Chemistry of Phosphorylmethyl Isocyanides, 6[◇]

cis- and *trans*-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane – Synthesis and Structure of the First Chiral Isocyanomethylphosphonate Synthons

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Both *cis*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (**1a**) and the *trans* epimer **1b** have been prepared as potentially useful chiral isocyanomethylphosphonate synthons. 2-Methoxy-1,3,2-dioxaphosphorinanes **5** and the corresponding 2-ethoxy analog **6** were prepared from 2,2-dimethyl-1-phenyl-1,3-propanediol (**2**) and were converted in an Arbuzov-type reaction to 2-(formamidomethyl)oxo-1,3,2-dioxaphosphorinane **7**, which upon dehydration gave **1a**. Thus, both (±)-**1a** and (2*S*,4*S*)-(−)-**1a** were prepared, and their molecular structures were determined by single-crystal X-ray analysis. Treatment of (2*S*,4*S*)-(–)-**1a** with KF gave a 1:3 equilibrium mixture of the phosphorus epimers **1a** and **1b**, from which the predominant *trans* epimer (2*S*,4*R*)-(–)-**1b** was isolated by column chromatography and crystallization.

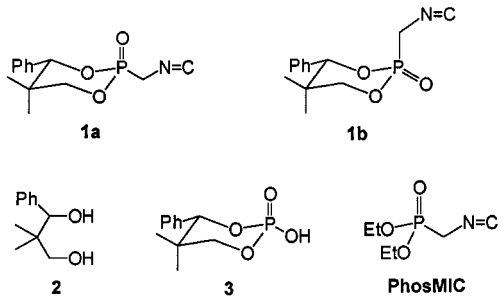
Introduction

Organic isocyano compounds have developed into an important category of synthesis reagents (synthons), covering a large variety of synthetic applications.[1] Two events of the last three decades have been crucial in this development: (1) the extension of the Passerini reaction (of 1921) into the Ugi Multi-Component Reactions (starting in 1961);[1a][2] (2) the introduction of α-metalated isocyanides in organic synthesis by the Schöllkopf group (from 1968 on).[3]

The scope of α-metalated isocyanides in organic synthesis is considerably enlarged by the introduction of α-substituents X in compounds XCHRN=C (R = H, alkyl, aryl), in particular when X is a carboxylate derivative[1b][1f][3] or one of certain hetero substituents.[1e][1g][1h][1i] A multitude of synthetic goals has been realized by the use of sulfonyl-substituted methyl isocyanides (X = RSO_2), with TosMIC as the most prominent representative.[1h][1i] Another important group of hetero-substituted methyl isocyanides is centered around diethyl isocyanomethylphosphonate (PhosMIC).[1e] Nitrogen- and boron-substituted methyl isocyanide, on the other hand, are still at infancy.[4]

For a group of synthons of established significance, the application of chirality in isocyanide-based syntheses is lagging behind remarkably. So far, achiral $EtO_2CCH_2N{=}C$, TosMIC, and PhosMIC have been successfully applied in the stereoselective synthesis of chiral oxazolines and chiral β-hydroxy amines by Hayashi, Ito, and coworkers using chiral gold or, silver catalysts.[5] Similar results were achieved by Solladie-Cavallo et al. in the reaction of TosMIC with chiral chromium complexes of benzaldehyde.[6] A number of chiral TosMIC analogs $R^*SO_2CH_2N{=}C$, together with $PhS^*(O)(NTos)CH_2N{=}C$ have been reported, but their use has been limited.[1i][7] The same holds for a few chiral isocyanoacetates $R^*O_2CCH_2N{=}C$, derived, for example, from (−)-menthol and (+)-borneol,[8] and the recently reported (4*R*)- and (4*S*)-3-(isocyanoacetyl)-4-(phenylmethyl)-2-oxazolidinones.[9]

We wish to report the synthesis of the first chiral analogs of PhosMIC: *cis*- and *trans*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane, **1a** and **1b**. Isocyanides **1a** and **1b**, unlike PhosMIC, are crystalline compounds, both in the racemic as well as in the optically active forms. Generally speaking, crystalline isocyanides are more stable, which usually means improved storability.



