Synthesis and Characterization of the Enantiomerically Pure *cis*- and *trans*-2,4-Dioxa-3-fluoro-3-phosphadecalins as Inhibitors of Acetylcholinesterase

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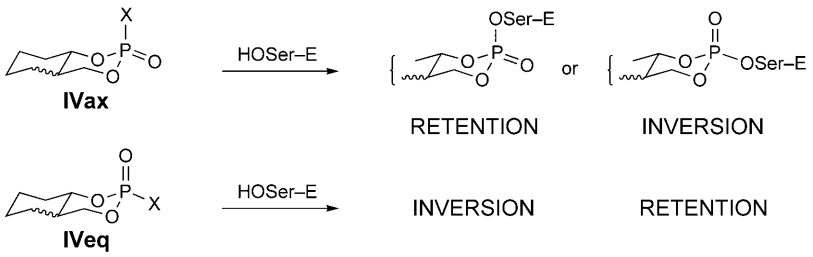
The title compounds, the *P(3)*-axially- and *P(3)*-equatorially-substituted *cis*- and *trans*-configured 3-fluoro-2,4-dioxa-3-phosphadecalin 3-oxides (= 3-fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-oxides) have been prepared (ee > 99%) and fully characterized. The compounds are irreversible inhibitors of acetylcholinesterase, and both the kinetic data and the mechanisms of the inhibition are determined by a novel enzyme-kinetic approach that is described in the preceding report. The inhibitors display pronounced stereoselectivity, and several of them are significantly stronger than diisopropyl fluorophosphate that is generally used as a potent standard.

1. Introduction. – In earlier reports, we have presented the preparation and characterization of the optically active *P(3)*-axially- and *P(3)*-equatorially-substituted *cis*- and *trans*-configured 3-(2,4-dinitrophenoxy)-2,4-dioxa-3-phosphadecalin 3-oxides (= 3-(2,4-dinitrophenoxy)-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-oxides = 2-(2,4-dinitrophenoxy)hexahydro-4*H*-1,3,2-benzodioxaphosphorin 2-oxides, type **IV**; *Fig.*), and the stereochemical course of the irreversible inhibition reaction of δ-chymotrypsin with **IVax** and **IVeq** according to the general *Scheme 1* [1]. These results were confirmed and extended to the establishment of the covalent nature of the 'Ser^{195}' (CH_2O-P) bond in the inhibited enzyme by means of the enantiomerically pure, X-substituted 2,4-dioxa-3-phospha(1,5,5-$^2H_3$)bicyclo[4.4.0]decane 3-oxides (X = F, 2,4-

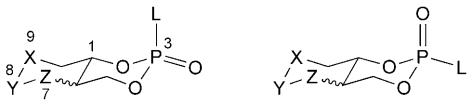
Scheme 1



E = enzyme: serine hydrolase (acetylcholinesterase, chymotrypsin)
X = F, 2,4-$(NO_2)_2C_6H_3O$)

dinitrophenoxy) [2]. However, the corresponding optically active 3-F-substituted ^{1}H-isomers have not yet been prepared[1]).

In the course of our current program concerning the synthesis of configuratively fixed and conformationally constrained organophosphates as inhibitors of acetylcholinesterase (AChE) and related serine hydrolases (*e.g.*, chymotrypsin), we have described the synthesis and characterization of racemic aza-3-phosphadecalins of the types **I**, **II**, and **III** (*Fig.*) [5]. Meanwhile, all optically active (ee > 99%) 3-fluoro-2,4-dioxa-3-phosphadecalins (**IV**) [6] and the 9-aza- (**I**) [7], 8-aza- (**II**) [8], and 7-aza-congeners (**III**) [9] have been synthesized and characterized, and the collection of enzyme kinetic data of the inhibition of AChE by these compounds has been completed according to the novel general approach described in detail in the preceding report [10]. Here, we present the synthesis and full characterization of the enantiomerically pure type-**IV** inhibitors.



I X = NR, $\overset{\oplus}{N}R_2$, Y = Z = CH_2

II X = CH_2, Y = NR, $\overset{\oplus}{N}R_2$, Z = CH_2

III X = Y = CH_2, Z = NR, $\overset{\oplus}{N}R_2$

IV X = Y = Z = CH_2

L = electron-withdrawing group
(F, Cl, 4-$NO_2C_6H_4O$, 2,4-$(NO_2)_2C_6H_3O$)

Figure. *The 2,4-Dioxa-3-phosphadecalins of Types* **I**–**IV**

2. Synthesis and Characterization of the 3-Fluoro-3-phosphadecalins. – 2.1. *Precursor Alcohols* **4** *and* **5**. The enantiomerically pure diols (+)- and (−)-**4**, and (+)- and (−)-**5**, respectively, were obtained after reduction of ethyl 2-oxocyclohexanecarboxylate (**1**) with $NaBH_4$ and chromatographic separation of the resulting (±)-*trans*- and (±)-*cis*-ethyl 2-hydroxycyclohexane carboxylates ((±)-**2** and (±)-**3**, resp.; *Scheme 2*). After reduction of the hydroxy esters (±)-**2** and (±)-**3** with $LiAlH_4$, the *trans*-diol (±)-**4** was esterified with (−)-(1*S*)-camphanoyl chloride to yield the mixture (*ca.* 1:1) of the diastereoisomeric bis-camphanates, **6**/**7**[2]), and the *cis*-diol (±)-**5** was transformed into the bis-4-bromobenzoate (±)-**8** (= **8**/*ent*-**8**). Preparative HPLC (*Chiralcel® OD*) of **6**/**7** afforded **6** and **7** (de > 99%), and the same procedure with (±)-**8** gave **8** and *ent*-**8** (ee > 99%). Saponification of **6** and **7** afforded the *trans*-configured (+)-(1*R*,2*S*)- and (−)-(1*S*,2*R*)-2-hydroxycyclohexanemethanols ((+)-**4** and (−)-**4**, resp., ee > 99%).

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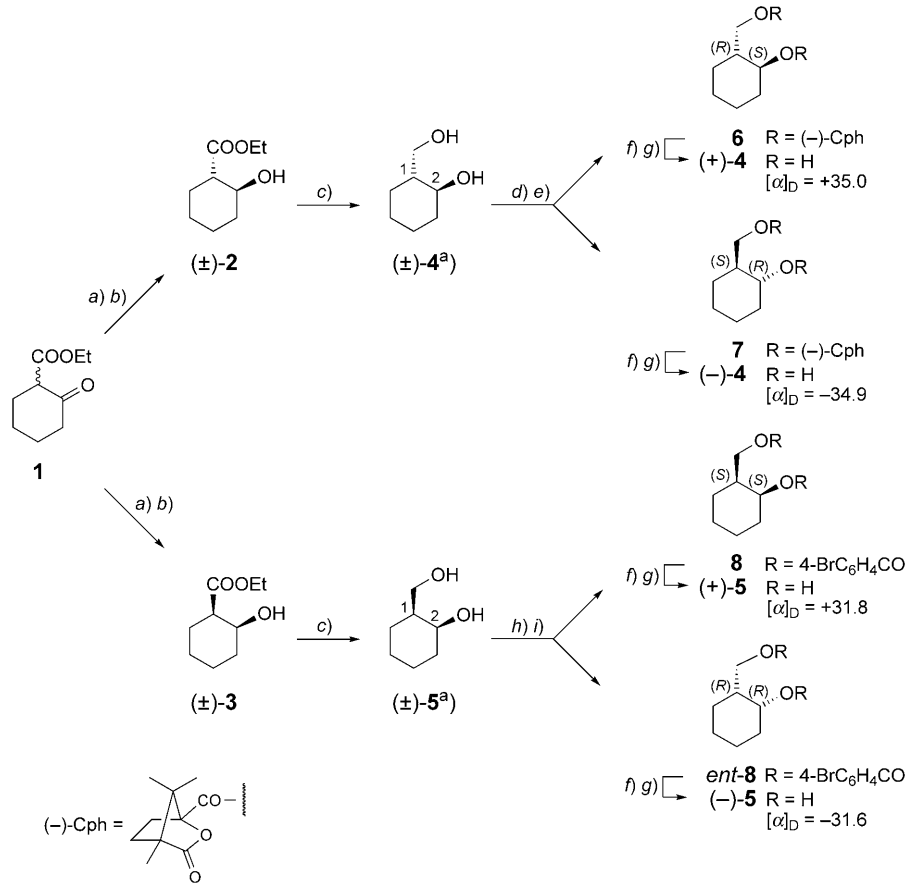
[1]) The racemic compounds have been prepared earlier by less efficient methods ((±)-**9a**/**9b**: [3], (±)-**10a**/**10b**: [4]).

