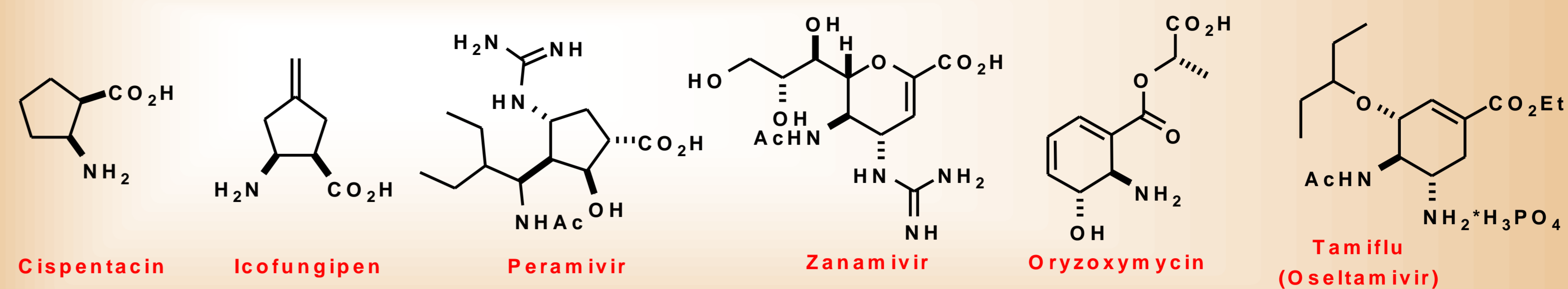


Introduction

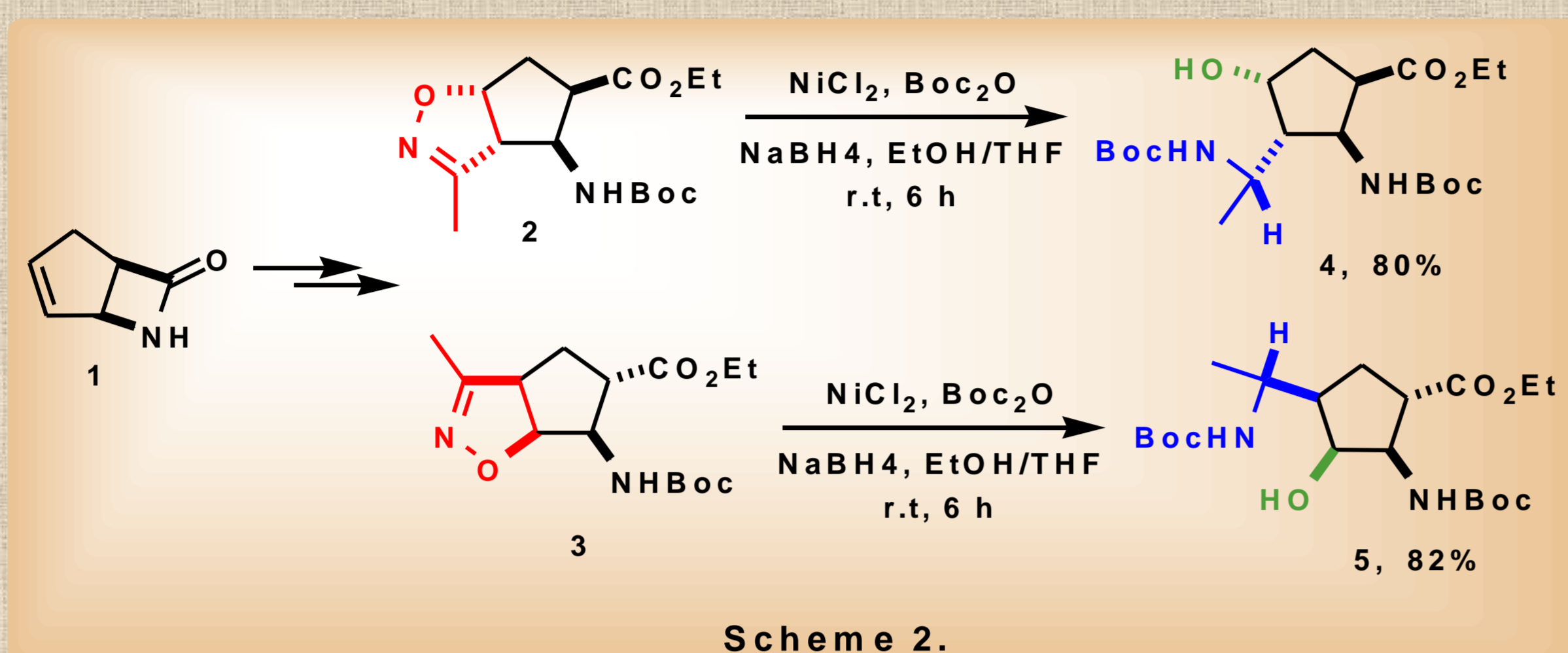
Alicyclic β -amino acids have attracted considerable interest in recent years because of their pharmacological potential, e.g. the naturally occurring Cispentacin or Icofungipen are antifungal agents, while Oryzoxymycin an antibiotic [1a-b]. A number of multifunctionalized cyclic amino acids such as Peramivir, Tamiflu or Zanamivir are known as neuraminidase inhibitors [1c-j] (Scheme 1). Fluorinated amino acids and peptides are considered of valuable derivatives in medicinal chemistry as enzyme inhibitors, antitumoural agents or antibiotics [2].