Synthesis of (Isocyanomethyl)dioxaphosphorinanes 1a and 1b − Considerations and Reaction Scheme

An obvious way to introduce chirality in compounds like PhosMIC involves replacement of the achiral alkoxy groups for a chiral alcohol. There are several reasons for selecting

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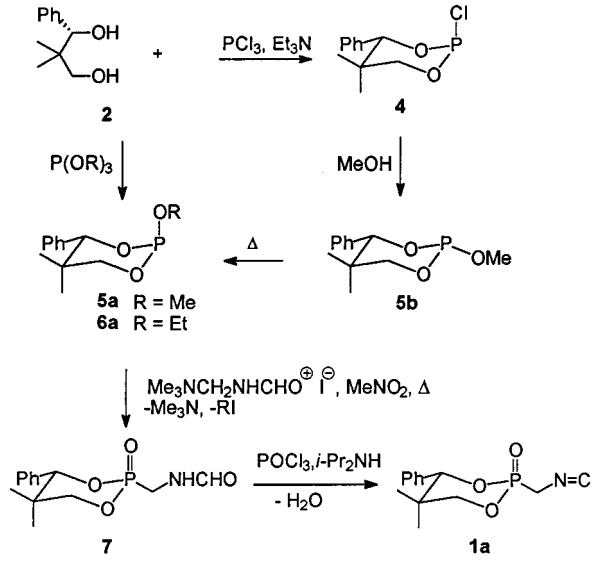
chiral 2,2-dimethyl-1-phenyl-1,3-propanediol (**2**) for this purpose. The major reasons are: (1) both enantiomers of **2** are readily available; (2) phosphoric acids **3**, derived from **2**, have been developed into commercially available resolving agents for amines, amino acids, and amino alcohols;[10] and (3), above all, the use of **2** will turn the phosphorus atom of compounds **1** into a second stereogenic center, as part of a rigid and chiral dioxaphosphorinane ring. Thus, a potentially important additional chiral center will be situated next to the main reaction site of compounds **1**: the exocyclic methylene group.

Our synthesis of (isocyanomethyl)dioxaphosphorinanes **1**, as outlined in Scheme 1, is based on an adaption of the Schöllkopf synthesis of PhosMIC (**2**),[11] in combination with the Wynberg preparation of enantiomerically pure **2**.[10][12] We have worked out the reactions of Scheme 1 with racemic diol **2** first. Subsequently, the same reactions were carried out with (*S*)-(+)-diol **2**. In fact, the latter reactions are depicted in Scheme 1, which is based on the reasonable assumption that the stereogenic center of **2** is unaffected during the entire series of reactions. This assumption has been substantiated by experiment. As is shown in Scheme 2, the configuration of the phosphorus stereocenter of compounds **1** can, however, be inverted in a separate reaction.

Scheme 1. Synthesis of isocyanomethylphosphorinane **1a**



2-Chloro-1,3,2-dioxaphosphorinane (4) and 2-Methoxy- and 2-Ethoxy-1,3,2-dioxaphosphorinanes (5 and 6a)

In the racemic series, reaction of (±)-diol **2** with PCl_3 (10 min, room temp.) gave the (highly) reactive tervalent 2-chloro-1,3,2-dioxaphosphorinane **4**, which, without being isolated, was converted to **5**. The latter reaction with MeOH (2 h, room temp.) gave, prior to distillation, a mixture of *trans*- and *cis*-phosphites **5a** and **5b**,[*] respectively, in ratios varying from ca. 1:4 to 1:6. Thermal epimerization of this mixture during distillation (at 70°C/0.4 Torr) led to the isolation of diastereomerically pure *trans*-**5a** as the single product in 72% yield based on **2**. The same *trans*-**5a** was obtained in 79% yield directly from **2** in one operation (avoiding the potentially explosive and highly water-sensitive chlorodioxaphosphorinane **4**) by a transesterification using trimethyl phosphite. The latter approach was also used to convert enantiomerically pure (*S*)-(+)-2,2-dimethyl-1-phenyl-1,3-propanediol **2** to (2*S*,4*S*)-(+)-2-methoxy-1,3,2-dioxaphosphorinane **5a** in 88% yield. Reaction of (*S*)-(+)-diol **2** with triethyl phosphite similarly gave (2*S*,4*S*)-(+)-**6a** in 89% yield.

