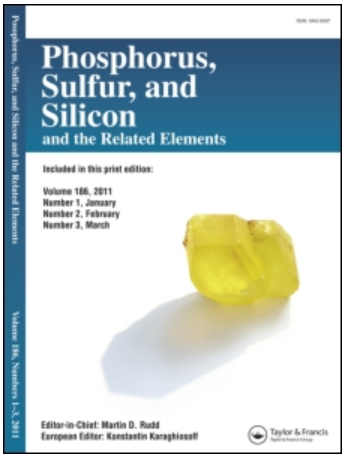

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K. Kellner[a]; C. Preußler[a]; K. Schnepp[a]
[a] Martin-Luther-Universität Halle-Wittenberg, Halle(S.), FRG

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DIASTEREOSELECTIVE SYNTHETIC WAYS TO P-ASPARTIC ACID DERIVATIVES

K. KELLNER, C. PREUßLER, and K. SCHNEPP
Martin-Luther-Universität Halle-Wittenberg,
Fachbereich Chemie, O-4010 Halle(S.), FRG

Abstract: α-Amino β-phosphono propionic acid derivatives are formed by reaction of alkali metal or triorganosilyl derivatives of 4-(P-substituted methyl) 5-hydroxy oxazoles with O- or N-nucleophiles. A high diastereoselectivity of the reaction is observed depending upon the reaction conditions. The source of stereoselectivity is a substrat and/or reagent chirality. The dominant effect of the phosphorus substituent in the sterochemical course is proposed.

INTRODUCTION

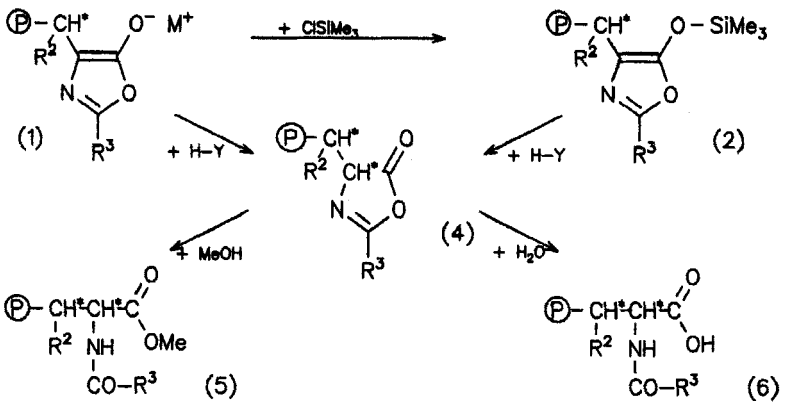
Many methods for the synthesis of aminoalkyl phosphonic acids have been studied. Nevertheless, synthetic ways to β-phosphorus substituted aspartic acid derivatives are limited to few procedures. In previous papers we have shown that 4-methylene oxazolinones can be used for the preparation of α-amino β-phosphonyl propionic acid derivatives by exploiting the acceptor reactivity of the α,β-unsaturated carbonyl moiety. In this way diastereoselective P-C-bond formation is possible with phosphonic and phosphinic acid esters [1-3].

RESULTS AND DISCUSSIONS

We have found that 4-(P-substituted methyl) 5-hydroxy oxazoles as their alkalimetal derivatives (1) and their O-silylderivatives (2), respectively, are excellent synthons for β-P-aspartic acid synthesis. The synthesis of the key-substance 1 involves addition of alkali metal derivatives of PH-acidic compounds to 4-alkylidene 4,5-dihydro 5-oxazolones (3). The O-silyl compounds 2 result after silylation of 1 or by direct reaction of phosphonus(III) O-silylesters with 3 at higher temperature.

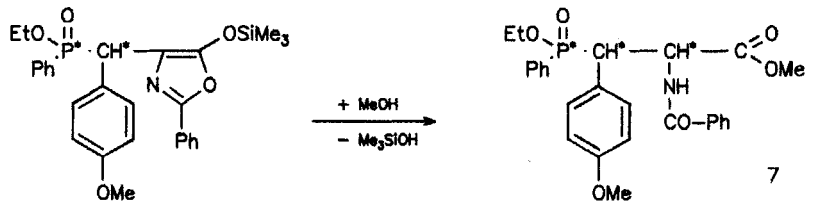
4-(Dialkoxyphosphoryl methyl) 4,5-dihydro oxazolones (4), P-aspartic acid esters (5) or the free acid (6) are formed by solvolysis of the 4-(dialkoxyphosphoryl methyl) derivatives 1 or 2 with alcohols and water,

respectively. Depending upon the primary product 1 or 2 different diastereomeres are obtained. On the way 2 –> 4 –> 5(6) the RS/SR diastereomeres predominate. Contrary to this result the reaction from 1 –> 4 –> 5(6) leads to an excess of the RR/SS form. The dominant effect of the phosphonyl oxygen in the stereochemical course is proposed as demonstrated for both cases. In the ionic species 1 the metal atom is coordinated by oxygen atoms resulting in a fixed conformation. The hydrogen transfer to the stereogenic centre in 4-position of the heterocyclus is influenced by the chiral atom in the molecule. In case of the reaction of 2 the hydrogen transfer should proceed over onium derivatives assisted by hydrogen bridge bond at the phosphonyl oxygen.