[2]) As observed in the ^{2}H-isomer series [2], diastereoisomer **7** (1*S*,1′*S*,2′*R*) partly crystallized (de > 99%, whereas its enantiomer (*ent*-**7**, 1*R*,1′*R*,2′*S*), derivatized with (+)-(*R*)-camphanoyl chloride, did not crystallize from the mixture (see *Exper. Part*).

Scheme 2



a) $NaBH_4$, EtOH, reflux (*cis*/*trans* ≈ 2 : 1 from **1**). *b*) CC (SiO_2; hexane/Et_2O). *c*) $LiAlH_4$, Et_2O, reflux. *d*) (−)-Camphanoyl chloride, 4-(dimethylamino)pyridine (DMAP), pyridine, reflux. *e*) Prep. HPLC (*Chiralcel® OD*, hexane/EtOH). *f*) $LiAlH_4$, THF, 0° → r.t. *g*) CC (SiO_2, CH_2Cl_2, AcOEt). *h*) 4-BrC_6H_4COCl, DMAP, pyridine, reflux. *i*) Prep. HPLC (*Chiralcel® OD*, hexane/EtOH). $[\alpha]_D$ in EtOH ($c = 1.00$), ee > 99%.

[a]) According to *Chemical Abstracts*, the compound is a substituted methanol. The IUPAC numbering system is different as it considers the same compound as a substituted cyclohexanol.

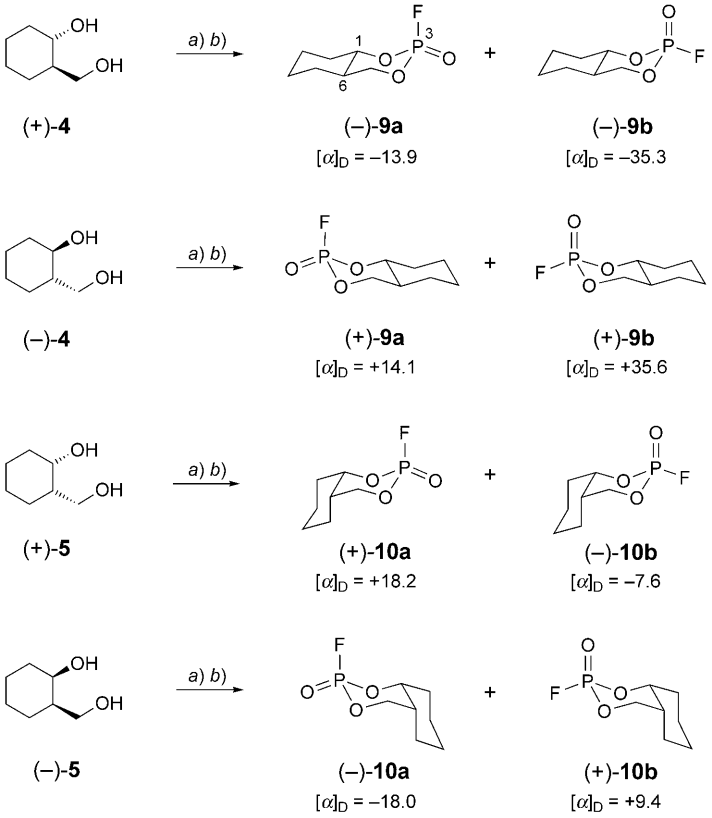
Saponification of **8** and *ent*-**8** gave the *cis*-configured (+)-(1*S*,2*S*)- and (−)-(1*R*,2*R*)-2-hydroxycyclohexanemethanols ((+)-**5** and (−)-**5**, resp.; ee > 99%). The absolute configurations of the precursor diols were corroborated by chiroptical correlations[3]) and direct

[3]) Another preparation of the optically active *trans*- and *cis*-diols was reported earlier [1], and the absolute configurations were unambiguously confirmed [2] as previously assigned [11].

X-ray crystallographic determinations of corresponding 3-fluoro-3-phosphadecalins [5][10][4]).

2.2. *3-Fluoro-2,4-dioxa-3-phosphadecalins* **9** *and* **10**. The *trans*-3-fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-oxides **9** and **10** (*Scheme 3*) were prepared from (+)- or (−)-**4** by reaction with $POCl_2F$ and chromatographic separation of the resulting *P(3)*-epimeric mixture (axial/equatorial *ca.* 1:1) into the pure axial ((+)-**9a** and (−)-**9a**) and equatorial epimers ((+)-**9b** and (−)-**9b**; ee > 99%). Similarly, starting from (+)- or (−)-**5**, the *cis*-3-fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-oxides (+)- and (−)-**10a**, and (+)- and (−)-**10b** were obtained (*Scheme 3*). Due to facile epimerization at P(3) and conformational changes of (+)- and (−)-**10b** [6][12], the magnitude of the $[\alpha]_D$ values differed despite of ee > 99%.

Scheme 3



a) $Cl_2P(O)F$, pyridine, 0°. *b*) CC (SiO_2; hexane/Et_2O). $[\alpha]_D$ in acetone ($c = 1.00$), ee > 99%.

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[4]) In the context of detailed conformational studies [6][12], X-ray crystallographic analyses of high-quality crystals of (+)- and (−)-**6a**, (+)- and (−)-**6b**, and (+)- and (−)-**10b** were performed.

The NMR data of the phosphadecalins **9** and **10** (see *Exper. Part*) exhibit the same essential features as the 2,4-dinitrophenoxy-substituted congeners [1]. In particular, the ^{31}P-NMR spectra confirm the relative configuration at the P-atom, the double chair conformations of the axial epimers (**9a** and **10a**), and distorted conformations [6][12][13] of the 2,4-dioxa-3-phospha moiety in the equatorial epimers (*i.e.*, **9b** and **10b**)[5]). Due to the strongly electronegative F-substituent, the chemical-shift difference ($\Delta\delta = \delta_{eq} - \delta_{ax}$) is very small in the *trans*-couple **9a**/**9b** ($\Delta\delta = +0.1$ ppm) and even negative in the *cis*-couple **10a**/**10b** ($\Delta\delta = -0.2$ ppm) as discussed earlier [5][13][5]).

