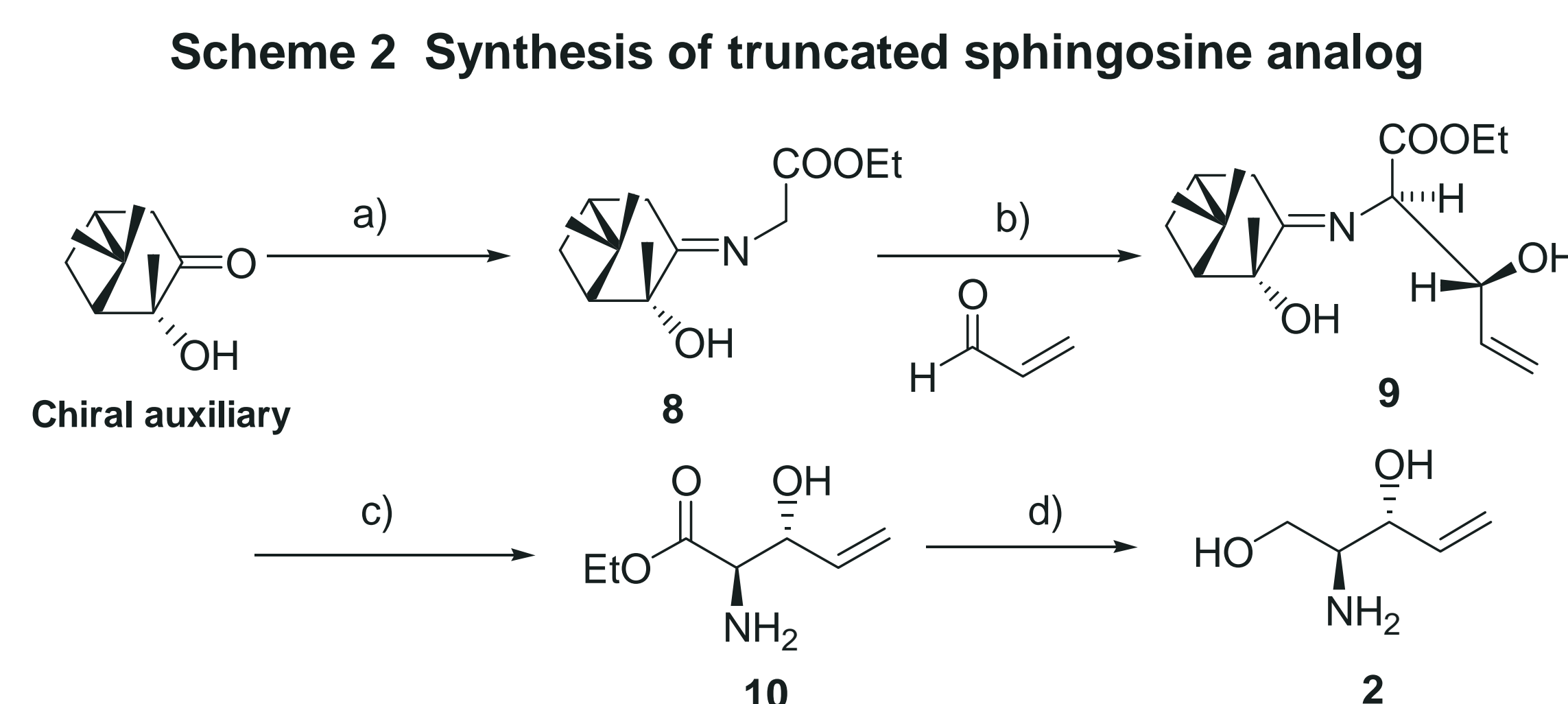
Sphingolipids, such as sphingosine, sphinganine and phytosphingosine, are important structural components of cellular membranes. They play a critical role in many physiological processes, including modulation of immune response, signaling and cellular recognition<sup>1</sup>. Due to their biological significance, as well as the complication of isolation from natural sources in homogeneous form, a great deal of effort has been devoted to synthetic studies of this class of compounds<sup>2</sup>.

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**<sup>3</sup>. 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.



