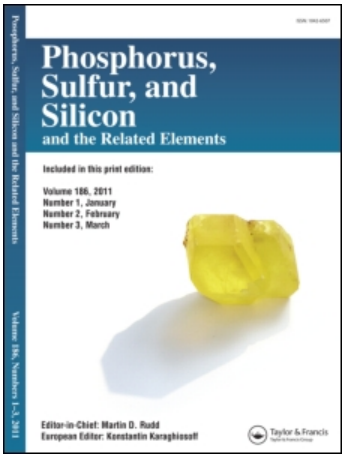

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New P-Chiral Phosphates, Phosphorothioates and Phosphoroselenothioates

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NEW P-CHIRAL PHOSPHATES, PHOSPHOROTHIOATES AND PHOSPHOROSELENOTHIOATES

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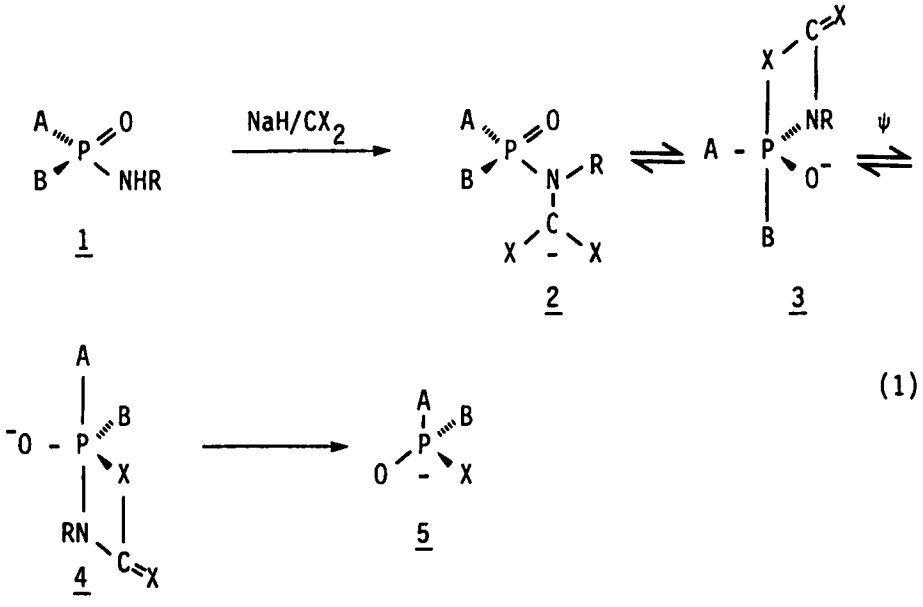
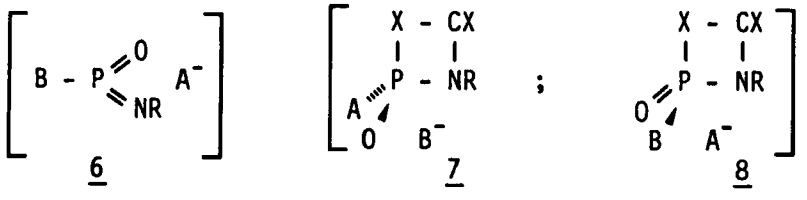
Abstract Easily available pure diastereoisomers of (Rp,Rc)- and (Sp,Sc)-O,Se-dimethyl N-α-methylbenzyl phosphoramidoselenoate (12) and S-methyl-N-phenyl-N'-α-methylbenzyl phosphordiamidothioate (9) are converted into enantiomers of O,S,Se-trimethyl phosphoroselenothioate (16) and S-methyl-S-ethyl-S-n-propyl phosphorotrithioate (two-step procedure)(15), respectively. Partial P-epimerizations observed during these conversions are discussed in terms of stereomutation of pentacoordinated phosphorus intermediates, while metaphosphoramidates are responsible for the formation of side-products.

The methodology for cleavage of a P-N bond in phosphoramidates (1) derived from primary amines has been developed in this Laboratory (PN→PX conversion), and has been used for chirospecific synthesis of dialkyl phosphates (5, X=^{18}O), phosphorothioates (5, X=S), and phosphoroselenoates (5, X=Se)[1]. Reactions of N-metallated P-chiral phosphoramidates with electrophilic reagents like benzaldehyde, carbon dioxide, carbon disulphide or carbon diselenide have been shown to occur with high stereoselectivity and with retention of configuration at phosphorus, and have been rationalized in terms of a single pseudorotation followed by collapse of a pentacoordinated intermediate (4)(eq. 1). This rationale was sufficient for PN→PX conversions within compounds 1 provided that ligands A and/or B are bound to phosphorus via "strong" chemical bonds; if A and/or B had the distinction of being good leaving groups, one could consider



(1)

the collapse of 1 with formation of "metaphosphoramidate" (6) accompanied by the released anion A^-, and such a reversible reaction

