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[A0034]

Synthesis, *ee*-Determination and Absolute Configuration of Chiral Organophosphorus Inhibitors of Serine Hydrolases

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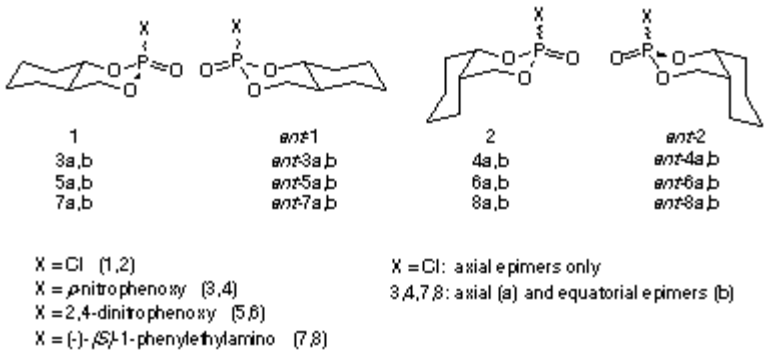
Abstract: In the course of our investigations concerning the regio- and stereochemical course of the inhibition of chymotrypsin and acetylcholinesterase (F.A. Merckling, P. Rüedi, *Chimia* **1994**, *48*, 279) we have prepared the chiral 2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decan-3-ones (**1**-**8**). Being configurationally and conformationally locked, these *cis*- and *trans*-decaline-type congeners are good probes for the investigation of stereochemical implications by ^{31}P-NMR spectroscopy (W. Ganci, E.J.M. Meier, G. Przibille, U. Ringeisen, P. Rüedi, *Chimia* **1996**, *50*, 345; iid. *Helv. Chim. Acta*, **1997**, *80*, 421).



The bicyclic organophosphates were synthesized from the corresponding optically active 2-hydroxycyclohexane-1-carboxylic acid derivatives and their absolute configurations unambiguously established by X-ray analyses of the diasteroisomers (-)-*ent*-**7a**, (-)-*ent*-**7b**, (+)-**8a**, and (-)-**8b**. The chiral starting materials were obtained after classical enantioseparation, by reduction with bakers' yeast or enantioselective hydrogenation according to *Noyori*'s procedure. Their *ee*'s were determined by chiral HPLC and those of the heterocycles **1** and **2** by ^{31}P-NMR spectroscopy after *in situ* derivatization with (-)-(*S*)- and (+)-(*R*)-1-phenylethyl-amine. This method was recently established by us; it represents the inverse of the commonly utilized procedure when checking the optical purity of amines and alcohols with enantiomerically pure organophosphorous compounds.

Optically active 2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decan-3-ones have not been characterized before. They are irreversible inhibitors of the enzymes mentioned above and display significant enantioselectivity, the (S_P)-enantiomer always being more potent.

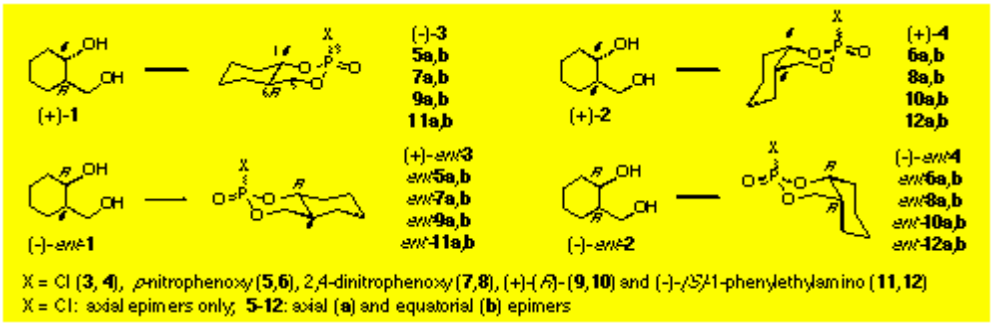
Introduction

In continuation of our investigations concerning the regio- and stereochemical course of the inhibition of

chymotrypsin and acetylcholinesterase [1] we have prepared the optically active 2,4-dioxa-3λ^5-phosphabicyclo[4.4.0]decan-3-ones (**3**-**10**). Being configurationally and conformationally locked, these *cis*- and *trans*-decaline-type congeners are good probes for the investigation of stereochemical implications by ^{31}P-NMR spectroscopy [2].