Crude 2-chloro-1,3,2-dioxaphosphorinane **4** (not reported previously) gave one signal only in ^{31}P NMR at δ = 150.3, both in the racemic and in the optically active reaction series. This means that of the conceivable *cis* and *trans* isomers of **4**, only one (the *trans* isomer as depicted in Scheme 1) is formed. In *trans*-**4** the dioxaphosphorinane ring is fixed in the chair conformation by the equatorial 4-phenyl ring, with the 2-chlorine in axial position, as is expected on the basis of gauche[13] and anomeric[14] effects. Several other examples are known of 1,3,2-dioxaphosphorinanes with axial 2-chloro substituents.[15] Also, the *trans* structure assigned to **4** is consistent with the stereochemistry of the next reactions of Scheme 1.

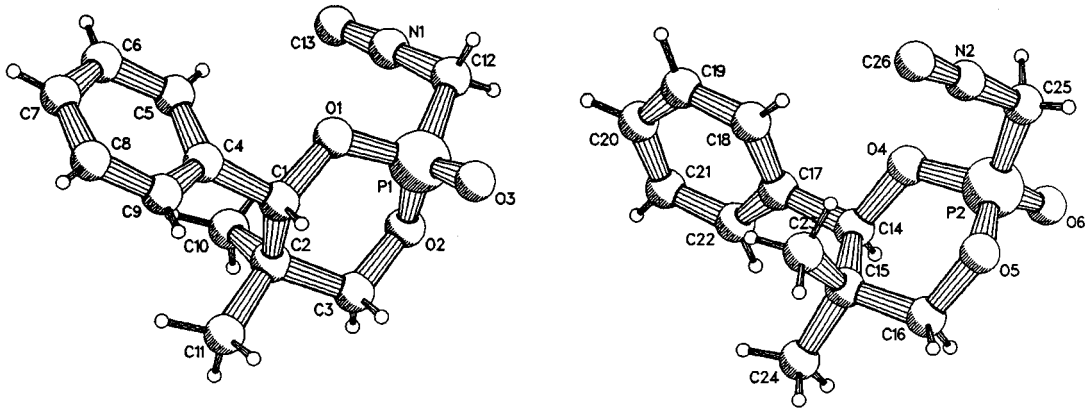
Reaction of **4** with MeOH at room temperature led predominantly to *cis*-dioxaphosphorinane **5b**, which is assumed to be the kinetically favored isomer formed by displacement of chlorine in an $S_N2(P)$-type reaction with inversion at the phosphorus atom.[15a][16] The product mixture showed two signals in ^{31}P NMR: one at δ = 134.8 for **5b** and the other at δ = 127.6 of **5a**. The peak at δ = 134.8 disappeared completely when a solution of **5b** in toluene was heated for 2 h, to only give a signal at δ = 127.6 of the thermodynamically more stable *trans* isomer **5a**. The assignment of the *trans* configuration to **5a** is based on the $^3J_{PH}$ coupling constants of the ring protons.[17][18] The observed $^3J_{PH}$ coupling constants (see Experimental Section) are consistent with a 1,3,2-dioxaphosphorinane ring in a chair conformation with the 4-phenyl group and the free electron pair on the phosphorus atom in equatorial positions.