Scheme 1.

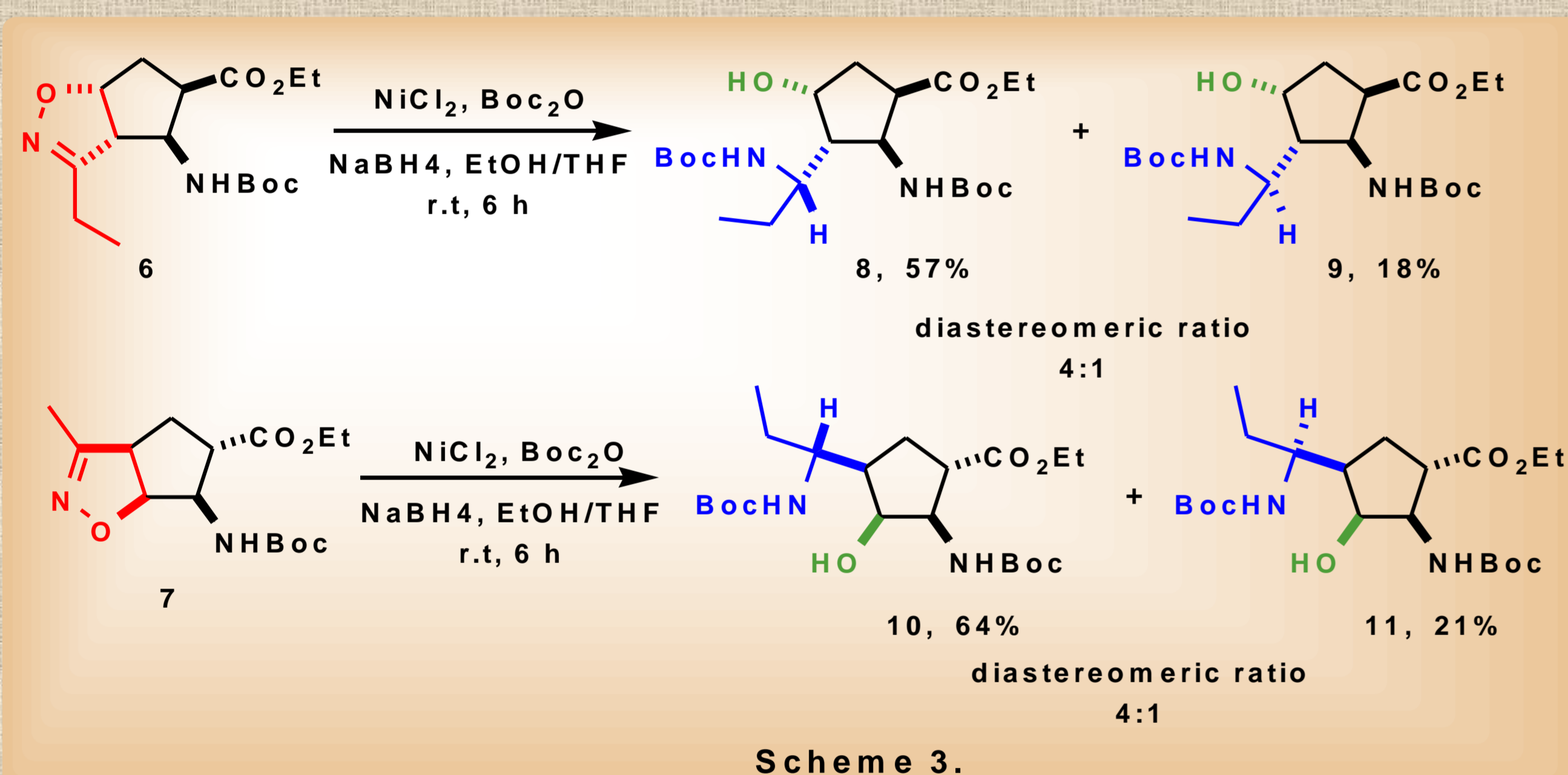
Results

Recently, our group reported the formation of a highly functionalized cispentacin stereoisomers **4** and **5** from the bicyclic β -lactam **1** by the 1,3-dipolar cycloaddition of nitrile oxide to the ethyl *cis*- and *trans*-2-aminocyclopentanecarboxylates [3] (Scheme 2).



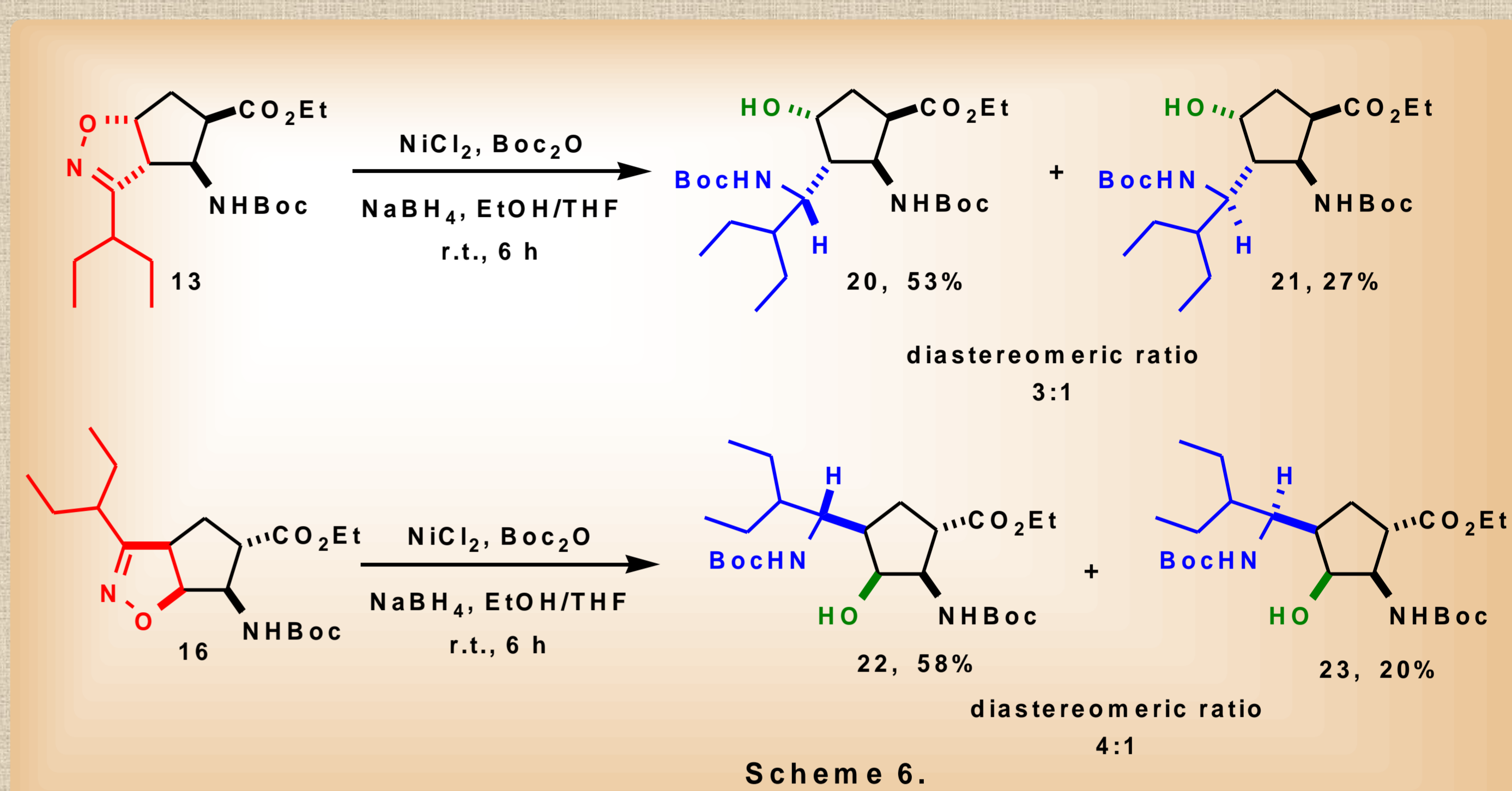
Scheme 2.

