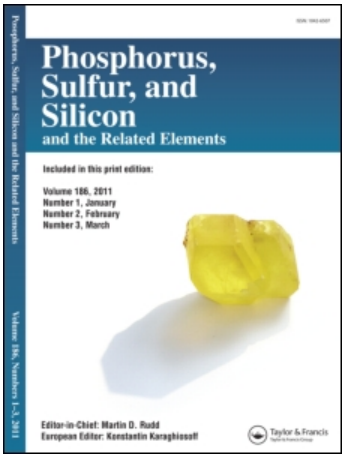

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New Methods and Strategies for Asymmetric Synthesis of Organophosphorus Compounds

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New Methods and Strategies for Asymmetric Synthesis of Organophosphorus Compounds

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New methods for the asymmetric synthesis of organophosphorus compounds were developed and applied for the preparation of a number of biologically important enantiomerically pure products.

Keywords Asymmetric induction; asymmetric reduction; chiral hydroxyphosphonates; stereoselectivity

INTRODUCTION

The account is devoted to development of highly stereoselective methods and reagents and their application for the asymmetric synthesis of enantiomerically pure organophosphorus compounds.[1–12]

RESULTS AND DISCUSSION

Strategy *of multistereoselectivity* is an effective method to increase the stereoselectivity of organic reactions[1] that is achieved by summarizing of asymmetric inductions. Additive effect of asymmetric inductions of several asymmetric centers participating synchronously in one reactionary process was observed in the reaction of (R)-glyceraldehyde acetonide with chiral dialkylphosphites im the presence of chiral binol catalysts. Absolute configurations of (R)-glyceraldehyde, (*1R,2S,5R)*-menthyl groups, and (S)-binol acted in coordination to increase the total stereoselectivity of reaction, whereas the absolute configuration of (R)-glyceraldehyde, (*1R,2S,5R*)-menthyl groups and (R)-binol decreased the stereoselectivity of reaction.[2,3]

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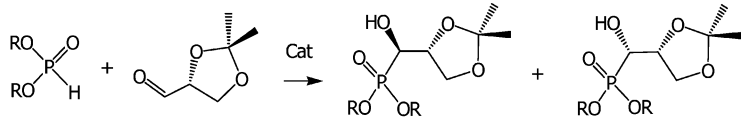


R =Et	Cat=DBU[b]	dr=45 : 55	Single AI
R =Et	(S)-ALB	dr=20 : 80	Double AI
Mnt	DBU	20 : 80	Double AI
Mnt	(S)-ALB[c]	5 : 95	Triple matched AI
Mnt	(R)-ALB	22 : 78	Triple mismatched AI

ALB = Al-Li-bis(binaphthoxide)

SCHEME 1 Single, double, and triple asymmetric induction.

The absolute configurations of reaction products were determined by NMR spectra, and X-ray crystal analysis. It was shown, that the stereochemistry of phospho-aldol reaction proceeds according to the Cram's rule (Figure 1).

The method was applied for the synthesis of organophosphorus analogues of taxoids.[4] The chiral 1-hydroxy-2-aminophosphonic acids were used for modification of 10-deacetylbaccatin III in the synthesis of new taxoids - potential anticancer agents (Scheme 2).

The reduction of ketophosphonates with a reagent prepared from sodium borohydride and tartaric acid yields (S) and (R)-enantiomers