2-(Formamidomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (7) and *rac*-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (1a)

The formamidomethyl group of **7** was introduced by an Arbuzov-type reaction, analogous to the one previously used by Schöllkopf et al. in the synthesis of PhosMIC.[11] Thus, *trans*-(±)-**5a** (or **6a**) was refluxed for 2 h with 1.5 equivalents of *N*-(formamidomethyl)-*N,N,N*-trimethylammonium iodide in nitromethane to give (±)-**7** in 63% yield (Scheme 1). Compound **7** gave one signal in ^{31}P NMR at δ = 22.1. The $^3J_{PH}$ coupling constants of the ring protons of **7** are consistent with a chair conformation, as in compound **5a**. The positions of the formamidomethyl group and the phosphoryl oxygen atom of **7** follow from the X-ray structure of **1a**, which is obtained as the sole product

[*] For all dioxaphosphorinanes in this report, the terms *cis* and *trans* refer to the relative positions of the phenyl group at C4 and the single-bonded substituent at P.

Figure 1. Single-crystal X-ray structure of (±)-**1a**[a]



[a] Selected torsion angles [°] of the two crystallographically independent molecules of (±)-**1a**: P1−O1−C1−C4 177.6(3), O3−P1−O1−C1 −77.2(3), C12−P1−O1−C1 158.8(3), O3−P1−C12−N1 −168.0(4), P2−O4−C14−C17 −177.1(3), O6−P2−O4−C14 78.3(4), C25−P2−O4−C14 −158.1(4), O6−P2−C25−N2 172.1(4).

upon dehydration of **7**. Also, the stereochemistry of **7** is consistent with the earlier proposed mechanism of comparable Arbuzov reactions.[19]

Dehydration of (±)-**7** with $POCl_3$ gave racemic isocyanomethylphosphonate **1a** in 69% yield when either Et_3N or iPr_2NH was used as base in CH_2Cl_2 at −20°C (Scheme 1). In contrast to PhosMIC, **1a** is a stable, odorless solid, which crystallizes in colorless needles, melting at 145°C. The IR stretch vibrations of N≡C and P=O are found at 2154 and 1251 cm^{-1}, respectively, the only ^{31}P-NMR peak at δ = 13.9.

A single-crystal X-ray structure of (±)-**1a** was determined from crystals obtained from $CHCl_3$/hexane (1:3). The asymmetric unit contains two crystallographically independent molecules (Figure 1). The X-ray structure clearly shows the chair conformation of the 1,3,2-dioxaphosphorinane ring, the equatorial positions of the phenyl and isocyanomethyl substituents, and the axial phosphoryl oxygen atom.

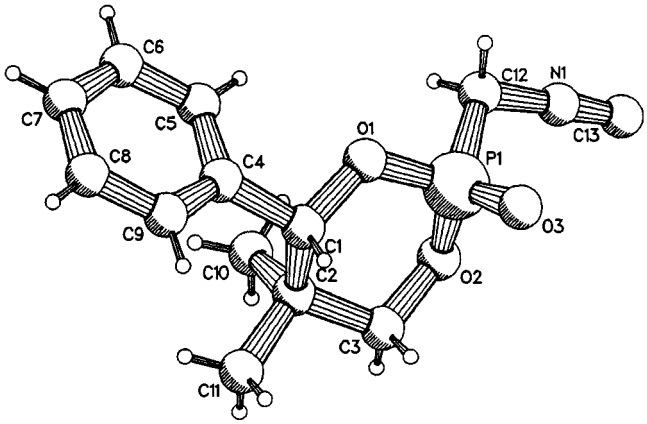
(2*S*,4*S*)-(−)-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (1a) and the (2*R*,4*S*)-(−) Epimer 1b

In analogy to the racemic series, transesterification of $P(OEt)_3$ with (*S*)-(+)-**2** gave (2*S*,4*S*)-(+)-**6a**, which was converted into formamide (2*S*,4*S*)-(+)-**7** in 77% yield. Subsequent dehydration of (2*S*,4*S*)-(+)-**7** gave, after column chromatography, pure (2*S*,4*S*)-(−)-**1a** in 31% yield, which melted at 133°C.

Recrystallization of (2*S*,4*S*)-(−)-**1a** from $CHCl_3$/hexane/MeOH (1:3:0.25) gave colorless plate-shaped crystals, from which a single-crystal X-ray structure was obtained (Figure 2). The asymmetric unit contains one complete molecule.