Our aim was to synthesize fluorine containing β - and γ -aminocyclopentanecarboxylate regio- and stereoisomers, which may be regarded as fluorinated precursors for the synthesis of Peramivir analogues. The hydroxyl containing, multifunctionalized amino carboxylates were prepared, by reductive ring opening of the isoxazoline skeleton of **6** and **7** and furnished two diastereomers **8**, **9** and **10**, **11** respectively, in a ratio of 4:1 (Scheme 3).

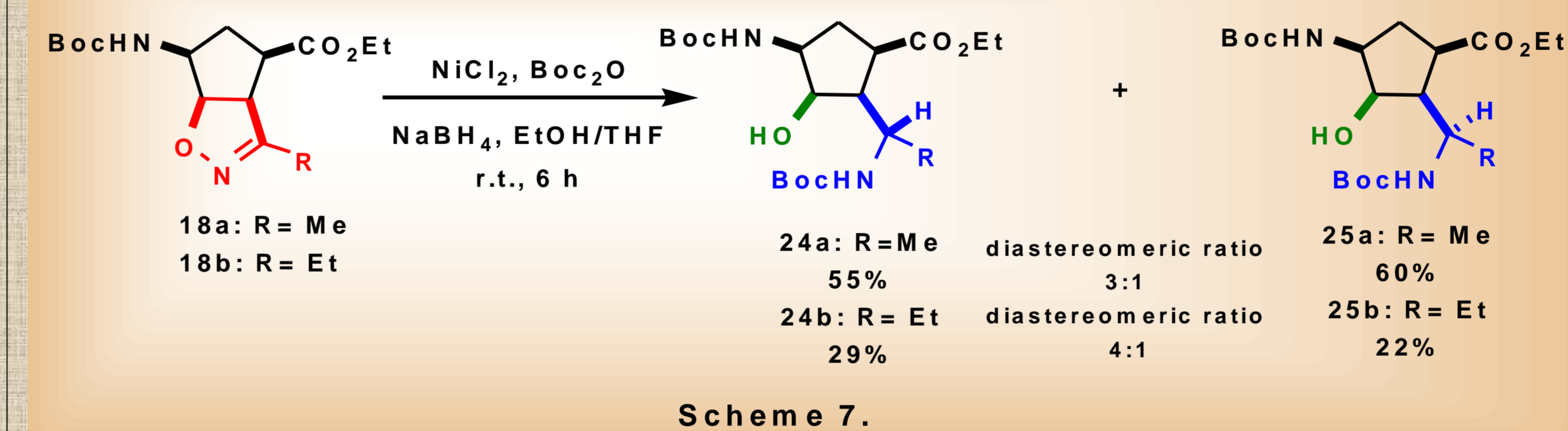


Scheme 3.

