Diastereoselective Synthesis of Phosphoramidate Prodrugs

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Introduction

Arylphosphoramidate prodrugs represent a class of highly effective pronucleotides of antiviral active nucleoside analogues. Due to their synthesis, these prodrugs are formed as mixtures of two diastereomers with respect to the configuration at the phosphorus center. The separation of the diastereomers was often a difficult task to achieve.[1] However, the diastereomers showed different biological activity and pharmacokinetic profiles.[2] Therefore, here we focussed on the development of a synthesis route of isomerically pure phosphoramidate nucleotide prodrugs.

General concept

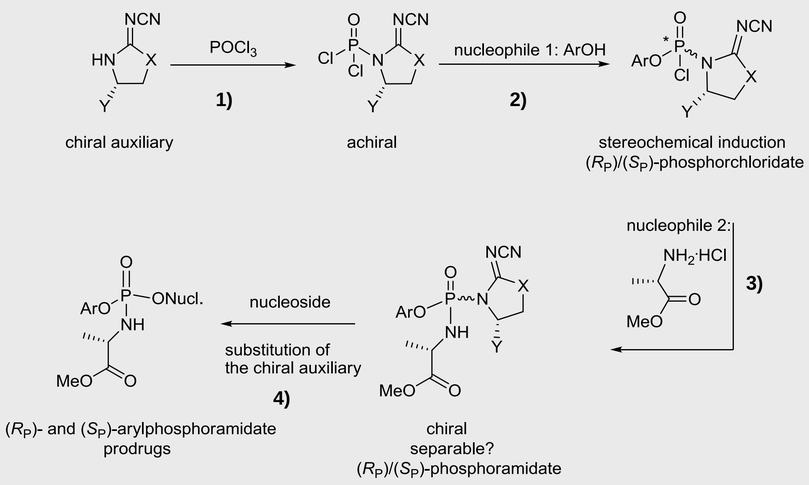
The developed diastereoselective synthesis is based on chiral auxiliaries and consist of four steps:[3]

1) The reaction of the chiral auxiliary with $P(O)Cl_3$ should lead to a phosphorodichloridate to introduce the chiral auxiliary in the very first step.

2) The conversion of the phosphorodichloridate with a first nucleophile like a phenol derivative should lead to the diastereoselective formation of (R_P)/(S_P)-phosphorochloridate derivatives. In this step the stereochemical induction should take place at the phosphorus atom.

3) The coupling of the phosphorochloridate with a second nucleophile like an L-amino acid ester should lead to the corresponding chiral phosphoramidate derivatives.

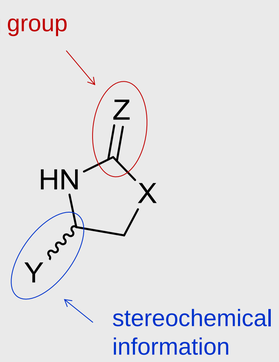
4) The substitution of the auxiliary by the nucleoside analogue should afford the phosphoramidate prodrugs.



Chiral Auxiliary

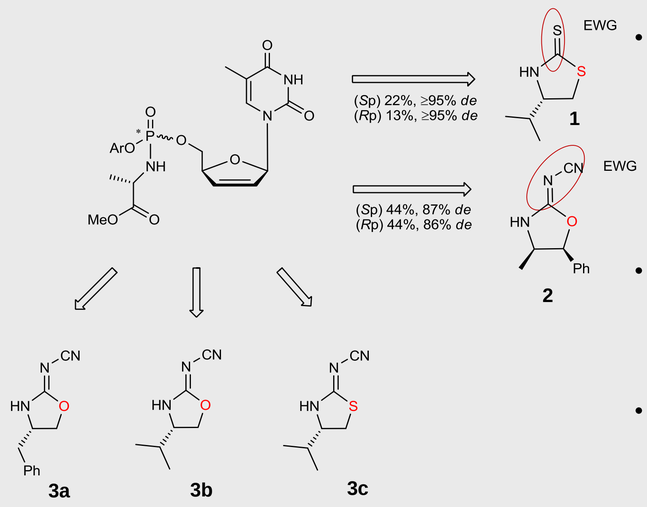
The auxiliary has to fulfill further important criteria:[4]