An unexpected, but interesting observation was made during an attempt to condense **1a** with *tert*-butyl methyl ketone. When **1a** and the ketone were heated at 100°C in DMF with 0.4 equivalent of KF (the intended condensation catalyst), partial epimerization of **1a** to **1b** was the only reaction that was observed (Scheme 2). No epimerization was observed when **1a** (without ketone) was heated in DMSO at 100°C, unless KF was added. In that case equilibration into a 1:3 mixture of **1a**/**1b** was achieved in 4 h. At room temperature, equilibration of **1a** in DMSO with KF took several weeks. The formation of **1b** is marked by the appearance of a second ^{31}P-NMR signal at δ = 8.0, in addition to the peak of **1a** at δ = 14.6. Starting with **1b**, the same 1:3 ratio of **1a**/**1b** was obtained with 0.4 equivalent of KF in 5 h in DMSO at 100°C. Isolation of pure *trans* epimer **1b** from the equilibrium mixture was achieved by column chromatograpy and repeated crystallization from hexane/$CHCl_3$ (2:1). In this way, (2*R*, 4*S*)-(−)-**1b** (mp 155°C) was obtained in 60% yield from (2*S*,4*S*)-(−)-**1a**.

Figure 2. Single-crystal X-ray structure of (2*S*,4*S*)-(−)-**1a**[a]



[a] Selected torsion angles [°]: P1−O1−C1−C4 −175.4(2), O3−P1−O1−C1 −82.6(2), C12−P1−O1−C1 152.7(2), O3−P1−C12−N1 60.1(3).

Table 1. Selected spectroscopic data for compounds **1a** and **1b**

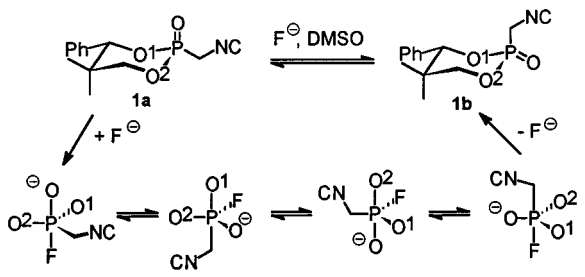
	ν(P=O)	δ^{31}P		δ^{1}H			δ^{13}C	
	[cm^{-1}]	$CDCl_3$	[D_6]DMSO	4-H	6-H_{ax}	6-H_{eq}	C-4	C-6
1a	1253/1244	13.9	14.6	5.52	4.56	4.01	85.2	75.8
1b	1291/1278	2.3	8.0	5.68	4.71	4.24	91.9	81.7

The spectroscopic data of the epimeric compounds **1a** and **1b** (Table 1) are consistent with the previously reported observation that 2-oxo-1,3,2-dioxaphosphorinanes with an equatorially oriented phosphoryl oxygen atom (as in **1b**) show a higher ν(P=O) and a lower δ^{31}P value than the isomers in which the oxygen atom is oriented axially (as in **1a**).[20][21] The P=O stretch vibration is observed as a split peak due to rotational isomerism of the isocyanomethyl group.

The epimerization at the phosphorus atom of **1a** and **1b** is readily explained by (axial) attack of F^- at the four-coordinated phosphorus atom of **1a** (or **1b**) to form a 5-coordinated intermediate that loses F^- after (minimal) three Berry pseudorotations[22] as depicted in Scheme 2.

A corresponding epimerization at the phosphorus atom has also been effected with the (formamidomethyl)dioxaphosphorinane **7**. In this case a 1:2 equilibrium mixture was obtained after 16 h with KF in DMSO at 100°C, again in favour of the *trans* epimer.