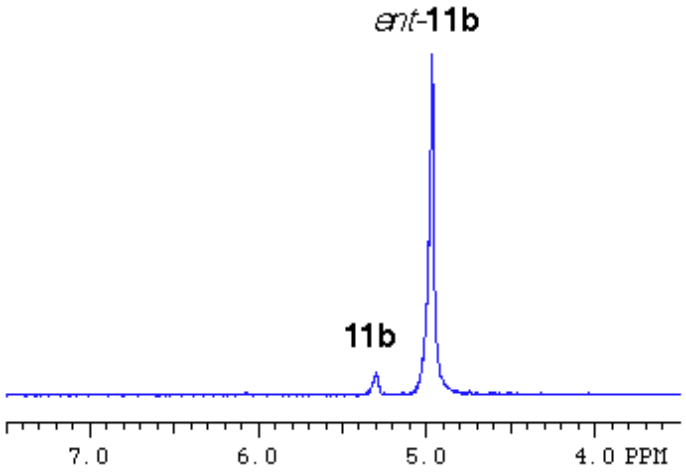
Synthesis

The bicyclic organophosphates were synthesized from the corresponding 2-(hydroxymethyl)cyclohexan-1-ols (**1**,**2**) after reaction with $POCl_3$ (**3**,**4**) and nucleophilic displacement at phosphorus by the corresponding phenolates to yield the phenoxy esters **4**-**8**. The optically active starting materials were obtained after classical enantioseparation of the 2-hydroxycyclohexane-1-carboxylic acids with known absolute configuration, by reduction of ethyl-2-oxocyclohexane-carboxylate with baker's yeast or enantioselective hydrogenation according to *Noyori*'s procedure.

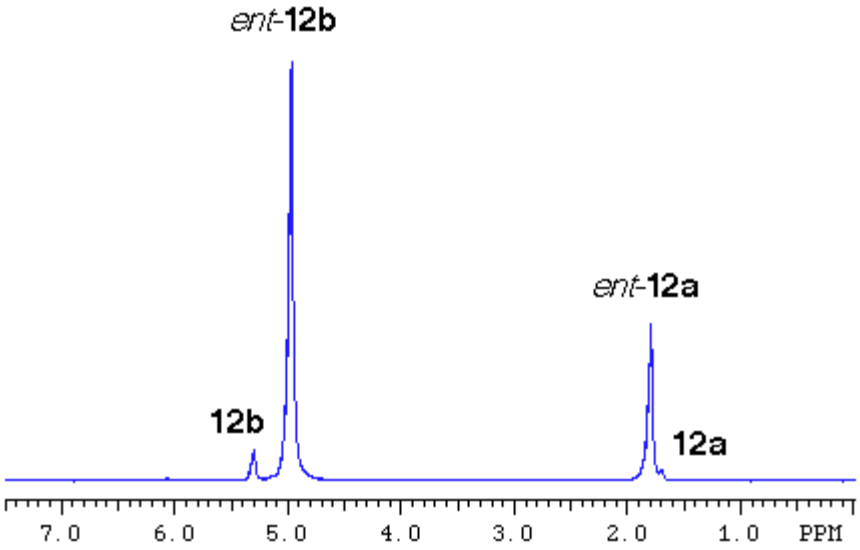


The *ee*-values of the starting materials were monitored by HPLC (Chiralcel-OD) as the 3,5-dinitrobenzoyl derivatives. The *ee*'s of the heterocycles **3** and **4** were determined by ^{31}PMR spectroscopy after *in situ* derivatization with (+)-(*R*)- and (-)-(*S*)-1-phenylethylamine (PhA) (Figures). The best samples could be obtained with *ee*>0.90 throughout (Table 1). This method was recently established by us [3]; it represents the reverse of the commonly utilized procedure when checking the optical purity of amines and alcohols with enantiomerically pure organophosphorous compounds. The absolute configurations of the heterocycles are based on **1** and **2**, and they have been unambiguously confirmed by X-ray analyses of the diasteroisomers (-)-*ent*-**11a**, (-)-*ent*-**11b**, (+)-**12a**, and (-)-**12b** (Figures).