3. Enzyme Kinetics. – The inhibitory potency of the enantiomerically pure 3-fluoro-3-phosphadecalins **9** and **10**, and the mechanisms of their mode of action were determined according to the procedure and notations[6]) explicitly described in the preceding article [10]. The experimental results are summarized in the *Table*. The compounds are remarkably strong irreversible inhibitors (inactivators [10]) of AChE, and several of them are significantly stronger than diisopropyl fluorophosphate (DFP) that is generally used as a very potent standard reference. Moreover, they display pronounced diastereoselectivity in favor of the (3*S*)-configured diastereoisomers and, in part, enantioselectivity with respect to the individual mechanisms. As discussed in detail in [10], the assignment of mechanism **2C** for (−)-**9eq** was preferred over **1C**, because statistical criteria from the nonlinear regression of the progress curves suggest a better fit with mechanism **2C** rather than **1C**. However, as the curves are very similar, the inhibition by (−)-**9eq** could also be described by mechanism **1C**. Considering mechanism **1C**, the calculated second-order inhibition constant $k_3 = 30\ \text{M}^{-1}\,\text{s}^{-1}$, whereas with mechanism **2C** $k_i = 37\ \text{M}^{-1}\,\text{s}^{-1}$, thus a minimal discrepancy when considering the complexity of the entire process. The overall inhibition of (+)-**10b** follows the general mechanism **2D**: during the reaction with the enzyme, (+)-**10b** is transformed in parallel to an inert hydrolysis product, 2,4-dioxa-3-hydroxy-3-phosphabicyclo[4.4.0]decane 3-oxide, and the *P(3)*-epimer (−)-**10a**. Since the latter also acts as an inhibitor – albeit at a

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5) Generally, the ^{31}P-NMR resonance of the axial epimer is shifted upfield with respect to the equatorial one, and the chemical-shift difference ($\Delta\delta = \delta_{eq} - \delta_{ax}$) is >0, and its magnitude is inversely proportional to the electronegativity of the substituent at the P-atom. However, the cyclic phosphorofluoridates of the *cis*-series of the type **I**–**IV** compounds (L = F) display $\Delta\delta < 0$, a fact that can only be explained by significant conformational changes. Due to the anomeric effect, electronegative substituents X occupy the stereoelectronically favored axial position. As a consequence, axially substituted cyclic phosphates adopt the chair and its equatorial counterparts a distorted conformation. The magnitude of the ^3J(P,H) in the ^{1}H-coupled ^{31}P-NMR is indicative of the conformation of the heterocyclic ring: diagnostically relevant values for the axial epimers are $^3J(\text{P},\text{H}_{ax}-\text{C}(5)) \approx 0$ and $^3J(\text{P},\text{H}_{eq}-\text{C}(5)) \approx 25$ Hz, whereas the equatorial ones display $^3J(\text{P},\text{H}_{ax}-\text{C}(5)) \approx {}^3J(\text{P},\text{H}_{eq}-\text{C}(5)) \approx 10-15$ Hz. Hence, the axial epimers exhibit a *d*-type and the equatorial ones a *m*-type splitting pattern.

6) The multiple equilibria and the mechanistic notation have been introduced in [10]: the numbers denote one-step (**1**), and two-step irreversible enzyme inhibition (**2**), respectively. Mechanism **A** is the 'straightforward' case, **B** describes an unstable modifier that undergoes spontaneous, nonenzymatic decomposition (*e.g.*, hydrolysis), **C** stands for temporary inhibition in which the inhibited enzyme decays to free enzyme, which is recycled, and an inert species, whereas the expression **D** denotes a chemically unstable modifier, which, at the same time, exerts temporary inhibition.

much lower rate – the mathematical solution of this complex process results from a combination of nonlinear regression and numerical integration analysis [10] giving the kinetic constants shown in the *Table*.

Table. *Kinetic Data of the Inhibition of AChE with the Enantiomerically Pure 3-Fluoro-2,4-dioxa-3-phosphadecalins and Assigned Mechanisms.* DFP ($(i\text{-PrO})_2POF$) as reference. Numbers indicate best-fit parameters ± standard errors from nonlinear regression, with the exception of (+)-**10b**, for which the parameters represent values optimized by numerical integration of a set of differential equations corresponding to mechanism **1D** obtained with *Matlab–Simulink* software (www.mathworks.com).

Compound	Kinetic Parameters	Mechanism
(+)-**9a**	$k_3 = 60 \pm 2$ м$^{-1}$ s^{-1}	**1A**
(−)-**9a**	$k_3 = 968 \pm 43$ м$^{-1}$ s^{-1}	**1A**
(+)-**9b**	$k_i = 1280 \pm 150$ м$^{-1}$ s^{-1}	**2C**
	$K_i = 20.8 \pm 1.3$ μм	
	$k_4 = 0.037 \pm 0.004$ s^{-1}	
	$k_6 = 0.014 \pm 0.002$ s^{-1}	
(−)-**9b**	$k_i = 37 \pm 9$ м$^{-1}$ s^{-1}	**2C**
	$K_i = 463 \pm 47$ μм	
	$k_4 = 0.017 \pm 0.004$ s^{-1}	
	$k_6 = 0.0013 \pm 0.0007$ s^{-1}	
(+)-**10a**	$k_i = 306 \pm 16$ м$^{-1}$ s^{-1}	**2A**
	$K_i = 85 \pm 3$ μм	
	$k_4 = 0.026 \pm 0.001$ s^{-1}	
(−)-**10a**	$k_i = 54 \pm 13$ м$^{-1}$ s^{-1}	**2C**
	$K_i = 95 \pm 14$ μм	
	$k_4 = 0.005 \pm 0.001$ s^{-1}	
	$k_6 = 0.0009 \pm 0.0007$ s^{-1}	
(+)-**10b**	$k_3 = 2260$ м$^{-1}$ s^{-1}	**1D**
	$k_5 = 0.026$ s^{-1}	
	$k_6 = 0.00004$ s^{-1}	
(−)-**10b**	$k_3 = 29 \pm 1$ м$^{-1}$ s^{-1}	**1C**
	$k_5 = 0.00016 \pm 0.00003$ s^{-1}	
DFP	$k_3 = 181 \pm 28$ м$^{-1}$ s^{-1}	**1A**

4. Conclusions. – Meanwhile, the complete data set for the 3-fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-oxides **I**–**IV** (*Fig.*) has been collected. However, there is no consistent pattern allowing a reliable rationalization with respect to a structure–mechanism relationship. To provide deeper insight into the mechanistic implications of the inhibition of AchE, molecular modeling and docking experiments with selected 3-substituted 3-phosphadecalins are being performed [9]. Further aspects will be discussed in subsequent publications presenting the virtual ACh-mimetics of type **I**–**III**. As demonstrated in the series of the $^{31}P\{^2H\}$-NMR experiments with the ^2H-isomers of **9** and **10** [2], the strongest inhibitor of AChE, (+)**10b**, did not inhibit δ-chymotrypsin. This fact is worth mentioning and clearly demonstrates that eventual conclusions and generalizations with respect to the mode of action of related active sites in otherwise different enzymes are not allowed. In particular, mechanistic considerations cannot be reduced to the catalytic active site, because the entire surrounding of an enzyme

determines its mode of action, and even very closely related active sites follow individual reaction pathways that have been optimized by evolutionary processes.

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Experimental Part

1. *General*. See [1][2][5]. All assignments of strongly overlapping ^{1}H-signals in the P-heterocycles are based on extensive 2D-NMR experiments. The enzyme kinetic experiments were performed as described in [10].

2. *(±)*-trans- *and (±)*-cis-*Ethyl 2-Hydroxycyclohexanecarboxylates* ((±)-**2** and (±)-**3**, resp.). To a cooled soln. (*ca.* 0°) of *ethyl 2-oxocyclohexanecarboxylate* (**1**; 20.3 g, 119.3 mmol) in anh. EtOH (300 ml), $NaBH_4$ (4.5 g, 37 mmol) was added in portions, and the mixture was kept for 3 h at *ca.* 0°. Workup and continuous extraction with Et_2O yielded the mixture of the hydroxy esters (±)-**2**/(±)-**3** as a yellowish oil (17.5 g, 85%). CC (SiO_2, hexane/Et_2O 5:4) afforded pure (±)-**2** (*trans*-isomer; 4.7 g, 23%) and (±)-**3** (*cis*-isomer; 10.3 g, 50%) as colorless oils.