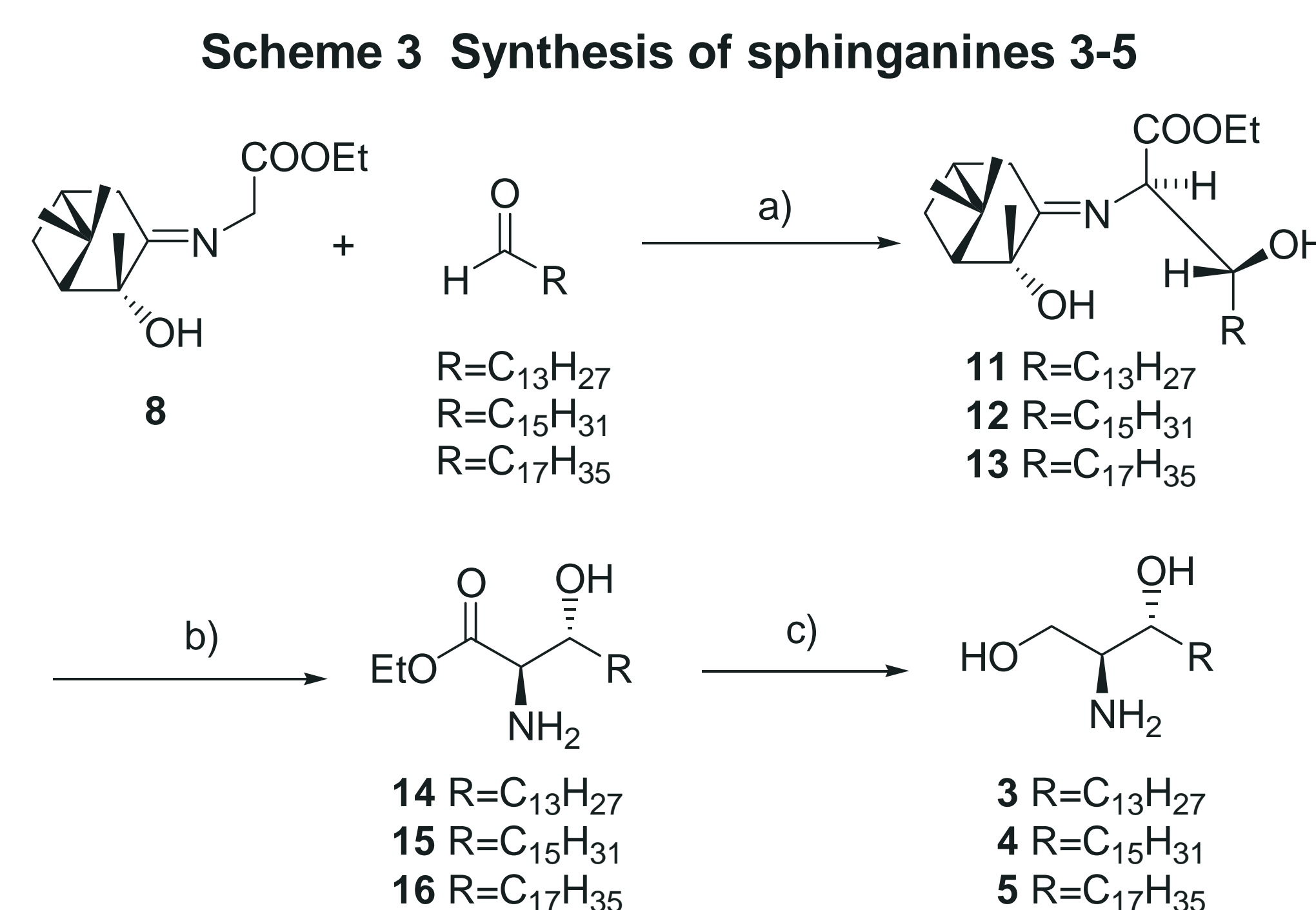
## Results and discussion

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)<sub>3</sub> (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 LiBH<sub>4</sub> to give the truncated sphingosine analog (**2**).



