Chiral Configurations of Spirane-Bridged Cyclotriphosphazenes

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The stereogenic properties of carbocyclic spiranes with two interlocking rings are well-established. Although some cyclophosphazene analogues of dispiranes have been reported, the molecules did not have any centres of chirality because they were symmetrically substituted. Linear tetraspiranes, in which the two inner rings are carbocyclic and symmetrical and the two outer rings are unsymmetrically-substituted cyclotriphosphazenes, are expected to give rise to chiral molecules. We now report on the synthesis and stereogenic properties of the three structural types of pentaerythritol-bridged disubstituted cyclophosphazenes, which all have centres of chirality.

Introduction

Carbocyclic spiranes with two interlocking rings are well-established, and their chirality has been elucidated.[1] Cyclophosphazene analogues of dispiranes have also been reported,[2,3] but their symmetrical substitution precluded any chiral properties. We now report on the stereogenic properties of linear tetraspiranes, in which the two inner rings are carbocyclic and symmetrical and the two outer rings are cyclotriphosphazenes, whose substitution gives rise to chiral molecules.

The possibility that tetra-coordinated phosphorus(v) atoms may lead to chiral structures in cyclophosphazenes was realised many years ago,[4] but has been demonstrated only recently by a series of piperazine-bridged macrocyclic-phosphazene compounds[5] and spermine-bridged cyclotriphosphazene derivatives.[6] The only other examples of chirality in cyclophosphazene derivatives are those in which an optically active acyclic precursor was cyclised,[7] or in which the substituent group was stereogenic.[8] The chirality originally considered for the cyclophosphazene framework wasconfined to one type of substituent in a single cyclophosphazene ring,[4] giving rise to (*R*) and (*S*) forms, which have not been separated in any derivative to date. On the other hand, singly bridged macrocyclic phosphazene compounds (e.g. containing piperazine[5] and diamine[9,10]) and spermine-bridged cyclotriphosphazene derivatives[6] have disubstituted cyclotriphosphazene rings, which provide multiple stereocenters and the possibility of diastereoisomers. For example, the *meso* and racemic forms of piperazine-bridged macrocyclic phosphazenes have been separated by column chromatography and characterised by X-ray crystallography and by ^{31}P NMR spectroscopy[5] [after addition of a lanthanide-containing chiral shift reagent (CSR)]. Similar X-ray crystal data and NMR spectra have been observed for the *meso* and racemic forms of spermine-bridged cyclotriphosphazene derivatives, though, in this case, a chiral solvating agent (CSA) was added to show the stereogenic properties by ^{31}P NMR spectroscopy.[6]

By analogy with the chiral properties of tetrahedral carbon compounds, one might expect tetra-coordinated phosphorus(v) atoms in cyclophosphazenes to exhibit other forms of chirality, such as that observed in spiranes.[1] It is known that reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, (**1**) with a tetrafunctional alcohol such as pentaerythritol, $C(CH_2OH)_4$, (**2**), gives a spirane-bridged compound **3**, whose structure [Figure 1(a)] consists of four six-membered rings, each joined by a tetrahedral atom (phosphorus or carbon) to the next ring, with each six-membered ring being orthogonal to its neighbours.[11] The spirocyclic compound **3** has a plane of symmetry and is achiral. Examination of molecular models indicates that derivatives of compound **3** should exhibit a wide range of configurational isomers, many of which are chiral. For example, disubstituted derivatives of general formula $(N_3P_3Cl_2X_2)(OCH_2)_2C(CH_2O)_2(N_3P_3Cl_2X_2)$, shown in Fig-