Scheme 2. Epimerization of **1a** and **1b** induced by F^-



Experimental Section

General: Melting points (uncorrected): Mettler FP1/FP51. − Optical rotations: Perkin Elmer 241 polarimeter (Hg lamp, 578 nm, 20°C). − NMR: Varian VXR-300S (300 MHz and 75.5 MHz for ^{1}H and ^{13}C, respectively) or Varian Gemini-200BB (200 MHz and 81.0 MHz for ^{1}H and ^{31}P, respectively). Chemical shifts are denoted in ppm relative to TMS (^{1}H and ^{13}C) or external H_3PO_4 (^{31}P). − MS: AEI-MS-992 (acc. voltage 8 kV, voltage 70 eV). − IR: Perkin-Elmer 841 Infrared Spectrophotometer (KBr, cm^{-1}). − Elemental analyses were performed in the Microanalytical Department of this laboratory. − Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre under number CCDC-100935. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk). − All reactions were carried out in oven-dried (120°C) glassware under N_2. Solvents were distilled prior to use: Et_2O, CH_2Cl_2, $CHCl_3$, and hexane from P_2O_5; MeOH and EtOH from Mg; toluene and THF from Na/benzophenone; DMF from CaH_2. Diols (±)-**2**[10] and (+)-**2**[12], and *N*-formamidomethyl-*N,N,N*-trimethylammonium iodide[23] were synthesized according to literature procedures. All other commercial reagents were used as received.

trans-2-Methoxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane [(±)-**5a** and (2*S*,4*S*)-(+)-**5a**]: *Compound* (±)-**5a**. − *Method 1* (via in situ formed chlorodioxaphosphorinane **4**): A solution of PCl_3 (0.8 ml, 9.2 mmol) in CH_2Cl_2 (60 ml) was added dropwise to a stirred solution of (±)-diol **2** (1.81 g, 10.1 mmol) and Et_3N (3.5 ml, 25.0 mmol) in CH_2Cl_2 (30 ml) at −10°C. The solution turned yellow, while a white precipitate was formed. After 10 min, the ^{31}P-NMR signal of PCl_3 at δ = 220.0 had disappeared and one new signal of chlorophosphite **4** (not isolated) at δ = 150.3 was present. MeOH (1.2 ml, 30.0 mmol) was added to the mixture at room temp. After stirring for 2 h, the ^{31}P NMR signal of **4** had disappeared and two new signals at δ = 127.6 and 134.8 were observed corresponding to *trans*- and *cis*-methoxydioxaphosphorinanes **5a** and **5b**, respectively, in a *trans*/*cis* ratio of 1:6. The solvent was removed under reduced pressure and the residue was distilled at 70°C (0.4 mbar) yielding 1.60 g (6.7 mmol, 72%) of solid (±)-**5a**, m.p. 45°C. During distillation, *cis*-**5b** is converted to *trans*-**5a**, see text. − ***Caution:*** Phosphites react violently with oxygen or with water and an explosion may result.[24] − ^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3 H, CH_3); 1.04 (s, 3 H, CH_3); 3.40 (dd, $^2J_{AB}$ = 10.6 Hz, $^3J_{PH}$ = 11.0 Hz, 1 H, 6-H_{eq}); 3.58 (d, $^3J_{PH}$ = 12.0 Hz, 3 H, OCH_3); 4.32 (dd, $^2J_{AB}$ = 10.6 Hz, $^3J_{PH}$ = 2.6 Hz, 1 H, 6-H_{ax}); 5.28 (d, $^3J_{PH}$ = 3.0 Hz, 1 H, 4-H); 7.32 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 17.5 (CH_3); 22.7 (CH_3); 36.4 (C5); 50.0 (OCH_3); 70.3 (C6); 78.5 (C4); 127.4, 127.6, 137.6 (Ar C). − ^{31}P NMR ($CDCl_3$): δ = 127.6. − HRMS: $C_{12}H_{17}O_3P$: calcd. 240.092; found 240.091.

Method 2 [by transesterification of $P(OMe)_3$]: A solution of (±)-diol-**2** (10.02 g, 55.6 mmol), $P(OMe)_3$ (11.8 ml, 100 mmol), and a catalytical amount of Et_3N (0.9 ml, 6.5 mmol) in toluene (60 ml) was refluxed for 10 h. The precipitate was removed and the solution was concentrated under reduced pressure to give 10.55 g (43.9 mmol, 79%) of solid (±)-**5a**, m.p. 45°C.