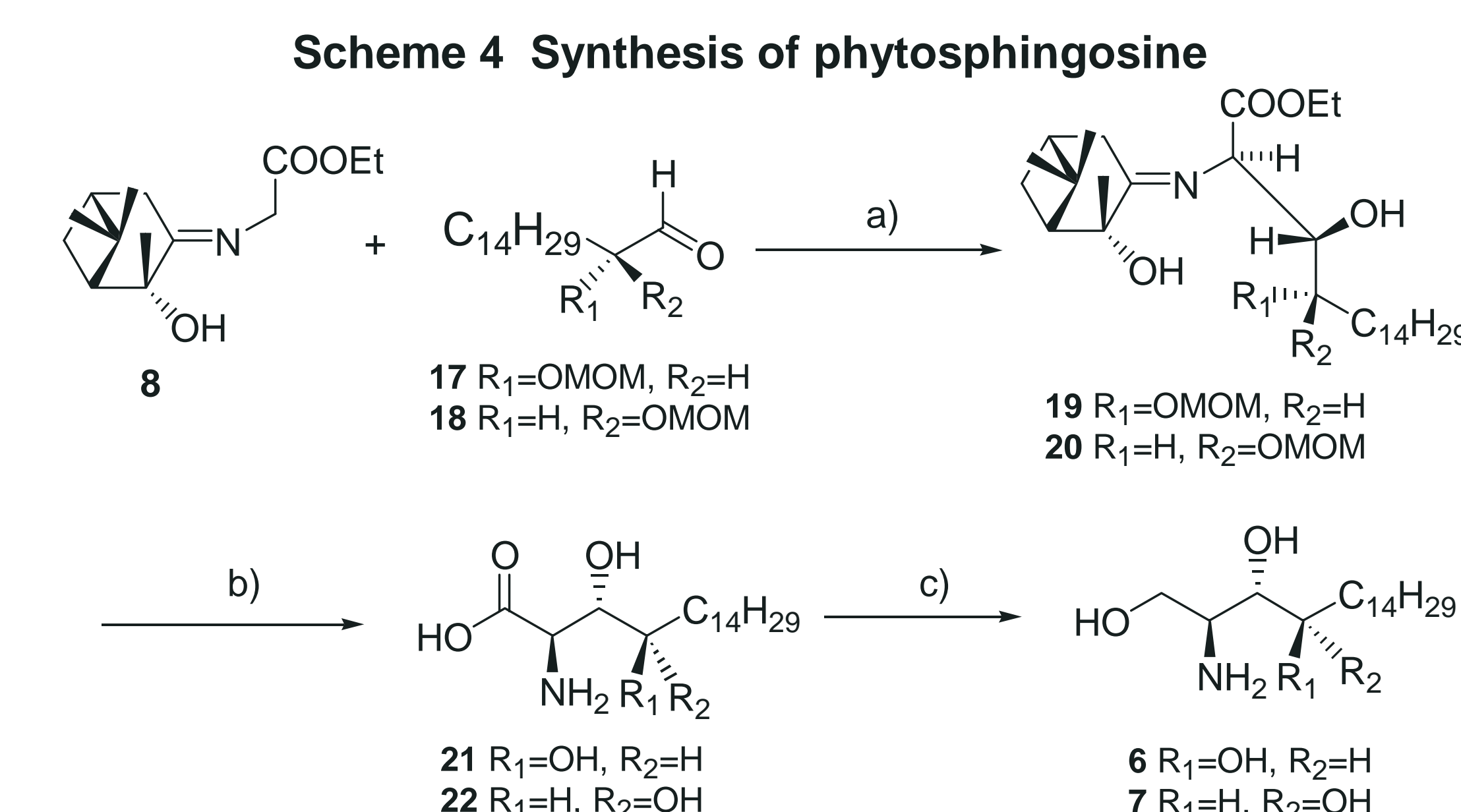
Reagents and conditions: a) H<sub>2</sub>NCH<sub>2</sub>COOEt, BF<sub>3</sub>OEt<sub>2</sub>, quantitatively; b) CITi(O-*i*Pr)<sub>3</sub>, Acrolein, NEt<sub>3</sub>, 72%; c) 1N HCl, THF, 85%; d) 2M LiBH<sub>4</sub> in THF, MeOH, 75%.