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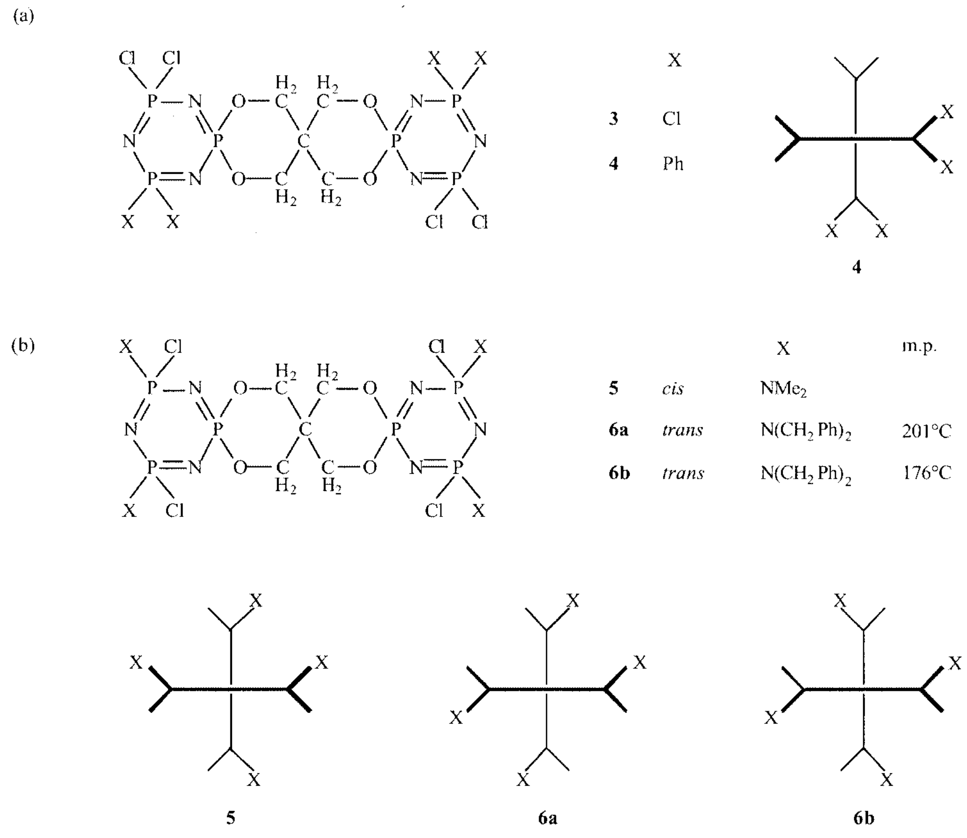

Figure 1. Structures of spirane-bridged unsubstituted (**3**), and disubstituted cyclotriphosphazenes; (a) geminal (**4**) and (b) non-geminal, with *cis* (**5**) and two *trans* (**6a**, **6b**) derivatives; a diagrammatic representation is also shown for one of the enantiomers for each compound (**4−6**), which have different substitution patterns of the cyclophosphazene rings. For clarity, the inner carbocyclic rings have been omitted and the outer cyclophosphazene rings, which are orthogonal to each other, are shown in the same projection with the ring to the front in bold

ure 1, should give rise to a racemate when the substituent, X, has either a geminal (**4**) or *cis*-non-geminal (**5**) disposition, and give rise to a pair of configurational isomers (both of which are racemates) when the substituents are in a *trans*-non-geminal relationship (**6a** and **6b**). A diagrammatic representation of one of the enantiomers for each of the compounds **4−6** is shown in Figure 1, in terms of the substitution patterns of the cyclophosphazene rings, which are orthogonal to each other. In this work, an example of each type of configurational isomer (**4−6**) has been synthesised and the chirality confirmed by X-ray crystallography and ^{31}P NMR spectroscopy using a chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**7**).[12]

Results and Discussion

The three structural types of the pentaerythritol-bridged disubstituted cyclophosphazenes (**4**, **5** and **6**) were synthesised by the following routes:

(a) For compound **4** (geminal substitution): pentaerythritol (**2**) was allowed to react with *gem*-diphenylcyclotriphosphazene[13] to give **4**, m.p. 150 °C. The crystal structure of **4**, shown in Figure 2, confirms that it exists as a racemate.

$\mathbf{2} + N_3P_3Ph_2Cl_4 \rightarrow \mathbf{4}$

(b) For compound **5** (*cis*-non-geminal substitution): Compound **3**[11] was treated with dimethylamine to give **5**, m.p. 272 °C. The crystal structure of **5**, shown in Figure 3, confirms that it exists as a racemate.