Compound (2*S*,4*S*)-(+)-**5a**: A neat mixture of (*S*)-(+)-diol **2** (2.25 g, 12.5 mmol) and $P(OMe)_3$ (2.0 g, 16.1 mmol) was heated at 150°C for 6 h. The solution was concentrated under reduced pressure and the residue was distilled (100°C, 0.1 mbar) to give 2.63 g (11.0 mmol, 88%) of solid (2*S*,4*S*)-(+)-**5a**, m.p. 90°C. − $[\alpha]_{578}^{20}$ = +97.5 (*c* = 0.5, $CHCl_3$).

(2S,4S)-(+)-trans-2-Ethoxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane (**6a**): A neat mixture of (*S*)-(+)-diol **2** (4.68 g, 26.0 mmol) and $P(OEt)_3$ (4.5 g, 27.0 mmol) was heated at 120°C for 5 d. The solution was concentrated under reduced pressure and the solid residue was crystallized from hexane to give 5.9 g (23.2 mmol, 89%) of solid (2*S*,4*S*)-(+)-**6a**, m.p. 52°C. − $[\alpha]_{578}^{20}$ = +135.2 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.70 (s, 3 H, CH_3); 1.04 (s, 3 H, CH_3); 1.31 (t, *J* = 7 Hz, CH_3); 3.40 (dd, $^2J_{AB}$ = 10.7 Hz, $^3J_{PH}$ = 11.0 Hz, 1 H, 6-H_{eq}); 3.90 (qd, *J* = 7 Hz, $^3J_{PH}$ = 1.0 Hz, 2 H, CH_2); 4.34 (dd, $^2J_{AB}$ = 10.7 Hz, $^3J_{PH}$ = 3.0 Hz, 1 H, 6-H_{ax}); 5.30 (d, $^3J_{PH}$ = 3.0 Hz, 1 H, 4-H); 7.32 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 17.1 (CH_3); 17.8 (CH_3); 22.9 (CH_3); 36.7 (C5); 58.9 (OCH_2); 70.6 (C6); 78.7 (C4); 127.5, 127.7, 137.7 (Ar C). − ^{31}P NMR ($CDCl_3$): δ = 126.0. − $C_{13}H_{19}O_3P$ (254): calcd. C 61.41, H 7.53, P 12.18; found C 60.27, H 7.57, P 12.00. − HRMS: calcd 254.107; found 254.107.

cis-2-(Formamidomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane [(±)-**7** and (2*S*,4*S*)-(+)-**7**]: *Compound* (±)-**7**: A solution of (±)-**5a** (10.0 g, 42.1 mmol) and *N*-formamidomethyl-*N,N,N*-trimethylammonium iodide[23] (10.3 g, 62 mmol) in CH_3NO_2 (150 ml) was refluxed for 2 h, during which a precipitate was formed. The precipitate was removed and H_2O (100 ml) was added. The solution was extracted with $CHCl_3$ (3 × 30 ml) and the combined extracts were washed with H_2O (50 ml), dried ($MgSO_4$), and concentrated to give 10.1 g of crude **7** as a yellow oil, which crystallized on standing at room temp. Precipitation from Et_2O gave 7.54 g of (±)-**7** (26.6 mmol, 63%), pure according to ^{31}P and ^{1}H NMR. An analytically pure sample was obtained