Data of (±)-**2**. R_f (hexane/Et_2O 5:4) 0.15. IR (film): 3458*s*, 2934*s*, 2859*s*, 2667*w*, 1887*w*, 1731*s*, 1449*s*, 1374*s*, 1249*s*, 1041*s*, 869*m*, 744*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.17 (*q*, $^3J = 7.1$, OCH_2Me); 3.76 (*td*, $^3J(2,1) = {}^3J(2,3ax) = 10.1$, $^3J(2,3eq) = 4.6$, H–C(2)); 2.89 (br. *s*, OH); 2.24 (*ddd*, $^3J(1,6ax) = 11.9$, $^3J(1,2) = 10.1$, $^3J(1,6eq) = 3.7$, H–C(1)); 2.07–1.99 (*m*, 2 H); 1.79–1.68 (*m*, 2 H); 1.43–1.17 (*m*, 4 H); 1.27 (*t*, $^3J = 7.1$, OCH_2Me). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 175.3 (CO); 70.9 (C(2)); 60.6 (OCH_2Me); 51.4 (C(1)); 33.7 (C(3)); 28.1 (C(5)); 25.1 (C(6)); 24.4 (C(4)); 14.2 (OCH_2Me). EI-MS: 172 (<1, M^+), 154 (3, $[M-H_2O]^+$), 144 (32, $[M+1-C_2H_5]^+$), 127 (16), 101 (100), 81 (58), 73 (94), 55 (86).

Data of (±)-**3**. R_f (hexane/Et_2O 5:4) 0.26. IR (film): 3519*s*, 2934*s*, 2857*s*, 2665*w*, 1713*s*, 1447*s*, 1372*s*, 1308*s*, 1039*s*, 894*m*, 765*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.17 (*q*, $^3J = 7.1$, OCH_2Me); 4.16–4.11 (*m*, H–C(2)); 3.12 (br. *s*, OH); 2.47 (*ddd*, $^3J(1,6ax) = 11.1$, $^3J(1,6eq) = 3.8$, $^3J(1,2) = 2.7$, H–C(1)); 1.97–1.81 (*m*, 2 H); 1.76–1.63 (*m*, 4 H); 1.52–1.31 (*m*, 2 H); 1.27 (*t*, $^3J = 7.1$, OCH_2Me). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 175.9 (CO); 66.7 (C(2)); 60.6 (OCH_2Me); 46.7 (C(1)); 31.7 (C(3)); 24.8 (C(5)); 24.0 (C(6)); 20.1 (C(4)); 14.1 (OCH_2Me). EI-MS: 172 (1, M^+), 154 (4, $[M-H_2O]^+$), 144 (38, $[M+1-C_2H_5]^+$), 109 (15), 101 (100), 81 (55), 73 (85), 55 (53).

3. *(±)*-trans- *and (±)*-cis-*2-(Hydroxymethyl)cyclohexan-1-ols* (=(±)-trans- *and* (±)-cis-*2-(Hydroxymethyl)cyclohexanemethanols*; (±)-**4** and (±)-**5**, resp.). To a cooled soln. (*ca.* 0°) of (±)-**2** (4.7 g, 27.3 mmol) in anh. Et_2O (100 ml), $LiAlH_4$ (1.4 g, 29 mmol, 1.4 equiv.) was added in portions. After 40 min at 0°, the mixture was refluxed overnight, then usual workup and continuous extraction with Et_2O afforded (±)-**4** (2.44 g, 68%) as a colorless viscous oil. Starting from (±)-**3** (5.0 g, 29 mmol) in Et_2O (150 ml) and $LiAlH_4$ (1.65 g, 44 mmol, 1.5 equiv.), the analogous procedure yielded (±)-**5** (2.7 g, 72%) as a colorless viscous oil that solidified in the refrigerator.

Data of (±)-**4**. R_f (hexane/Et_2O 5:4) 0.25. IR (Film): 3305*s* (br.), 2923*s*, 2856*s*, 2665*m*, 1449*s*, 1351*s*, 1297*s*, 1193*m*, 1015*s*, 926*m*, 845*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.69 (*A* of *ABX*, $^2J = 10.7$, $^3J = 3.5$, 1 H, CH_2OH); 3.62 (*B* of *ABX*, $^2J = 10.7$, $^3J = 8.8$, 1 H, CH_2OH); 3.48 (*dt*, $^3J(2,1) \approx {}^3J(2,3ax) \approx 10.0$, $^3J(2,3eq) \approx 4.5$, H–C(2)); 1.95 (*m*, br. *d*-like, $^2J \approx 13$, H_{eq}–C(3)); 1.76–1.52 (*m*, *X* of *ABX*, H–C(1), $CH_2(4)$, H_{eq}–C(6)); 1.31–1.18 (*m*, H_{ax}–C(3), $CH_2(5)$); 0.89 (*dq*, $^2J \approx {}^3J(6ax,1) \approx {}^3J(6ax,5ax) \approx 12$, $^3J(6ax,5eq) \approx 4$, H_{ax}–C(6)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 76.5 (C(2)); 68.9 (CH_2OH); 46.1 (C(1)); 35.4 (C(3)); 27.2 (C(6)); 25.1 (C(5)); 24.5 (C(4)). EI-MS: 130 (<1, M^+); 112 (25, $[M-H_2O]^+$), 94 (40), 84 (23), 79 (48), 68 (100), 57 (58), 55 (60).

Data of (±)-**5**. Colorless crystals. M.p. 48–50°. R_f (hexane/Et_2O 5:4) 0.29. IR ($CHCl_3$): 3334*s* (br.), 2924*s*, 2857*s*, 2665*m*, 2036*w*, 1445*s*, 1190*s*, 1093*s*, 1021*s*, 808*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.11 (*dd*, $^3J = 7.2$, $^3J = 3.0$, H–C(2)); 3.75 (*A* of *ABX*, $^2J = 10.8$, $^3J = 5.5$, 1 H, CH_2OH); 3.74 (*B* of *ABX*, $^2J = 10.8$, $^3J = 3.5$, 1 H, CH_2OH); 2.70 (*s*, HO–C(2); 2.59 (*s*, CH_2OH); 1.79 (*X* of *ABX*, *dt*-like, H–C(1)); 1.70–1.23 (*m*, $CH_2(3)$, $CH_2(4)$, $CH_2(5)$, $CH_2(6)$). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 70.0 (C(2)); 66.3 (CH_2OH); 42.5 (C(1)); 33.0 (C(3)); 25.0 (C(6)); 23.6 (C(5)); 20.5 (C(4)). EI-MS: 130 (<1, M^+); 112 (10, $[M-H_2O]^+$), 94 (30), 79 (40), 68 (100), 57 (75), 55 (55).