$\mathbf{3} + HNMe_2 \rightarrow \mathbf{5}$

(c) For the diastereoisomeric compounds **6a** and **6b** (*trans*-non-geminal substitution): The *trans* non-geminal disubstituted compound $N_3P_3[N(CH_2Ph)_2]_2Cl_4$ [14] was allowed to react with pentaerythritol (**2**) to give **6a** and **6b**, which were separated by silica gel chromatography using dichloromethane/hexane (1:2) as eluent. The two isomers were crystallised from dichloromethane/hexane (1:5) and had melting points of 201 °C (**6a**) and 176 °C (**6b**). The crystal structures of **6a** and **6b** (Figure 4) confirm the structures of the two diastereoisomers, and also show that each exists as a racemate.

$\mathbf{2} + N_3P_3[N(CH_2Ph)_2]_2Cl_4 \rightarrow \mathbf{6a} + \mathbf{6b}$

The stereogenic properties of all five compounds (**3**, **4**, **5**, **6a** and **6b**) were investigated by proton-decoupled ^{31}P

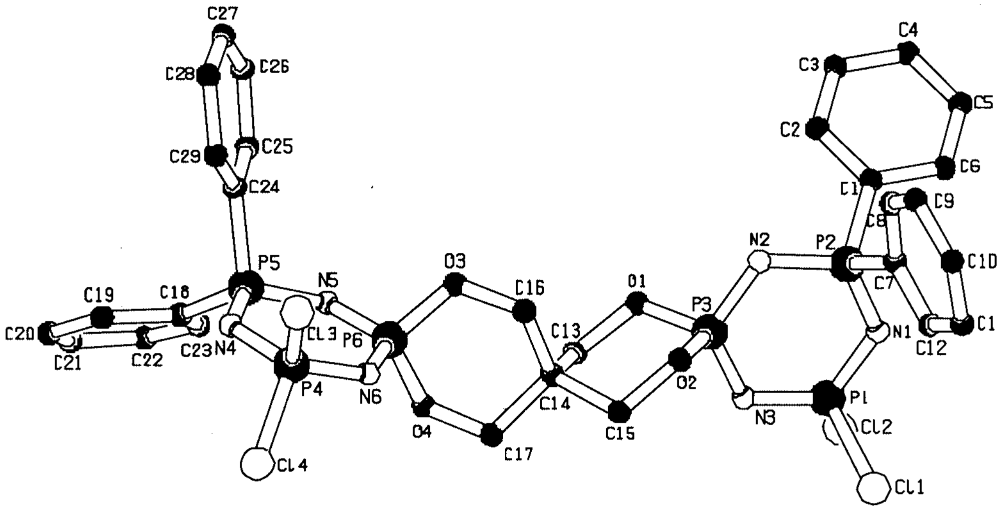

Figure 2. X-ray crystal structure of one enantiomer of the spirane-bridged geminally disubstituted cyclotriphosphazene **4**

NMR spectroscopy on addition of the CSA **7**; the results are summarised in Table 1.

Addition of the CSA causes small changes in chemical shifts of all compounds indicating complexation, including the achiral compound **3**. Although the small changes to the chemical shifts of the >P(spiro) group are about the same for all chiral compounds (**4**, **5**, **6a** and **6b**), the effect on the other signals for **4** (which contains phenyl groups attached to the cyclophosphazene ring) is much greater than for the derivatives containing NMe_2 (**5**) or $N(CH_2Ph)_2$ (**6a** and **6b**). Addition of the CSA to all compounds (**4**, **5**, **6a** and **6b**) also causes each signal to split into two resonances (ratio 1:1), confirming that each molecule exists as a racemate, whereas there is no splitting of signals for the achiral molecule **3**, as expected. Again, the separation of signals for the >P(spiro) group of the enantiomers is about the same for each chiral compound, but the effects on the two other signals (>PCl_2 and >PPh_2) in compound **4** are greater than for the >PCl(X) signals for **5**, **6a** and **6b**.

In conclusion, we have been able to synthesise and characterise all four structural variations of spirane-bridged disubstituted-cyclotriphosphazene derivatives of general formula $N_3P_3Cl_2X_2(OCH_2)_2C(CH_2O)_2N_3P_3Cl_2X_2$, in which the two N_3P_3 rings of each compound have the same substitution pattern, as shown in Figure 1. The prediction from molecular models that all four compounds (**4**, **5**, **6a** and **6b**) exist as racemates was confirmed by the X-ray crystal structures (Figures 2−4) and by ^{31}P NMR spectroscopy on addition of a chiral solvating agent (Table 1). These results on linear tetraspiranes open up the possibility of synthesising new types of supramolecular structures with defined stereogenic properties.