The reductive ring opening reactions were accomplished with NaBH_4 in the presence of NiCl_2 resulting in from **13** two diastereomers **20** and **21** as well as from **16** compounds **22** and **23** (Scheme 6), which were separated.



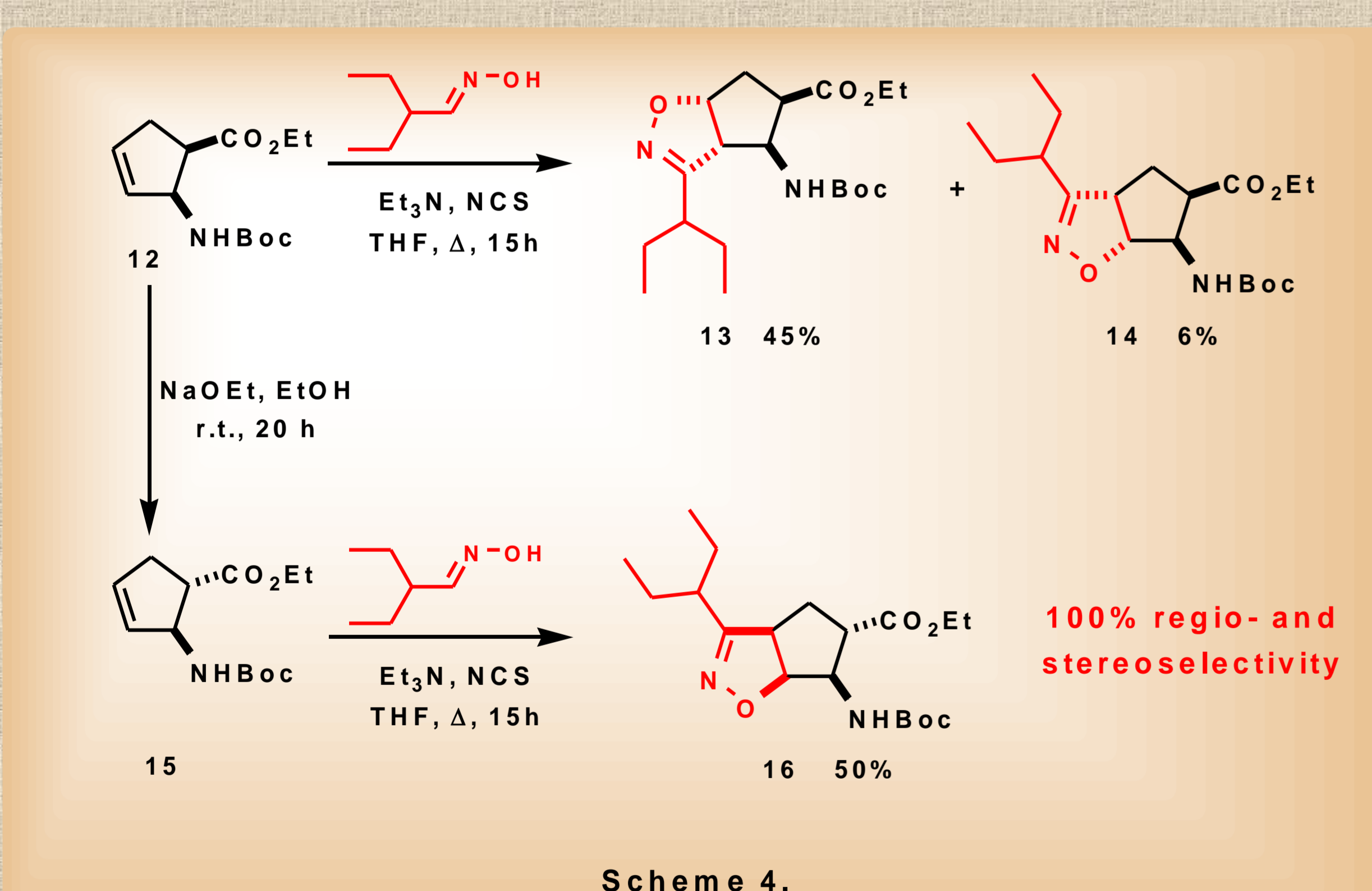
Scheme 6.