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

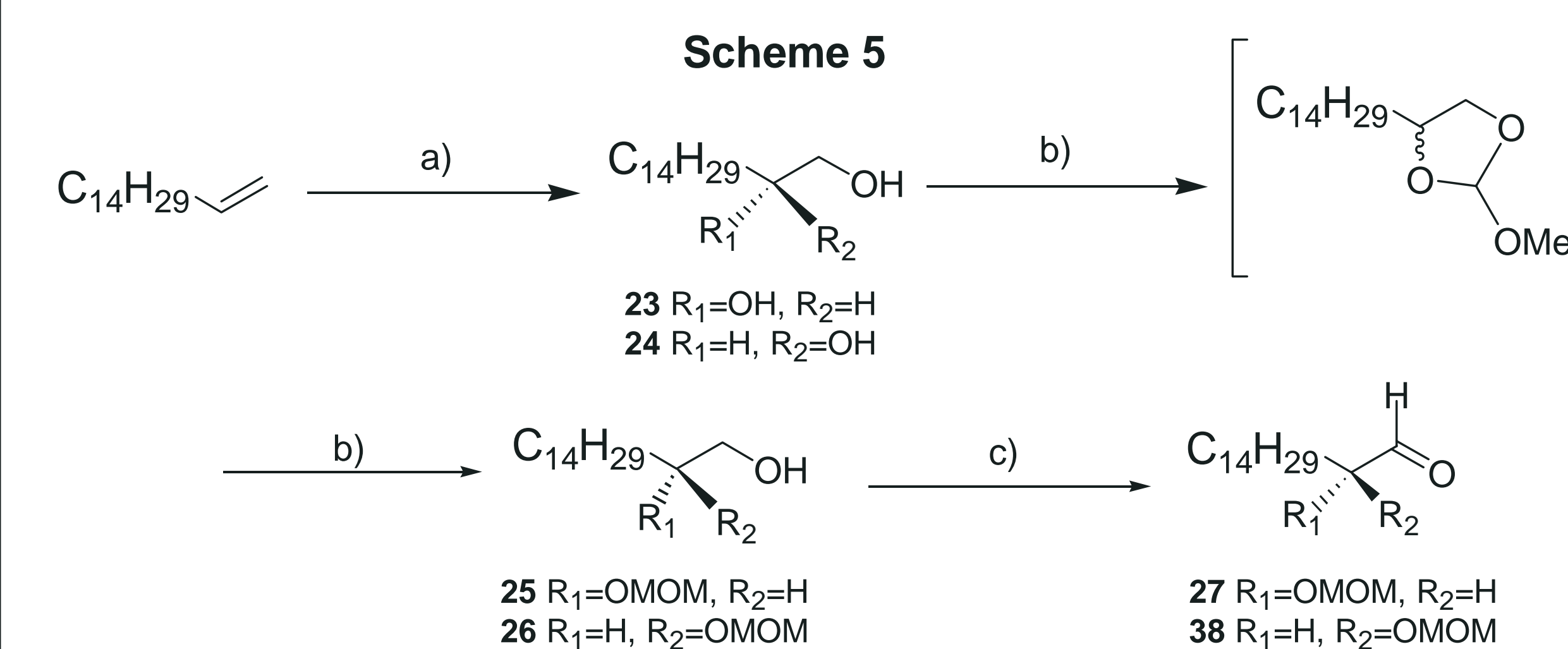


Reagents and conditions: a) CITi(OEt)<sub>3</sub>, NEt<sub>3</sub>, 83-88%; b) 1N HCl, THF, 85%; c) 2M LiBH<sub>4</sub> in THF, MeOH, 70-75%.

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 LiAlH<sub>4</sub>, the desired phytosphingosine **6** and its 4-epimer were obtained in good yield. The aldehyde **17** and **18** were prepared according to scheme 5.



Reagents and conditions: a) CITi(OEt)<sub>3</sub>, NEt<sub>3</sub>, 91%; b) 1N HCl, THF, 85%; c) 2M LiBH<sub>4</sub> in THF, MeOH, 70%.



Reagents and conditions: a) AD-mix- $\alpha$  or AD-mix- $\beta$ , 95%; b) (i) CH(OMe)<sub>3</sub>, (ii) DIBAL-H, 88%; c) DMP oxidation, 90%

## References

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- Koskinen, P. M.; Koskinen, A. M.P. *Synthesis* **1998**, 1075-1091
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## 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.