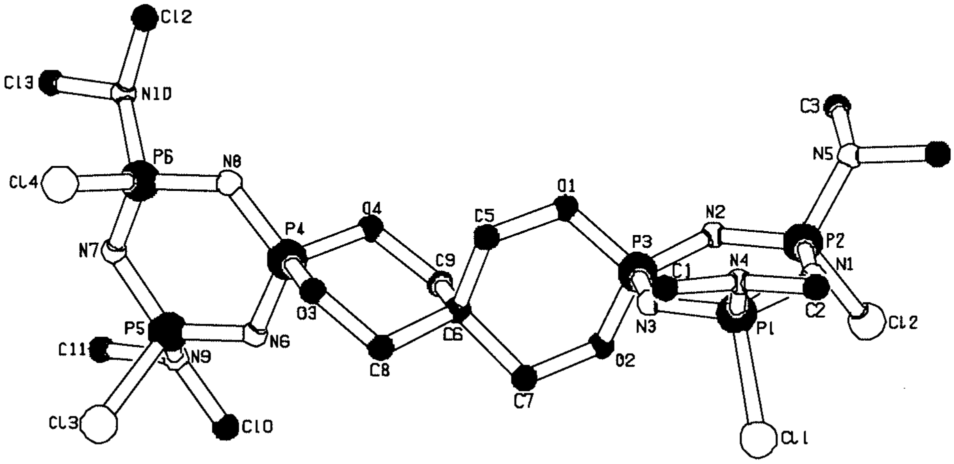

Figure 3. X-ray crystal structure of one enantiomer of the spirane-bridged *cis*-non-geminally disubstituted cyclotriphosphazene **5**