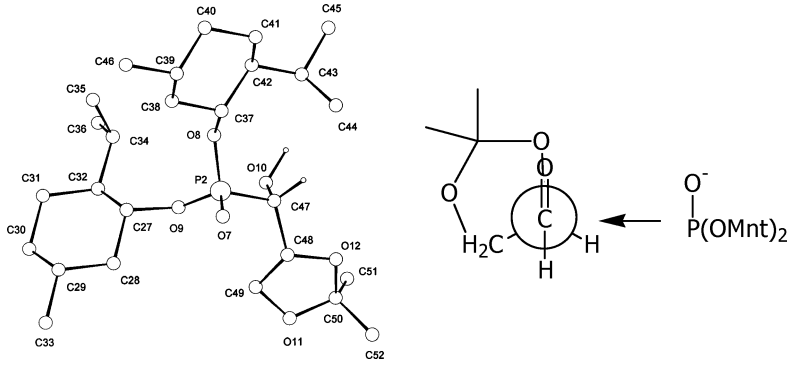
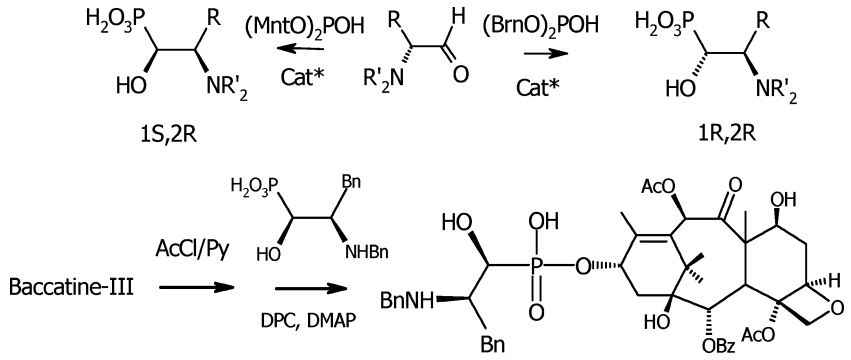
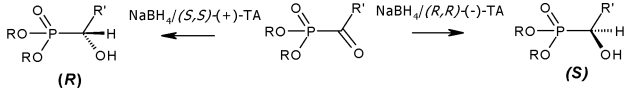


FIGURE 1 Stereochemistry of phospho-aldol reaction.

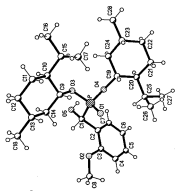


SCHEME 2 Synthesis of phosphono-taxoid.

of hydroxyphosphonates with high stereoselectivity.[5] Reductions of dimenthyl ketophosphonates yielded (1S)-hydroxybenzylphosphonates (I) with 80–96% de. High stereoselectivity of reduction of dimenthyl arylketophosphonates is explained by effect of a double asymmetric induction because in this case are summarized asymmetric an induction of menthyl groups and tartaric acid. The asymmetric induction (*1R,2S,5R*)-menthyl groups and (*R,R*)-tartaric acid increased the resultant stereoselectivity whereas the asymmetric induction of (*1R,2S,5R*)-menthyl groups and (S,S)-tartaric acid acted non-coordinated to reduce the resultant stereoselectivity Hydroxyphosphonates (S)-(IV) were purified by crystallization from acetonitrile and were obtained with ~100% de. The reductions of ketophosphonates with $NaBH_4$/(R)-TA resulted in the formation of (S)-hydroxyphosphonates, and the reductions by $NaBH_4$/(S)-TA yielded (R)-hydroxyphosphonates (Scheme 3).

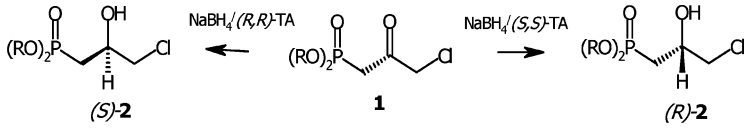


Et	Ph	*R,R*	80	*S*	Single
Mnt	Ph	*R,R*	92.5	*S*	Matched double AI
Mnt	Ph	*S,S*	46	*R*	Mismatched double AI



SCHEME 3 Asymmetric reduction of α-ketophosphonates.

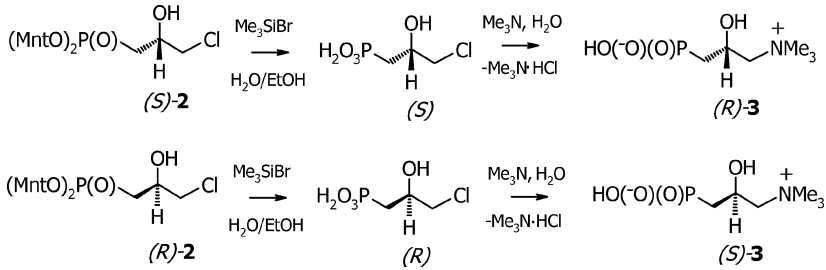
Optically pure dimenthyl(2*R*)-and (2S)-2-hydroxy-3-chloropropylph osphonates **2** were synthesized by reaction of the ketophosphonate **1** with the chiral complex $NaBH_4$/TA (Scheme 4).[7]