1) Simple and low-cost synthesis;
2) It should has an electron-withdrawing group next to the N-atom;
3) High stereochemical induction at phosphorus atom;
4) It should allow the chromatographic separation of the diastereomers in the third step;
5) It has to be replaceable by a nucleoside analogue in the last step using mild reaction conditions. The cleavage property of this type of auxiliaries was already proven in earlier approaches.[3,4]



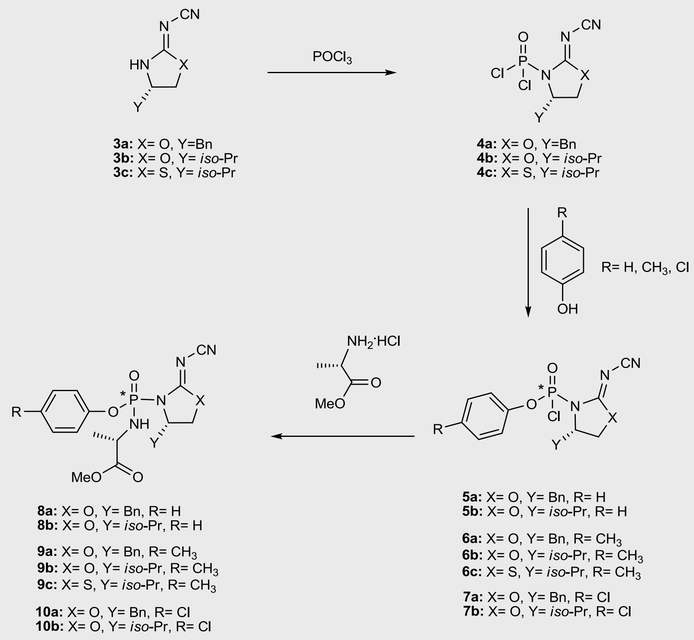
Z= NCN
X= S, O
Y= Alkyl, Aryl

First Approaches



- A first approach was based on the chiral auxiliary **1** which allowed the synthesis of single diastereomers of the phosphoramidate prodrugs in very good diastereomeric excess but only in modest yields.[3]
- Using *N*-cyanoiminooxazolidine **2** as chiral auxiliary the yields were increased but the diastereomeric excess decreased slightly.[4]
- Further improvement of this approach using different chiral auxiliaries is now in progress.