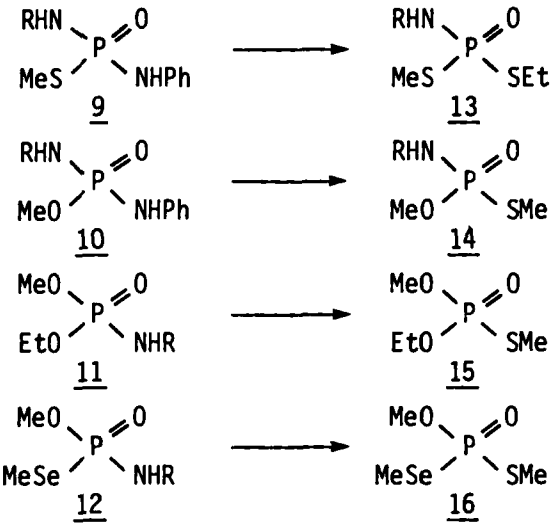


would be responsible for P-epimerization of 1 and, as a consequence, the lack of stereoselectivity of the PN→PX conversion. Alternatively, one could consider the collapse of pentacoordinated intermediates 3 or 4 and participation in the reaction pathways of other intermediates such as 7 or 8 ("irregular process"). Release of A^- or B^- from 3 or 4 would be responsible for a different course of reaction and the formation of products different than 5, while the reversibility of processes 3 ≠ 7 and 4 ≠ 8 could lead to epimerized product 5. However, an alternative process responsible for the lack of stereoselectivity of the PN→PX conversion could be pseudorotation around pentacoordinated phosphorus leading to rapid stereo-

mutation at the chiral phosphorus centre[2].

Earlier studies on the synthesis of diastereoisomers of adenosine 5'-(4-nitrophenyl)phosphorothioate have shown, that the desired products were formed from diastereoisomers of adenosine 5'-(4-nitrophenyl)phosphoranilidate without detectable P-epimerization[6], and averted our suspicions about rapid stereomutation or epimerization via an "irregular process", since 4-nitrophenoxyl can be considered as being a "good" leaving group.

In this report we wish to present the results of our extended studies on the scope and limitations of PN→PX conversions for the synthesis of new P-chiral organophosphorus compounds. Four pairs of diastereoisomeric phosphoramidates 9, 10, 11 and 12, derivatives of enantiomeric α-methylbenzylamines, were prepared and fully characterized by physicochemical methods (TABLE 1).



R = -CH(Me)Ph

Their absolute configurations were assigned by means of stereochemical correlations:

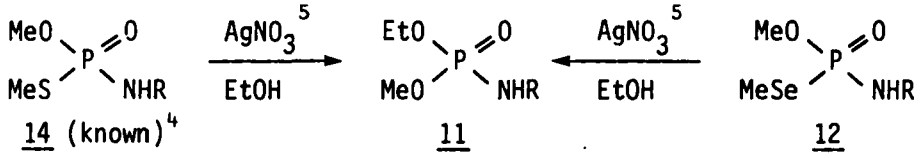
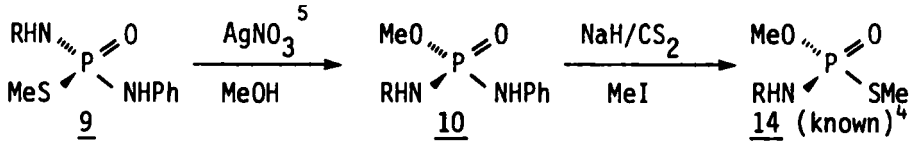


TABLE 1. Physicochemical characteristics of compounds ABZPO

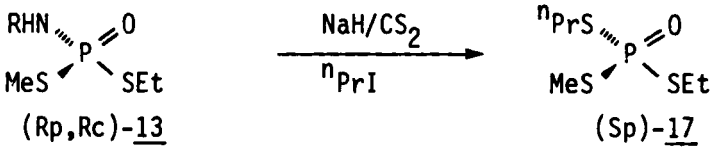
No of compound	A	B	Z	$\delta_P(CHCl_3)$[a]	$\lvert\alpha\rvert_D^{20}$[b] (MeOH)	m.p. (°C)	Absolute configuration
9	RNH[c]	MeS	PhNH	24.9	+39.1	170-2	Rp,Rc
				24.78	-41.0	169-71	Sp,Sc
				25.8			Sp,Rc
				25.68			Rp,Sc
10	RNH	MeO	PhNH	9.17	+31.5	82-5	Sp,Rc[d]
11	MeO	EtO	NHR	8.46	+51.6	83-5	Sp,Rc[e]
				8.36	+49.1	82-5	Sp,Rc[f]
12	MeO	MeSe	NHR	26.89 (435)[g]	+61.7	121-3	Rp,Rc
				26.29			Sp,Rc
				26.89	-60.6	120-3	Sp,Sc
				26.19			Rp,Sc
13	MeS	EtS	NHR	48.3	+41.5	68-72	Rp,Rc[h]
				48.2	-41.9	69-71	Sp,Sc[i]
14	MeO	MeS	NHR	34.45[j]	+84.8	129-30	Rp,Rc[4]
				34.14	+22.0	82-3	Sp,Rc[4]
				34.45	-84.5	129-30	Sp,Sc[4]
				34.14	-22.0	82-3	Rp,Sc[6]
15	MeO	EtO	MeS	30.1	+0.2±0.1		Rp[k,7]
				30.1	+0.3±0.1		Rp[l,7]
16	MeO	MeS	MeSe	51.27 (486)[g]	1.95[m]		Sp[o]
				51.06 (483)[g]	-1.79[m]		Rp[n]
17	MeS	EtS	[n]PrS	66.1	+1.05[m]		Sp[q]
				61.9[p]	-1.3 [m]		Rp[s]