Scheme 7.

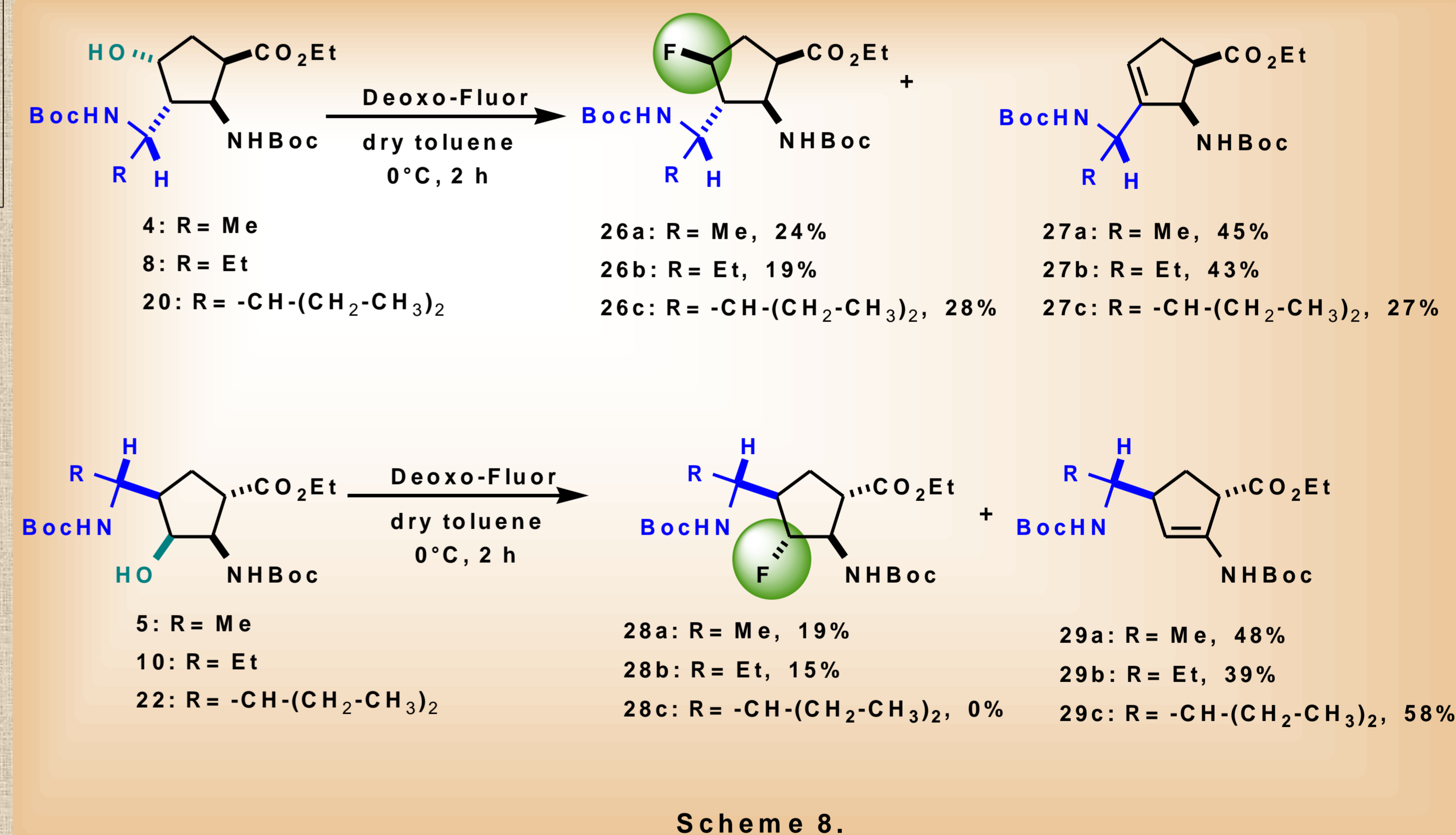
The opening of the cycloadduct **18a,b** resulted in two hydroxyl group containing diastereomers **24a**, **24b** and **25a**, **25b** on a ratio of 3:1 and 4:1 respectively (Scheme 7).