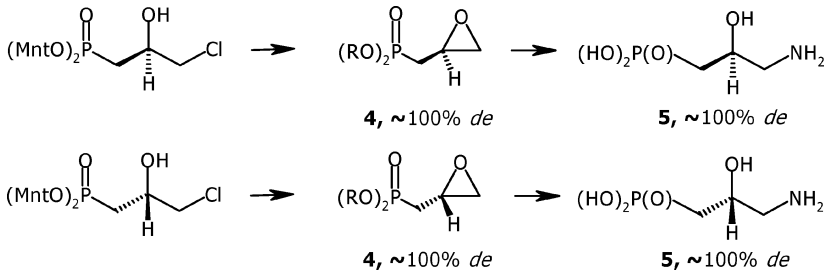
R=Et	*R,R-TA*	81%de	Single AI
R=Mnt	*R,R-TA*	96%de	Matched double
Mnt	*S,S-TA*	80%de	Mismatched double

SCHEME 4 Asymmetric reduction of β-ketophosphonates.

The reduction of the ketophosphonate with this complex proceeded under the control of double asymmetric induction and resulted in the formation of the hydroxyphosphonates with high optical and chemical yields.[7–11] The compounds **2** were isolated as a crystalline stereochemically pure substance with ~100% *de* and used for the preparation of a number of enantiomerically pure products, such as both optical antipodes of phospho-carnitine (Scheme 5) and γ-amino-β-hydroxybutyric acid (phospho-GABOB) (Scheme 6), 2,3-aziridinopropylphosphonate, 2,3-epoxypropyl-phosphonate, etc in multigramme scale.

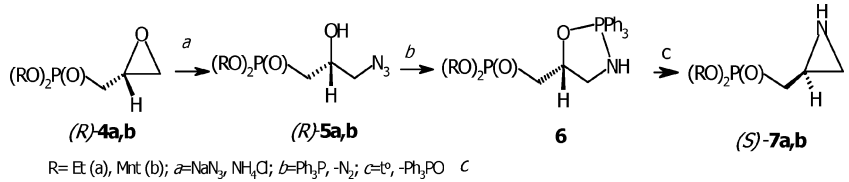


SCHEME 5 Asymmetric synthesis of (*R*)- and (S)-phospho-carnitines.



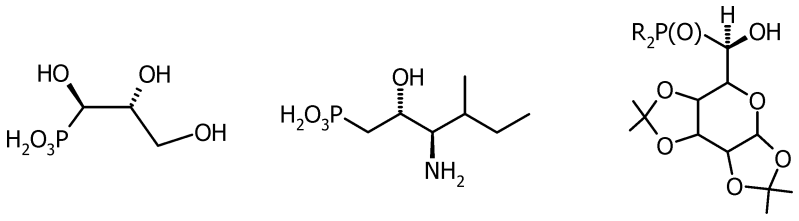
SCHEME 6 Asymmetric synthesis of (*R*)-phospho-GABOB.

The epoxide **4** was converted consequently into azides **5a**,**b** and aziridines **7a**, **b**. To the best of our knowledge, optically active 2,3-aziridinoalkylphosphonates have not been earlier reported in the literature. The reaction of azidophosphonate **5a,b** with triphenylphosphine at room temperature proceeded via the formation of unstable intermediate **6** bearing pentacoordinated phosphorus. In ^{31}P NMR spectra of the intermediate **6** were found two signals: P−55.1 (pentacoordinated phosphorus) and +26.9 ppm (tetracoordinated phosphorus) according to the structure of this compound. At heating **6** converts into triphenylphosphine oxide and aziridinophosphonate **7a**, **b** which were isolated in good yield. The aziridinophosphonate (*S*)-7a was purified by distillation under vacuum and isolated as colorless liquid (Scheme 7).



SCHEME 7 Asymmetric synthesis of aziridinophosphonate.

Using the developed methods were synthesized the phosphorthreonine acid, phosphorus analogues of statin, phosphorus derivatives of galactoso-phosphates (Scheme 8).[10–12]



SCHEME 8 Chiral functionalized phosphonic acids.

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