[a] *85% H_3PO_4 as an external reference.* [b] *Measured in MeOH, conc. in the range 0.65-5.0.* [c] *R=CH(CH_3)Ph.* [d] *Prepared via silver-assisted methanolysis of (Rp,Rc)-9.* [e] *Prepared via ethanolysis of (Rp,Rc)-14.* [f] *Prepared via solvolysis of (Rp,Rc)-12.* [g] *$^1|JP\text{-}Se|$ values given in parantesis.* [h] *Prepared from (Rp,Rc)-9.* [i] *Prepared from (Sp,Sc)-9.* [j] *Measured in $MeNO_2$.* [k] *Prepared via PN→PS conversion of (Sp,Rc)-11.* [l] *Prepared via silver-assisted ethanolysis of (Rp)-16.* [m] *Measured in C_6H_6.* [n] *Obtained from (Rp,Rc)-12.* [o] *Obtained from (Sp,Sc)-12.* [p] *Measured in DME.* [q] *Prepared from (Rp,Rc)-9.* [s] *Prepared from (Sp,Sc)-9.*



Reactions of compounds 9, 10, 11, 12 with NaH/CS_2, followed by corresponding alkyl halides, gave the compounds 13, 14, 15 and 16, respectively, and assignment of their absolute configuration was based on the well documented assumption that the PN→PX conversion proceeds with retention of configuration at P. Because compounds 13 and 14 are diastereoisomeric, ^{31}P n.m.r. and RP-HPLC were used for assignment of their diastereoisomeric purity. It has been found that conversions 9→13 and 10→14 are fully stereoselective. ^{31}P n.m.r. control has also proved that unreacted, recovered substrate 9 was not P-epimerized during conversion 9→13.

Diastereoisomers of 13 were used for further PN→PS conversion and the enantiomers of P-chiral S,S,S-trialkyl phosphorotrithioate (17) were obtained:



while compound (Rp)-16 was converted into compound (Rp)-15 in a solvolytic reaction ($EtOH/AgNO_3$), which according to earlier findings [5] is expected to be stereoinvertive.

Because compounds 16 and 17 have not been described, to the best of our knowledge, in the chemical literature, we attempted to assign the enantiomeric purity of 17 by means of ^1H n.m.r., running its spectra in the presence of $Eu(tfc)_3$. It appeared that compound (Rp)-17, obtained from diastereoisomerically pure (Sp,Sc) (Sp,Sc)-13 has been extensively epimerized (e.e. 60%). Also, the comparison of the value of the optical rotation of compound (Rp)-15 /prepared from pure (Sp,Rc)-11/ with that reported by Hall and Inch [6] for optically pure 15, indicated that the conversion 16→15

occurs with low stereoselectivity. Because the test of epimerization of 14 under conditions analogous to the PN→PS conversion (but without added CS_2) gave negative results [7], we have to accept the conclusion that "metaphosphoramidates" are not involved in the PN→PS transformation of the compounds under consideration here. In the light of recent findings of Buck et al. [2], the most plausible explanation for the lack of stereoselectivity in conversions 11→15 and 12→16 is pseudorotation of pentacoordinated intermediate 4 leading to rapid stereomutation at the stereogenic phosphorus atom, although the operation of "irregular processes" 3⇌7 and 4⇌8 has not been disproved [8]. Interestingly, P-epimerization was not observed in these PN→PS conversions, where the "chiral auxiliary" group $NHCH(CH_3)Ph$ attached to phosphorus is retained in the product.

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7. (Sp,Sc)-14, $|\alpha|_D$-82.3° (c 3.23, $CHCl_3$) was dissolved in dioxane and treated with sodium hydride (20% molar excess) under rigorously anhydrous conditions. After two hours the reaction mixture was treated with triethylammonium acetate buffer (pH 7) and organic compounds were extracted with $CHCl_3$. After standard work-up recovered (Sp,Sc)-14 was isolated by means of column chromatography on silica-gel, m.p. 128-130°C, $|\alpha|_D$-78.5° (c 1.04, $CHCl_3$).
8. ^{31}P n.m.r. spectra recorded for reaction mixtures under the conditions of PN→PX conversion did not contain any signals corresponding to pentacoordinated intermediates of type 4 or 4-membered cyclic intermediates of type 7 or 8.