In order to prepare several hydroxyl group containing cispentacin analogues, the cycloaddition with nitrile oxide derived from 2-ethylbutyraldehyde oxime was executed to **12** and **15** and (Scheme 4). The cycloaddition to **12** gave two regioisomers **13** and **14** in a ratio of 8:1 (Scheme 4), which were separated by chromatography. The *trans* representative **15**, gave only one cycloadduct **16** (Scheme 4).



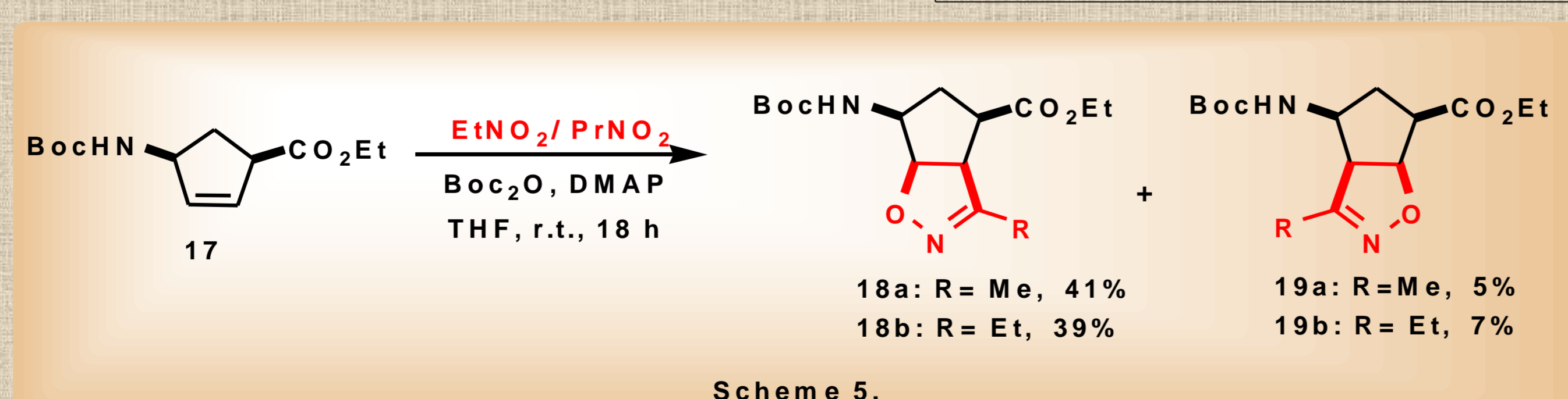
Scheme 4.

The fluorinations were performed with Deoxo-Fluor reagent in dry toluene at 0°C for 2 h, affording the fluorinated compounds **26a-c** and **28a,b** and elimination materials **27a-c** and **29a-c** respectively. (Scheme 8), which could be separated by column chromatography.