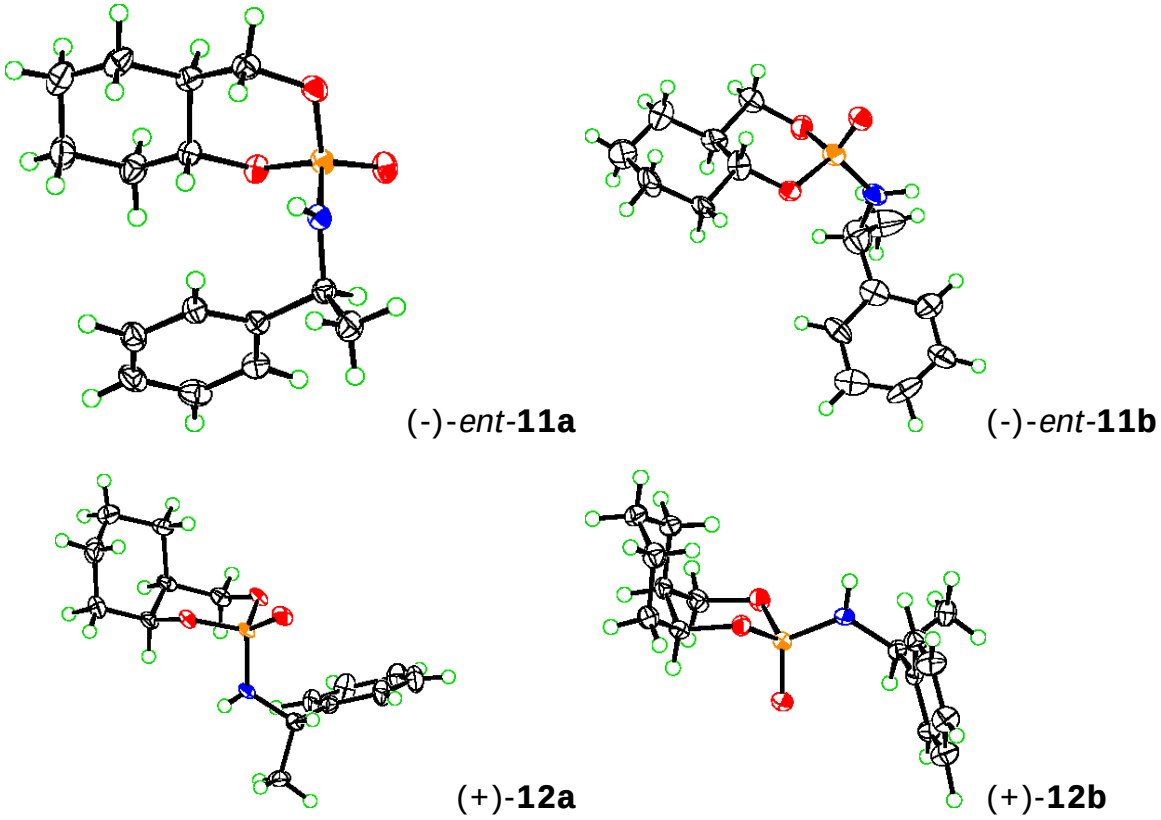
^{31}P-NMR (121 MHz) of (-)-3*l*(-)-(*S*)-PhA



^{31}P-NMR (121 MHz) of (-)-*ent*-**4l**(-)-(*S*)-PhA



^{31}P-NMR spectra.



(-)-*ent*-**11a** (-)-*ent*-**11b**

(+)-**12a** (+)-**12b**

ORTEP plots of the phosphoamidates:
black, C; green, H; red, O; blue, N; yellow, P.