Diastereoselective Synthesis of Phosphoramidate derivatives

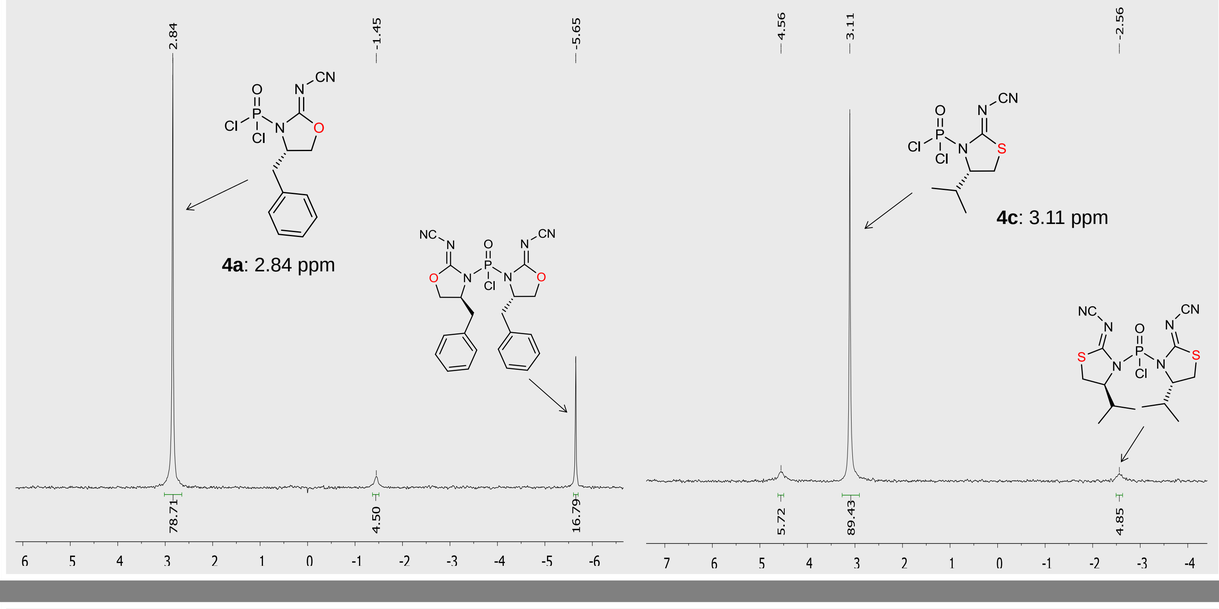


compound	*d.e.* [%][a]	Yield [%][a]
5a	70	80
5b	90	71
6a	96	88
6b	81	99
6c	77	96
7a	73	87
7b	83	85
8a	72	88
8b	76	82
9a	82	84
9b	22	98
9c	78	71
10a	72	83

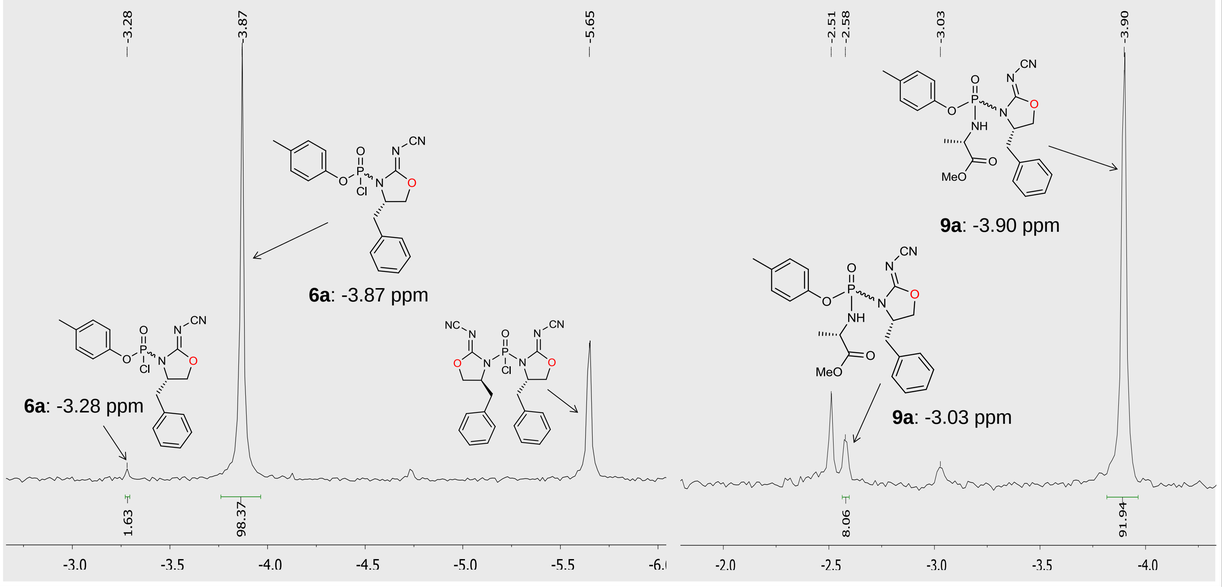
[a] Diastereomeric excess and yield determined by ^{31}P-NMR of the crude mixture

Comparison of the Reactivity of the Phosphorodichloridates

The chemical shift in the ^{31}P-NMR spectra correlated with the difference in reactivity of the phosphorodichloridates bearing different chiral auxiliaries



^{31}P-NMR-Spectroscopy of the (R_P)/(S_P)-Phosphorochloridate and (R_P)/(S_P)-Phosphoramidate



Conclusion

- A diastereoselective synthesis of phosphoramidate derivatives was developed using suitable chiral auxiliaries.
- The synthetic route led to almost diastereomerically pure phosphorodichloridates in good yields.
- The phosphoramidate derivatives were synthesized in good diastereomeric excess and excellent yields.
- The improvement of the purification of the phosphoramidates is now in progress.

References

[1] McGuigan *et al.*, *J. Med. Chem.* **2006**, *49*, 452-455. [2] Sofia, M. J. *et al.*, *J. Med. Chem.* **2010**, *53*, 7202-7218. [3] Arbelo Román, C.; Balzarini, J.; Meier, C. *J. Med. Chem.* **2010**, *53*, 7675-7681. [4] Rios Morales, E. H.; Balzarini, J.; Meier, C. *Chem. Eur. J.* **2011**, *17*, 1649-1659.

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