4. *(+)-(1*R*,2*S*)- and (−)-(1*S*,2*R*)-2-Hydroxycyclohexanemethanols* ((+)-**4** and (−)-**4**, resp.). 4.1. *Diastereoisomeric Bis-camphanoyl Derivatives* **6** *and* **7**. To a soln. of (±)-**4** (1.92 g, 14.8 mmol) in anh. pyridine (90 ml) and DMAP (50 mg) at r.t., (−)-(*S*)-camphanoyl chloride (6.8 g, 31.5 mmol, 2.1 equiv.) was added, and the mixture was refluxed for 18 h. After workup, treating the residue with charcoal/EtOH and crystallization, the *ca.* 1:1 mixture **6** (1*S*,1′*R*,2′*S*)/**7** (1*S*,1′*S*,2′*R*) was obtained as colorless crystals (6.6 g, 91%). Recrystallization from toluene afforded pure **7** (0.65 g, 9%, de = ee > 99%) as colorless cubes, m.p. 174°[2]). Repeated prep. HPLC of the mother liquor on *Chiralcel® OD* (hexane/EtOH 12:1; λ_{det} 220 nm; $\alpha = 1.24$; $R_s = 2.1$) afforded from the less polar fractions ($k' = 2.5$) pure **6** (1.2 g, 17%, de = ee > 99%) as colorless needles, m.p. 165°, and from the more polar ones ($k' = 3.1$) additional **7** (1.2 g, 17%, de = ee > 99%)[7]).

When (±)-**4** was treated analogously with (+)-(*R*)-camphanoyl chloride, *ent*-**7** (1*R*,1′*R*,2′*S*) did not crystallize as expected and prevented a simple enantiomer separation.

*Data of {(1*RS*,2*SR*)-2-{[[(1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-1-yl]carbonyl}oxy}-cyclohexyl}methyl (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate* (**6**/**7**)[8]). Colorless crystals. M.p. 168–169°. R_f (hexane/$CHCl_2$/Et_2O 4:6:1) 0.26. UV/VIS (EtOH): 230. IR (KBr): 2971*s*, 2940*s*, 2870*s*, 1789*s*, 1725*s*, 1593*w*, 1454*s*, 1276*s*, 1167*s*, 1103*s*, 1060*s*, 821*s*, 743*m*, 621*m*, 585*m*, 507*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.79 (*dt*, $^3J(2',1') \approx {}^3J(2',3'\text{ax}) \approx 10$, $^3J(2',3'\text{eq}) = 5.5$, 2 H−C(2′)); 4.29 (*A* of *ABX*, $^2J = 11.4$, $^3J = 5.4$, 2 H, 2 CH_2OCamph.); 4.13 (*B* of *ABX*, $^2J = 11.4$, $^3J = 2.8$, 2 H, 2 CH_2OCamph.); 2.43 (*ddd*, $^2J = 13.4$, $^3J(exo,endo) = 10.8$, $^3J(exo,exo) = 4.2$, 4 H_{exo}−C(6)); 2.12–1.86 (*m*, 2 H_{eq}−C(3′), 4 H_{endo}−C(6), 2 CH_2(5)); 1.81–1.65 (*m*, *X* of *ABX*, 2 H−C(1′), 2 H_{ax}−C(4′), 2 H_{eq}−C(5′), 2 H_{eq}−C(6′)); 1.41–1.22 (*m*, 2 H_{ax}−C(3′), 2 H_{ax}−C(5′), 2 H_{ax}−C(6′)); 1.12, 1.06, 0.97 (each *s*, 4 Me−C(4), 8 Me−C(7)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 178.2, 178.1 (4 C(3)); 167.3, 167.1 (4 *C*O−C(1)); 91.2, 91.1 (4 C(1)); 74.2 (2 C(2′)); 65.7, 65.6 (4 CH_2OCamph.); 54.8 (4 C(4)); 54.2, 54.1 (4 C(7)); 41.5, 41.4 (2 C(1′)); 31.7, 31.6 (2 C(3′)); 30.8, 30.7 (4 C(6)); 29.0, 28.9 (4 C(5)); 28.3, 28.2 (2 C(6′)); 24.7 (2 C(5′)); 24.3 (2 C(4′)); 16.9, 16.8, 16.7, 9.7 (4 *Me*−C(4), 8 *Me*−C(7)). CI-MS (NH_3): 508 (100, $[M + NH_4]^+$), 491 (12, $[M + H]^+$), 328 (12, $[M + NH_4 - \text{Camph.}]^+$).

4.2. trans-*Diols (+)- and (−)-***4**. To a cooled soln. (*ca.* 0°) of **6** (1.34 g, 2.7 mmol) in anh. THF (25 ml), $LiAlH_4$ (418 mg, 11 mmol, 4 equiv.) was slowly added in portions. After 30 min at 0°, the mixture was kept at r.t. for 2 h, then refluxed until no starting material was detected (TLC). Extraction with Et_2O and workup afforded a mixture of (+)-**4** (R_f (CH_2Cl_2/AcOEt 3:4) 0.14) and the reduction products of camphanic acid (R_f (CH_2Cl_2/AcOEt 3:4) 0.1) as a colorless viscous residue (1.2 g). CC (SiO_2; CH_2Cl_2 → CH_2Cl_2/AcOEt 4:1 → CH_2Cl_2/AcOEt 4:3 → CH_2Cl_2/AcOEt 3:4) afforded pure (+)-**4** (186 mg, 53%) as a colorless viscous oil. The analogous procedure, starting from **7** (1.08 g, 2.2 mmol) in THF (25 ml) and $LiAlH_4$ (340 mg, 8.8 mmol, 4 equiv.) yielded (−)-**4** (125 mg, 44%)[9]).

Data of (+)-**4**: $[\alpha]_D^{25} = +35.0$ ($c = 1.00$, EtOH). All other data were identical with those of (±)-**4** [5].

Data of (−)-**4**: $[\alpha]_D^{25} = -34.9$ ($c = 1.00$, EtOH). All other data were identical with those of (+)-**4** and (±)-**4** [5].

5. *(+)-(1*S*,2*S*)- and (−)-(1*R*,2*R*)-2-Hydroxycyclohexanemethanols* ((+)-**5** and (−)-**5**, resp.). *Bis[4-bromobenzoate]* (±)-**8**, *and Enantiomers* **8** (1*S*,2*S*) *and* ent-**8** (1*R*,2*R*). To a soln. of (±)-**5** (2.4 g, 18.5 mmol) and DMAP (200 mg) in pyridine (100 ml), 4-bromobenzoyl chloride (8.6 g, 38.8 mmol, 2.1 equiv.) was added, and the mixture was stirred at r.t. overnight. After workup, the crude residue was subjected to CC (SiO_2; hexane/CH_2Cl_2/Et_2O 6:4:1) to yield (±)-**8** (8.5 g, 92%) as colorless crystals. Repeated prep. HPLC on *Chiralcel® OD* (hexane/EtOH 12:1; λ_{det} 240 nm; $\alpha = 2.42$; $R_s > 6$) afforded

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[7]) Although the resolution is sufficient for a feasible prep. separation, the column was quickly overloaded. Therefore, only the optimum parts of the fractions were selected and pooled (HPLC control) to obtain a de > 99%. Fractions with a de ≤ 99% were not considered.

[8]) Only the data of the *ca.* 1:1 mixture **6**/**7** are given. The data only served as confirmation; see full data of the corresponding derivatives in [2].

[9]) Because the chromatographic separation of (+)- and (−)-**4** from the optically active reduction products of camphanic acid was laborious, only the very best fractions have been pooled (GC control) to obtain an ee > 99%.

from the less polar fractions ($k'=0.95$) pure *ent*-**8** (3.5 g, 42%, ee > 99%), and from the more polar ones ($k'=2.3$) pure **8** (3.5 g, 42%, ee > 99%).