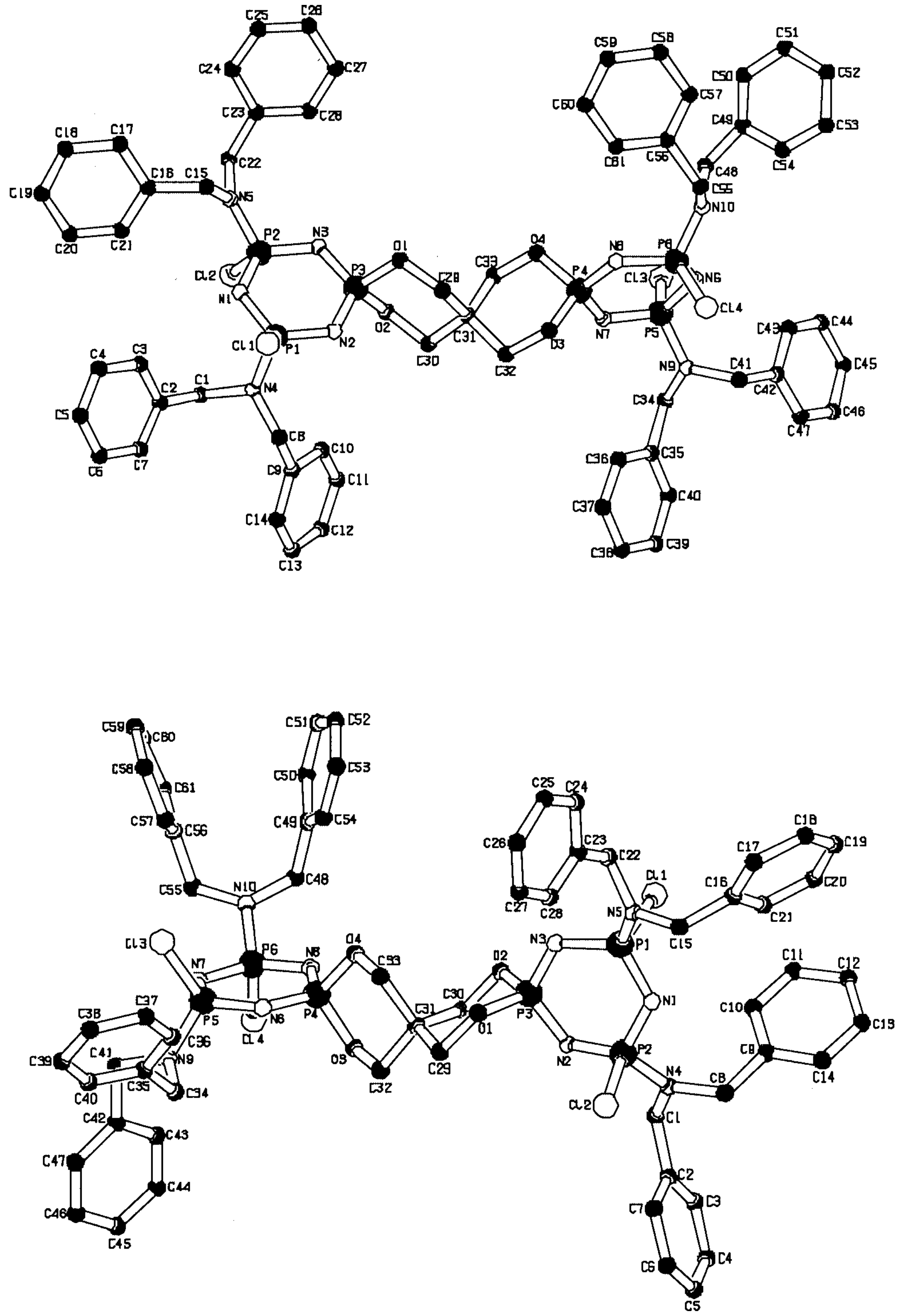

Figure 4. X-ray crystal structures of one enantiomer of the spirane-bridged *trans*-non-geminally disubstituted cyclotriphosphazenes **6a** (top) and **6b** (bottom)

Experimental Section

X-ray structural data were collected by means of combined φ and ω scans on a Bruker-Nonius KappaCCD area detector situated at the window of a rotating anode, λ(Mo-K_α) = 0.71073 Å. The structures were solved by direct methods (SHELXS-97) and refined using SHELXL-97.[15] Hydrogen atoms were included in the refinement, but thermal parameters and geometry were constrained to ride on the atom to which they are bonded. The data were corrected for absorption effects using SORTAV.[16] The structures of **4** and **6a** both contain two molecules in the asymmetric unit (not displayed in Figures 2 and 4, respectively) **6a** also exhibits posi-

Table 1. Effect of addition of the CSA **7** on the ^{31}P NMR parameters of pentaerythritol-bridged cyclophosphazenes

Compound	>P(spiro)	>PCl_2	>PPh_2	>PCl(X)	X	$^2J_{P,P}$/Hz
(i) ^{31}P NMR chemical shifts (ppm)						
3	4.5	24.6				69.9[a]
4 (*gem*)	6.6	22.5	22.9			16.1, 34.5, 46.1[b]
5 (*cis*)	10.2			31.8, 31.3	NMe_2	47.8, 62.0, 56.8[c]
6a (*trans*1)	9.5			28.1	$N(CH_2Ph)_2$	63.3[a]
6b (*trans*2)	9.4			28.1	$N(CH_2Ph)_2$	63.4[a]
(ii) Change in chemical shifts (ppb)[d]						
3	−35	53				69.8[a]
4 (*gem*)	−8	130	263			15.9, 34.1, 45.9[b]
5 (*cis*)	−8			27	NMe_2	47.5, 61.8, 56.7[c]
6a (*trans*1)	−5			10	$N(CH_2Ph)_2$	63.2[a]
6b (*trans*2)	5			11	$N(CH_2Ph)_2$	63.3[a]
(iii) Separation of signals of enantiomers (ppb)[d]						
4 (*gem*)	13	80	82			
5 (*cis*)	[e]			26	NMe_2	
6a (*trans*1)	15			8	$N(CH_2Ph)_2$	
6b (*trans*2)	5			8	$N(CH_2Ph)_2$	