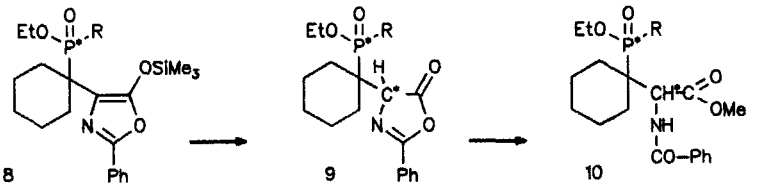
P = P(O)(OR)$_2$, P(O)(OR)R^1, Y = OMe, OH

This hypothesis is supported by the observed dominance of two from four possible diasteromeres of 3-(phenyl O-ethyl phosphounus) aspartic acid ester (7) formed by reaction of phenyl O-ethyl phosphinate sodium with 4-benzylidene 4,5-dihydro oxazolinone and methanolysis successively.

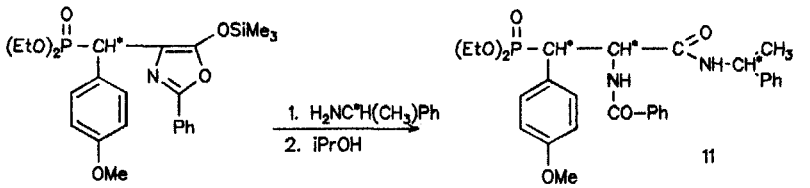


^{31}P-NMR δ[ppm] / rel. intergral			
44,7 / 1	41,6 / 1	40,7 / 3	39,9 /2,5

A silyloxazol (**8**) with an exocyclic chiral phosphorus is yielded by addition of alkyl O-ethyl O-silyl phosphinates to 4-cyclohexylidene oxazolinone . After methanolysis the second chiral centre in **9** is formed stereoselectively (ratio 5:1). Work up procedure to **10** deminish this diastereoselecticity by racemisation on cyclic structure. In the synthesis of **7** one or both of the two chiral centres of the first addition product can create an asymmetric induction. In the later exam-ple only the asymmetric phosphorus in **8** acts as internal chiral centre for chirality transfer.

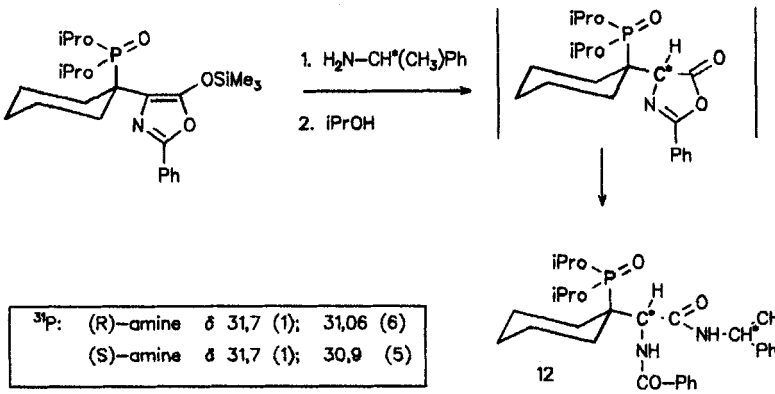


In the reaction of 4-(phosphonomethyl) 5-siloxyoxazols **2** with NH-nucleophiles the corresponding amides are formed. Ammonia reacts with compounds of typ **2** only after addition of alcohols to the primary amide, under the same conditions with morpholine or pyrrolidine the tertiary amides are formed. With these reagents no diastereoselectivity in the reaction is observed. In the reaction of **2** with isopropylamine the two diastereomeres are formed in a ratio 2:1. An excellent diastereoselective reaction proceeds with the optically active phenylethylamine. The use of the (R)-amine in the solvolysis reaction of **2** leads to compounds (**11**) with the same chemical shift in the ^{31}P-nmr as formed by use of the (S)-amine. The only one explanation for this result is the formation of the enantiomeres of both diastereomeres with a strong asymmetric induction by the chiral amine reagent.



(R)–Amin	(23,5), (24,6),	25,4	26,3
(S)–Amin		25,5	26,3

The preference of one conficuration in the protonation reaction of the siloxyoxazoles using the optically active phenylethylamine as an external chiral reagent is also remarkable for such reaction where in the siloxyoxazol **2** no asymmetric centre is located. In the reaction of 4-(diisopropoxyphosphonyl-pentamethylenemethyl) 5-siloxyoxazole with phenyl ethyl amine and iPrOH successively the amide **12** is formed in high diastereoselectivity. Indepentendly of the amine configuration the same chemical shift in the ^{31}P-nmr is found for both products, that means the both enantiomeres of the diastereomere are synthesized on this way in separate reactions.



^{31}P:	(R)–amine	δ 31,7 (1);	31,06 (6)
	(S)–amine	δ 31,7 (1);	30,9 (5)

The 4-(P-substituted methyl) 5-hydroxy oxazoles are as there alkali metal derivatives or there 5-siloxy derivatives easily synthesized intermediates which can be used for a wide range of substituted β-P-aspartic acid derivatives. We believe the reagents described here are reagents of choice for the synthesis of the different diastereoisomers and enantiomers.

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