Data of {(1S,2S)-2-[(4-Bromobenzoyl)oxy]cyclohexyl}methyl 4-Bromobenzoate (**8**): Colorless needles. M.p. 130–132°. R_f (hexane/CH_2Cl_2/Et_2O 4:6:1) 0.59. IR (KBr): 2939*s*, 2855*m*, 1929*w*, 1789*w*, 1716*s*, 1590*s*, 1267*s*, 1065*s*, 753*s*, 682*s*, 471*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.86 (*dd*, $^3J=8.7$, $^4J=1.9$, 4 H_o); 7.55 (*dd*, $^3J=8.7$, $^4J=1.9$, 4 H_m); 5.47 (*m*, $w_{1/2}\approx10$, H–C(2)); 4.30 (*A* of *ABX*, $^2J=11.0$, $^3J=6.3$, 1 H, CH_2OCO); 4.19 (*B* of *ABX*, $^2J=11.0$, $^3J=8.2$, 1 H, CH_2OCO); 2.24–2.04 (*m*, *X* of *ABX*, H–C(1), H_{eq}–C(3)); 1.85 (*m*, br. *d*-like, $w_{1/2}\approx22$, H_{ax}–C(3)); 1.78–1.39 (*m*, CH_2(4), CH_2(5), CH_2(6). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 165.7, 165.0 (CO); 131.8, 131.7 (C_o); 131.1, 131.0 (C_m); 129.5, 129.1 (C_p); 128.1 (C_{ipso}); 70.5 (C(2)); 65.9 (CH_2OCO); 39.8 (C(1)); 29.8 (C(6)); 24.6 (C(6)); 24.4 (C(5)); 20.9 (C(4)). EI-MS: 498, 496, 494 (<1, 1, <1, $[M(^{81}Br)]^+$, $[M(^{81}Br^{79}Br)]^+$, $[M(^{79}Br)]^+$, $[C_{21}H_{20}Br_2O_4]^+$), 296 (3, $[M-{}^{81}BrC_6H_4COO]^+$), 294, (3, $[M-{}^{79}BrC_6H_4COO]^+$), 204 (2), 200 (3), 185 (70, $[{}^{81}BrC_6H_4CO]^+$), 183 (71, $[{}^{79}BrC_6H_4CO]^+$), 157 (8, [*185* – CO]$^+$), 155 (9, [*183* – CO]$^+$), 135 (3), 111 (7, $[C_7H_{11}O]^+$), 104 (7), 101 (8), 94 (100).

The analogous data were displayed by *ent*-**8**.

5.2. cis-*Diols (+)- and (–)*-**5**. To a cooled soln. (*ca.* 0°) of **8** (1.5 g, 3.03 mmol) in anh. THF (25 ml), $LiAlH_4$ (231 mg, 6.06 mmol, 2 equiv.) was slowly added in portions, and the reaction mixture then kept at r.t. for 2 h (TLC monitoring). Extraction with Et_2O, workup, and CC (SiO_2; AcOEt) gave (+)-**5** (484 mg, 86%) as a colorless viscous oil that solidified in the refrigerator. Starting from *ent*-**8** (1 g, 2.02 mmol) and $LiAlH_4$ (154 mg, 4.04 mmol), the analogous procedure afforded (–)-**5** (185 mg, 74%).

Data of (+)-**5**: $[\alpha]_D^{25}=+31.8$ ($c=1.00$, EtOH). All other data: identical with those of (±)-**5** [5].

Data of (–)-**5**: $[\alpha]_D^{25}=-31.6$ ($c=1.00$, EtOH). All other data: identical with those of (+)-**5** and (±)-**5** [5].

6. *Phosphorus Heterocycles* **9**–**10**. 6.1. *Phosphorous Reagents.* $POCl_2F$ was prepared according to [14]: $POCl_3$ (100 g) and dry, finely crystalline NH_4F (48 g, *Fluka 09737, puriss. p.a.*) were heated at 110° (15 h) in a flask fitted with a condenser. The volatile fluorinated compounds passing through the condenser ($POCl_2F$ (b.p. 54°), $POClF_2$ (b.p. 3°), and POF_3 (b.p. –40°)) were trapped at –78°. The mixture from the cold trap was fractionally distilled (*Vigreux*, 50 cm) to afford $POCl_2F$ as a colorless liquid (11.6 g, 13%). B.p. 52°. ^{31}P-NMR ($CDCl_3$): 1.80 (*d*, ^1J(P,F) = 1191).

6.2. trans- *and* cis-*3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxides* ((+)- and (–)-**9a**, (+)- and (–)-**9b**, (+)- and (–)-**10a**, and (+)- and (–)-**10b**, resp.). To a cooled soln. (0°) of (+)-**4** (113 mg, 0.87 mmol) in Et_2O (3 ml) in a glove-box (N_2 atmosphere), anh. pyridine (125 µl (123 mg), 1.55 mmol) and a cooled soln (0°) of $POCl_2F$ (110 µl (173 mg), 1.26 mmol, *ca.*1.5 eqiv.) in Et_2O (1 ml) were added with a syringe, and the mixture was kept for *ca.* 2 min at 0°; then, the mixture was withdrawn and quickly passed through SiO_2 (pH 5.6 [5], Et_2O). The precipitated pyridinium salt in the reaction flask was thoroughly sonicated for 5 min with Et_2O, the combined solns. were gently evaporated (N_2 stream), and the residue was subjected to CC (SiO_2 pH 5.6 [5]; hexane/Et_2O 4:1) to yield (–)-**9a** (63 mg, 37%) and (–)-**9b** (63 mg, 37%). Applying the identical procedure, the following compounds were prepared from the different starting diols (each 100 mg): from (–)-**4**: (+)-**9a** (54 mg, 36%) and (+)-**9b** (57 mg, 38%); from (+)-**5**: (+)-**10a** (51 mg, 34%) and (–)-**10b** (25 mg, 17%); from (–)-**5**: (–)-**10a** (71 mg, 47%) and (+)-**10b** (56 mg, 37%); in all cases the axial epimer was less polar. According to the starting diols (ee > 99%), the phosphadecalins were obtained with ee > 99%. Due to facile conformational changes of the *cis*-equatorial compounds (+)- and (–)-**10**, the magnitudes of their $[\alpha]_D$ values differed more than the experimental inaccuracy.

(+)-(1R,3R,6S)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide ((+)-**9a**). Colorless prisms. M.p. 106–107°. R_f (hexane/Et_2O 1:3) 0.25. $[\alpha]_D^{25}=+14.1$ ($c=1.00$, acetone). IR ($CHCl_3$): 3030*w*, 2946*m*, 2866*w*, 1474*w*, 1453*w*, 1330*s*, 1248*w*, 1164*m*, 1134*w*, 1103*m*, 1094*m*, 1066*s*, 1053*s*, 1037*s*, 995*s*, 976*m*, 963*m*, 951*m*, 900, 886*s*, 868*m*, 854*m*, 838*w*, 626*m*. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 4.40 (*A* of *ABX-P*, $^2J=11.0$, ^3J(5eq,6) = 4.5, ^3J(5eq,P) = 24.8, H_{eq}–C(5)); 4.35 (*dt*, ^3J(1,6) = ^3J(1,10ax) = 10.8, ^3J(1,10eq) = 4.5, H–C(1)); 4.24 (*B* of *ABX-P*, $^2J=$ ^3J(5ax,6) = 11.0, ^3J(5ax,P) < 1, H_{ax}–C(5)); 2.09 (*m*, $w_{1/2}\approx20$, H_{eq}–C(10)); 2.03 (*m*, $w_{1/2}\approx25$, *X* of *ABX-P*, H–C(6)); 1.86 (*m*, br. *d*-like, $w_{1/2}\approx25$, $^2J\approx12$, H_{eq}–C(9)); 1.77–1.72 (*m*, H_{eq}–C(7), H_{eq}–C(8)); 1.56 (br. *qd*-like, $^2J\approx12.5$ $^3J(10ax,1)\approx{}^3J(10ax,9ax)\approx$ 11, ^3J(10ax,9eq) = 3.5, H_{ax}–C(10)); 1.38 (*sext.t*-like, $^2J\approx12.5$, $^3J(8ax,7ax)\approx{}^3J(8ax,9ax)\approx{}^3J(9ax,10ax)\approx$