[a] Analysed as an A_2B spin system. [b] Analysed as an ABX spin system with X = >P(spirane), A = >PCl_2 and B = >PPh_2; for example, $^2J_{P,P}$ = 16.1 (AB), 34.5 (BX), 46.1 (AX) Hz. [c] Analysed as an ABX spin system with X = >P(spirane), A and B = >$PCl(NMe_2)$; for example, $^2J_{P,P}$ = 47.8 (AB), 62.0 (AX), 56.8 (BX) Hz. [d] Mole ratio of chiral solvating agent:compound = 100:1. [e] Magnitude too small to measure at 202 MHz.

tional disorder (45:55 site occupancy) at atom C48. X-ray crystallographic data for the compounds are as follows:

4: $C_{29}H_{28}Cl_4N_6O_4P_6$, triclinic, $P\bar{1}$, a = 15.123(3), b = 15.721(3), c = 17.178(3) Å, α = 66.93(3), β = 77.43(3), γ = 89.98(3)°, V = 3651.2(13) Å^3, 120 K, Z = 4, D_c = 1.550 Mg/m^3, μ = 0.632 mm^{-1}, θ_{max} = 27.50°, 47740 measured and 14802 unique (R_{int} = 0.2369) reflections, R1 (obsd.) = 0.1928 and wR2 (all data) = 0.4795, ρ_{max}/ρ_{min} = 3.681/−0.784 e·Å^{-3}.

5: $C_{13}H_{32}Cl_4N_{10}O_4P_6$, triclinic, $P\bar{1}$, a = 8.8626(18), b = 9.7205(19), c = 19.481(4) Å, α = 98.17(3), β = 98.79(3), γ = 110.94(3)°, V = 1513.4(5) Å^3, 120 K, Z = 2, Dc = 1.580 Mg/m^3, μ = 0.749 mm^{-1}, θ_{max} = 27.50°, 15458 measured and 5783 unique (R_{int} = 0.0870) reflections, $R1$ (obsd.) = 0.0968 and wR2 (all data) = 0.2240, ρ_{max}/ρ_{min} = 0.690/−0.536 e·Å^{-3}.

6a: $C_{61}H_{64}Cl_4N_{10}O_4P_6$, triclinic, $P\bar{1}$, a = 15.508(3), b = 20.364(4), c = 21.857(4) Å, α = 77.66(3), β = 71.29(3), γ = 78.16(3)°, V = 6317(2) Å^3, 120 K, Z = 4, D_c = 1.397 Mg/m^3, μ = 0.395 mm^{-1}, θ_{max} = 26.35°, 46301 measured and 24221 unique (R_{int} = 0.2403) reflections, R1 (obsd.) = 0.1021 and wR2 (all data) = 0.2750, ρ_{max}/ρ_{min} = 0.545/−0.745 e·Å^{-3}.

6b: $C_{61}H_{64}Cl_4N_{10}O_4P_6$, triclinic, $P\bar{1}$, a = 10.635(2), b = 17.078(3), c = 18.972(4) Å, α = 107.56(3), β = 103.63(3), γ = 90.90(3)°, V = 3178.6(11) Å^3, 120 K, Z = 2, D_c = 1.388 Mg/m^3, μ = 0.393 mm^{-1}, θ_{max} = 25.98°, 23642 measured and 12158 unique (R_{int} = 0.1260) reflections, R1 (obsd.) = 0.0735 and wR2 (all data) = 0.2750, ρ_{max}/ρ_{min} = 1.082/−0.832 e·Å^{-3}.

Supplementary data in the form of CIF files have been deposited with the Cambridge Crystallographic Data Centre with the following deposition numbers: CCDC-226218 to -226221 for **4** to **6b**, respectively.

^{1}H and proton-decoupled ^{31}P NMR spectra were recorded in $CDCl_3$ solution on a Bruker DRX 500 MHz spectrometer using tetramethylsilane as an internal reference for ^{1}H and 85% H_3PO_4 as an external reference for ^{31}P. Proton-coupled ^{31}P NMR spectra were also recorded to aid the assignment of signals for compound **4**. Experiments involving the chiral solvating agent **7** were performed by addition of small aliquots of a concentrated solution of the CSA in the solvent used for NMR spectroscopy; the proton-decoupled ^{31}P NMR spectrum was recorded after each addition.

Supporting Information on the synthesis and analysis (MS, ^{1}H NMR, elemental analysis) of compounds **4−6** is available (see also the footnote on the first page of this article).

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