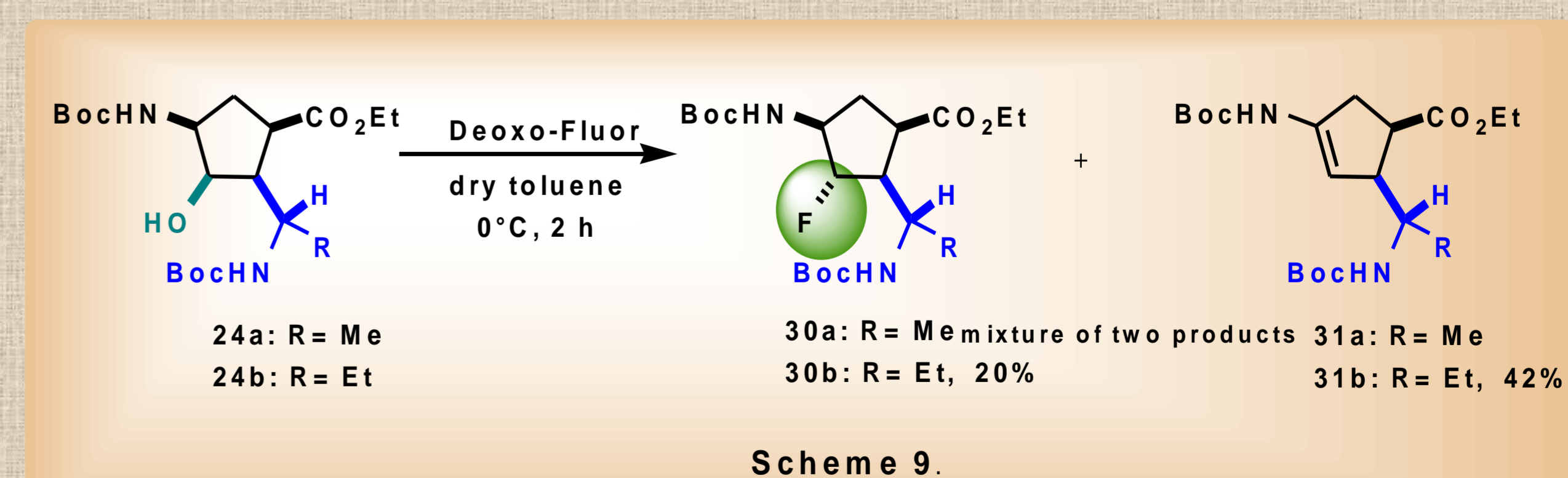


Scheme 8.

When compound **24a** underwent fluorination, an unseparable mixture of two products **30a** and **31a** was produced (Scheme 9). Fluorination of **24b** resulted in fluorinated product **30b** in 20% yield and the elimination product **31b** in 42% yield (Scheme 9), which could be separated.



Scheme 5.



Scheme 9.

Conclusion

Fluorinated aminocyclopentanecarboxylate regio- and stereoisomers have been synthesized from β - or γ -aminocyclopentanecarboxylates across the 1,3-dipolar cycloaddition of nitrile-oxides and the reductive ring opening of the isoxazoline skeleton, followed by hydroxyl-fluorine exchange. The synthesized fluorinated derivative may be regarded as precursors for the preparation of Peramivir analogues.

References

1. a) Kiss, L. et al Synthesis of carbocyclic β -amino acids. *Amino Acids, Peptides and Proteins in Organic Chemistry*. Vol. 1, Ed. A. B. Hughes, Wiley, Weinheim, **2009**, 367. b) Nonn, M. et al *Tetrahedron*, **2011**, 67, 4079. c) Ji, H. et al *J. Med. Chem.* **2006**, 49, 6254. d) Wang, G. T. et al *J. Med. Chem.* **2001**, 44, 1192. e) Yi, X. et al *Bioorg. Med. Chem.* **2003**, 11, 1465. f) Ishikawa, H. et al *Chem. Eur. J.* **2010**, 16, 12616. g) Ko, J. S. et al *J. Org. Chem.* **2010**, 75, 7006. h) Zhu, S. et al *Angew. Chem. Int. Ed.* **2010**, 49, 4656. i) Oakley, A. J. et al *J. Med. Chem.* **2010**, 53, 6421. j) Lu, W. J. et al *Eur. J. Med. Chem.* **2008**, 43, 569.
2. a) Acena, J. L. et al *Curr. Med. Chem.* **2010**, 14, 928. b) Mikami, K. et al *Synthesis* **2011**, 304. c) Kiss, L. et al *Eur J Org Chem* **2011**, 4993. d) Kiss, L. et al *Org Biomol Chem* **2011**, 9, 6528.
3. Nonn, M. et al *Beilstein J. Org. Chem.* **2012**, 8, 100.