11, ^3J(8ax,7eq)≈^3J(8ax,9eq)≈^3J(9ax,8eq)≈^3J(9ax,10eq)≈3.5, (H_{ax}–C(8), H_{ax}–C(9)); 1.11 (*qd*, ^2J = ^3J(7ax,6) = ^3J(7ax,8ax) = 12.5, ^3J(7ax,8eq) = 3.5, H_{ax}–C(7)). ^{13}C-NMR (100.6 MHz, $(CD_3)_2CO$): 85.5 (*dd*, ^2J(1,P) = 7.4, ^3J(1,F) = 1.8, C(1)); 74.9 (*dd*, ^2J(5,P) = 7.4, ^3J(5,F) = 1.2, C(5)); 41.6 (*d*, ^3J(6,P) = 6.2, C(6)); 33.1 (*d*, ^3J(10,P) = 9.2, C(10)); 25.4 (br. ^4J(7,P)≈1, C(7)); 24.9 (C(8)); 24.5 (*d*, ^2J(9,P) = 2.5, C(9)). ^{31}P-NMR (121.5 MHz, $(CD_3)_2CO$): −14.7 (*dd*, ^1J(P,F) = 998, ^3J(P,H_{eq}–C(5)) = 24.8). ^{19}F{^{1}H}-NMR (282.4 MHz, $(CD_3)_2CO$): −85.4 (*d*, ^1J(F,P) = 998). EI-MS: 194 (<1, M^+), 152 (7), 127 (2), 101 (9), 94 (30), 79 (100), 68 (16), 67 (19), 66 (12), 55 (15), 54 (14), 53 (12). CI-MS (NH_3): 406 (21, $[2M+NH_4]^+$) 212 (100, $[M+NH_4]^+$), 195 (3, $[M+H]^+$).

*(−)-(1*S*,3*S*,6*R*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((−)-**9a**). $[\alpha]_D^{25} = -13.9$ (c = 1.00, acetone). All other data were identical with those of (+)-**9a**.

*(+)-(1*R*,3*S*,6*S*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((+)-**9b**). Colorless plates (from Et_2O/hexane). M.p. 64–66°. R_f (hexane/Et_2O 1:3) 0.14. $[\alpha]_D^{25} = +35.6$ (c = 1.00, acetone). IR ($CHCl_3$): 3008*w*, 2945*m*, 2866*m*, 1604*w*, 1475*w*, 1451*w*, 1388*w*, 1327*s*, 1310*s*, 1158*w*, 1139*w*, 1095*m*, 1069*s*, 1055*m*, 1040*s*, 1007*m*, 962*m*, 900*m*, 883*m*, 868*m*, 854*m*, 836*w*, 635*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 4.47 (*A* of *ABX-P*, ^2J = ^3J(5eq,P) = 10.7, ^3J(5eq,6) = 5.2, H_{eq}–C(5))[10]; 4.46 (*m*, $w_{1/2}$≈25, H–C(1)); 4.28 (*B* of *ABX-P*, ^2J = ^3J(5ax,6) = ^3J(5ax,P) = 10.7, ^4J(5ax,F) = 1.7, H_{ax}–C(5))[10]; 2.19 (*m*, $w_{1/2}$≈25, *X* of *ABX-P*, H–C(6)); 2.13 (*m*, br. *d*-like, $w_{1/2}$≈20, ^2J≈12, H_{eq}–C(10)); 1.87–1.78 (*m*, H_{eq}–C(7), H_{eq}–C(9)); 1.74 (*m*, br. *d*-like, $w_{1/2}$≈18, ^2J≈12, H_{eq}–C(8)); 1.52 (br. *qd*, ^2J≈^3J(10ax,1)≈^3J(10ax,9ax)≈12, ^3J(10ax,9eq) = 3.7, H_{ax}–C(10)); 1.37 (*sext.t*-like, ^2J≈12.5, ^3J(8ax,7ax)≈^3J(8ax,9ax)≈^3J(9ax,10ax)≈11, ^3J(8ax,7eq)≈^3J(8ax,9eq)≈^3J(9ax,8eq)≈^3J(9ax,10eq)≈3.5, (H_{ax}–C(8), H_{ax}–C(9)); (1.12 (*qd*, ^2J = ^3J(7ax,6) = ^3J(7ax,8ax) = 12.5, ^3J (7ax,8eq) = 3.5, H_{ax}–C(7)). ^{13}C-NMR (100.6 MHz, $(CD_3)_2CO$): 85.1 (*d*, ^2J(1,P) = 5.8, C(1)); 74.7 (*d*, ^2J(5,P) = 7.1, C(5)); 40.3 (*d*, ^3J(6,P) = 13.2, C(6)); 33.4 (*d*, ^3J(10,P) = 5.9, C(10)); 26.4 (C(7)); 24.7 (C(8)); 24.3 (C(9)). ^{31}P-NMR (121.5 MHz, $(CD_3)_2CO$): −14.6 (*dt*, ^1J(P,F) = 983, ^3J(P,H_{ax}–C(5) = ^3J(P,H_{eq}–C(5) = 10.7))[10]). ^{19}F{^{1}H}-NMR (282.4 MHz, $(CD_3)_2CO$): −67.3 (*d*, ^1J(F,P) = 983). EI-MS: 194 (1, M^+), 152 (15), 139 (4), 127 (2), 101 (18), 94 (47), 79 (100), 68 (24), 67 (28), 66 (18), 55 (21), 54 (20), 53 (17). CI-MS (NH_3): 406 (21, $[2M+NH_4]^+$) 212 (100, $[M+NH_4]^+$), 195 (3, $[M+H]^+$). CI-MS (NH_3): 406 (9, $[2M+NH_4]^+$) 212 (100, $[M+NH_4]^+$), 195 (2, $[M+H]^+$).

*(−)-(1*S*,3*R*,6*R*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((−)-**9b**). $[\alpha]_D^{25} = -35.3$ (c = 1.00, acetone). All other data were identical with those of (+)-**9b**.