According to stereoelectronic considerations, axially substituted hexacyclic phosphates preferentially adopt a chair and its equatorial counterparts a twist-boat conformation, resulting in an upfield ^{31}P-NMR chemical

shift and a $J_{P,He(5)}$~25Hz for the axial epimers. Hence, the relative configurations (**a**) resp. (**b**) and, as a consequence, the absolute ones at phosphorus could be determined for the chloridates **3**-**4** and the (di)nitrophenoxy esters **4**-**8**.

In continuation of our former studies [4], the derivatization reaction prompted a closer investigation concerning the diastereoselectivity of the displacement at phosphorus by N-nucleophiles and to assign the P-epimers unambiguously. As the stereoelectronical control is reversed in the amidates, the chair is favoured in both epimers and equatorial P-substitutents (**9b**-**12b**) are strongly preferred in the *trans-,* less pronounced in the *cis*-series. The corresponding axial amidates (**11a**,**12a**) could be prepared by treatment of (+)-**1** and (+)-**2** with (-)-(*S*)-1-phenylethylaminophosphorodichloridate and chromatographic separation of the diastereoisomers (*ca.* 1:1). In addition, the $^1J_{P,N}$ proved to be of diagnostic value in assigning the stereochemistry at phosphorus (Table 2).

Table 1. *ee*-Determinations by ^{31}P-NMR (representatitve samples).

	ee
(-)-**3**/(+)-(*R*)-PhA -> **9b**	0.96
(-)-**3**/(-)-(*S*)-PhA -> *ent*-**11b**	0.97
(-)-*ent*-**4**/(-)-(*S*)-PhA -> *ent*-**12a**/*ent*-**12b**	0.88/0.89

Table 2. Selected Spectroscopic Data of the Phosphoamidates.

	(-)-*ent*-**9a**	(-)-*ent*-**9b**	(+)-**12a**	(-)-**12b**
d_P [ppm]	1.63	5.02	1.51	5.45
d_N [ppm]	-322	-321	-321	-321
$^1J_{PN}$ [Hz]	32	50	32	52

This is the first account of optically active 2,4-dioxa-3l^5-phosphabicyclo[4.4.0]decan-3-ones. They are irreversible inhibitors of the enzymes mentioned above and display significant enantioselectivity, the (S_P)-enantiomer predominantly being more potent (Table). Compared to nerve agents, their K_D-values are in the same order of magnitude or even higher (**3**,**4**), but the rate of phoshorylation (k_p) is at least 10^x slower.

Table 3. Inhibition of Serine Hydrolases:
a) Acetylcholinesterase,
b) d-Chymotrypsin (k_i [$M^{-1}sec^{-1}$], determined according to [5]).

	(-)-**3**	(+)-*ent*-**3**	(+)-**4**	(-)-*ent*-**4**	(+)-**7a**	(-)-*ent*-**7a**	(-)-**7b**	(+)-*ent*-**7b**	DFP	Soman
a)	$1.5\cdot10^5$	$2.2\cdot10^5$	$4.0\cdot10^4$	$2.5\cdot10^5$	$7.8\cdot10^4$	$1.3\cdot10^2$	$7.2\cdot10^2$	$1.0\cdot10^3$	$1.6\cdot10^2$	$9.5\cdot10^5$
b)					27.7	3.7	5.8	22.5		

References

[1] F.A. Merckling, P. Rüedi, *Chimia* **1994**, *48*, 279

[2] W. Ganci, E.J.M. Meier, F.A. Merckling, G. Przibille, U. Ringeisen, P. Rüedi, *Helv. Chim. Acta*, **1997**, *80*, 421.

[3] G. Przibille, PhD Thesis, in preparation.

[4] F.A. Merckling, P. Rüedi, *Tetrahedron Letters* **1996**, *37*, 2217.

[5] G.J. Hart, R.D. O'Brien, *Biochemistry* **1973**, *12*, 2940; P.J. Gray, R.G. Duggleby, *Biochem. J.* **1989**,

257, 419.

Comments

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