*(+)-(1*S*,3*S*,6*S*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((+)-**10a**). Slightly yellowish viscous oil. R_f (hexane/Et_2O 1:3) 0.15. $[\alpha]_D^{25} = +18.2$ (c = 1.00, acetone). IR ($CHCl_3$): 3030*w*, 2945*m*, 2871*w*, 1474*w*, 1450*m*, 1434*w*, 1371*w*, 1325*s*, 1157*w*, 1113*m*, 1092*s*, 1067*s*, 1014*s*, 987*s*, 959*m*, 916*m*, 899*s*, 874*m*, 846*m*, 826*m*, 621*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 4.98 (*q*-like, ^3J(1,6)≈^3J(1,10ax)≈^3J(1,10eq)≈2, H–C(1)); 4.63 (*A* of *ABX-P*, ^2J = 11.4, ^3J(5ax,P) = 2.7, ^3J(5ax,6)≈0, H_{ax}–C(5))[11]; 4.30 (*B* of *ABX-P*, ^2J = 11.4, ^3J(5eq,P) = 25.3, ^3J(5eq,6) = 1.3, H_{eq}–C(5))[10]; 2.02 (br. *d*-like, $w_{1/2}$≈18, ^2J≈13, H_{eq}–C(10)); 1.97 (*m*, $w_{1/2}$≈25, *X* of *ABX-P*, H–C(6)); 1.81 (*m*, *dt*-like, $w_{1/2}$≈25, H_{eq}–C(7)); H_{eq}–C(8)); 1.74–1.63 (*m*, H_{ax}–C(8), H_{ax}–C(10)); 1.58–1.49 (*m*, *tt*-like, CH_2(9)); 1.41 (*qd*-like, $w_{1/2}$≈25, H_{ax}–C(7)). ^{13}C-NMR (100.6 MHz, $(CD_3)_2CO$): 82.0 (*dd*, ^2J(1,P) = 7.1, ^3J(1,F) = 1.8, C(1)); 75.8 (*dd*, ^2J(5,P) = 7.12, ^3J(5,F) = 1.2, C(1), C(5)); 36.5 (*d*, ^3J(6,P) = 5.3, C(6)); 31.8 (*d*, ^3J(10,P) = 9.2, C(10)); 25.2 (C(7)); 23.6 (C(8)); 19.7 (C(9)). ^{31}P-NMR (121.5 MHz, $(CD_3)_2CO$): −14.9 (*dddd*, ^1J(P,F) = 996, ^3J(P,H_{eq}–C(5) = 25.3, ^3J(P,H_{ax}–C(5)) = 2.7, ^4J(P,H_{ax}–C(10)) = 7.3))[11]. ^{19}F{^{1}H}-NMR (282.4 MHz, $(CD_3)_2CO$): −85.2 (*d*, ^1J(F,P) = 996). EI-MS: 194 (<1, M^+), 152 (9), 139 (2), 127 (1), 101 (13), 94 (45), 79 (100), 68 (19), 67 (23), 66 (14), 55 (16), 54 (17), 53 (13). CI-MS (NH_3): 406 (100, $[2M+NH_4]^+$) 212 (97, $[M+NH_4]^+$), 389 (16, $[2M+H]^+$) 195 (2, $[M+H]^+$).

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[10]) The descriptors 'ax' and 'eq' for the H-atoms CH_2(5) are based on their relative positions in the chair conformation of the 2,4-dioxa-3-phospha moiety. Due to the anomeric effect, the heterocycle is rather a twist-boat than a chair in the *P(3)*-equatorially-substituted compounds. For reasons of simplicity, the notation 'ax' and 'eq' has been maintained; H_{ax}–C(5) is always *cis* to H–C(1), and H_{eq}–C(5) *trans* to H–C(1).

[11]) Unambiguously assigned by ^{1}H{^{31}P} and ^{31}P/^{1}H-correlated spectra (HMQC).

*(−)-(1*R*,3*R*,6*R*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((−)-**10a**). $[\alpha]_D^{25} = -18.0$ ($c = 1.00$, acetone). All other physical data were identical with those of (+)-**10a**.

*(+)-(1*R*,3*S*,6*R*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((+)-**10b**). Colorless, tiny tablets (from Et_2O/hexane). M.p. 56–58°. R_f (hexane/Et_2O 1:3) 0.04. $[\alpha]_D^{25} = +9.4$ ($c = 1.00$, acetone). IR ($CHCl_3$): 3008*w*, 2946*m*, 2869*w*, 1482*w*, 1453*w*, 1344*m*, 1324*s*, 1151*w*, 1116*w*, 1092*m*, 1076*m*, 1062*s*, 1017*m*, 1001*m*, 982*m*, 949*m*, 922*m*, 892*m*, 865*m*, 822*w*, 628*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 4.86 (*m*, *dquint.*-like, $^3J(1,P) = 14.8$, $^3J(1,10ax) = 9.1$, $^3J(1,6) = {}^3J(1,10eq) = {}^4J(1,F) = 4.4$, $^4J(1,5ax) < 1$, H–C(1))[12]; 4.62 (*A* of *ABX-P*, $^2J = 11.4$, $^3J(5eq,6) = 8.5$, $^3J(5eq,P) = 7.7$, H_{eq}–C(5))[10][12]; 4.50 (*B* of *ABX-P*, $^2J = 11.4$, $^3J(5ax,P) = 17.0$, $^3J(5ax,6) = 4.3$, $^4J(5ax,F) = 1.5$, H_{ax}–C(5))[10][12]; 2.49 (*m*, *sept.*-like, *X* of *ABX-P*, $w_{1/2} \approx 20$, H–C(6)); 1.96 (*m*, $w_{1/2} \approx 25$, CH_2(10)); 1.79 (*m*, $w_{1/2} \approx 20$, H_{eq}–C(7)); 1.74 (*m*, $w_{1/2} \approx 20$, H_{eq}–C(8)); 1.71 (*m*, br. *q*-like, $w_{1/2} \approx 25$, $^2J \approx {}^3J(7ax,6) \approx {}^3J(7ax,8ax) \approx 11$, $^3J(7ax,8eq) \approx 4$, CH_{ax}–C(8)); 1.45 (*m*, $w_{1/2} \approx 15$, CH_2(9)); 1.44 (*m*, br. *q*-like, $w_{1/2} \approx 25$, $^2J \approx {}^3J(8ax,7ax) \approx {}^3J(8ax,9ax) \approx 11$, $^3J(8ax,7eq) \approx {}^3J(8ax,9eq) \approx 4$, H_{ax}–C(8)). ^{13}C-NMR (100.6 MHz, $(CD_3)_2CO$): 83.5 (*d*, $^2J(1,P) = 7.3$, C(1)); 72.3 (*d*, $^2J(5,P) = 6.6$, C(5)); 35.9 (*d*, $^2J(6,P) = 7.8$, C(6)); 29.6 (*d*, $^3J(10,P) = 3.1$, C(10)); 25.5 (C(7)); 233 (C(8)); 22.5 (C(9)). ^{31}P-NMR (121.5 MHz, $(CD_3)_2CO$): −15.1 (*dtd*-like, $^1J(P,F) = 983$, $^3J(P,H_{ax}–C(5) = 17.0$, $^3J(P,H–C(1) = 14.8$, $^3J(P,H_{eq}–C5)) = 7.7$)[10][12]). ^{19}F{^{1}H}-NMR (282.4 MHz, $(CD_3)_2CO$): −75.1 (*d*, $^1J(F,P) = 983$). EI-MS: 194 (< 1, M^+), 152 (7), 139 (2), 127 (1), 101 (11), 94 (38), 79 (100), 68 (16), 67 (20), 66 (11), 55 (13), 54 (14), 53 (11). CI-MS (NH_3): 406 (9, $[2M + NH_4]^+$) 212 (100, $[M + NH_4]^+$), 195 (2, $[M + H]^+$).

*(−)-(1*S*,3*R*,6*S*)-3-Fluoro-2,4-dioxa-3-phosphabicyclo[4.4.0]decane 3-Oxide* ((−)-**10b**). $[\alpha]_D^{25} = -7.6$ ($c = 1.00$, acetone). All other physical data were identical with those of (+)-**10b**.

7. *Enzyme Kinetics.* Materials and methods are explicitely described in the preceding contribution [10].

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12) Unambiguously assigned by a series of NMR experiments (^{31}P/^{1}H-HMQC, ^{1}H{^{31}P}, ^{1}H{^{19}F}, ^{1}H{H–C(6)}, ^{31}P{H–C(1)}, ^{31}P{H_{ax}–C(5)}) and corroborated by simulation of the spin system. The coupling parameters clearly indicate a non-double-chair conformation. A detailed discussion of conformational implications in (+)- and (−)-**10b**, will be included in [12].

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