after three crystallizations from EtOH, m.p. 173°C. – ^{1}H NMR: δ = 0.76 (s, 3 H, 5-CH_3); 0.98 (s, 3 H, 5-CH_3); 3.83 (dd, J_{AB} = 11.0 Hz, J_{PH} = 22.0 Hz, 1 H, 6-H_{eq}); 3.96 (dd, J = 6.0 Hz, J_{PH} = 12.6 Hz, 2 H, CH_2); 4.42 (dd, J_{AB} = 11.0 Hz, J_{PH} = 2.3 Hz, 1 H, 6-H_{ax}); 5.41 (d, J_{PH} = 3.0 Hz, 4-H); 7.06 (br. s, 1 H, NH); 7.20 – 7.35 (m, 5 H, Ar H); 8.25 (s, 1 H, CHO). – ^{13}C NMR: δ = 17.0 and 21.2 (5-CH_3); 33.2 (J_{PC} = 160 Hz, CH_2); 36.2 (C5); 75.4 (C6); 84.5 (C4); 127.1, 127.8, 128.5, 135.0 (Ar C); 161.1 (CHO). – ^{31}P NMR δ = 21.9. – IR: ν = 3263 cm^{-1} (NH), 1682 (C=O), 1282 (P=O), 1040 (P–O). – $C_{13}H_{18}NO_4P$ (283): calcd. C 55.12, H 6.40, N 4.94, P 10.93; found C 54.80, H 6.62, N 4.80, P 10.68. – HRMS: calcd. 283.097; found 283.097. – The same procedure was performed with (±)-**6a** (18.1 g, 71 mmol) to give 10.2 g of (±)-**7** (36 mmol, 51%).

Compound (2*S*,4*S*)-(+)-**7** was prepared as described above for (±)-**7** from (2*S*,4*S*)-(+)-**6a** (4.3 g, 17 mmol) in 77% yield (3.7 g, 13 mmol), m.p. 141–142°C. – $[\alpha]_{578}^{20}$ = +20 (*c* = 0.5, $CHCl_3$).

cis-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane [(±)-**1a** and (2S,4S)-(–) **1a**]: *Compound* (±)-**1a**: A solution of $POCl_3$ (2.4 ml, 26.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of (±)-**7** (6.38 g, 22.5 mmol) and *i*Pr_2NH (9.5 ml, 67.5 mmol) in CH_2Cl_2 (130 ml) at –20°C and the reaction mixture was stirred for 2.5 h at 0°C. Aqueous $NaHCO_3$ (20 g in 150 ml of H_2O) was added carefully (evolution of CO_2) and the mixture was stirred for 20 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 5.8 g of crude (±)-**1a**, as a yellow solid. Column chromatography (SiO_2, AcOEt/hexane, 2:1) gave 4.52 g (17.0 mmol, 69%) of analytically pure (±)-**1a**, as transparant needles, m.p. 145°C. – ^{1}H NMR ($CDCl_3$): δ = 0.82 (s, 3 H, CH_3); 1.15 (s, 3 H, CH_3); 3.99 (dd, J_{AB} = 11 Hz, J_{PH} = 23 Hz, 1 H, 6-H_{eq}); 4.01 (d, J_{PH} = 16 Hz, 2 H, CH_2); 4.56 (dd, J_{AB} = 11 Hz, J_{PH} = 1.2 Hz, 1 H, 6-H_{ax}); 5.52 (d, J_{PH} = 1.4 Hz, 1 H, 4-H); 7.36 (s, 5 H, Ar H). – ^{13}C NMR: δ = 17.2 and 21.3 (5-CH_3); 36.3 (C5); 37.3 (J_{PC} = 157 Hz, CH_2); 75.8 (C6); 85.2 (C4); 127.1, 127.8, 128.5, 135.0 (Ar C); 161.2 (N=C). – ^{31}P NMR ($CDCl_3$): δ = 13.9. – IR: ν = 2156 cm^{-1} (N=C); 1253/1244 (P=O); 1044 (P–O). – $C_{13}H_{16}NO_3P$ (265): calcd. C 58.87, H 6.08, N 5.28, P 11.68; found C 58.65, H 6.18, N 5.26, P 11.62. – HRMS: calcd. 265.950; found 265.951. – X-ray structure (Figure 1): M_r = 265.25, monoclinic, $P2_1/c$, *a* = 7.687(1), *b* = 34.798(2), *c* = 10.725(1) A, β = 105.409(4)°, *V* = 2765.7(4) A^3, *Z* = 8, D_x = 1.274 g cm^{-3}, (Mo-K_α) = 0.71073 A, μ = 1.99 cm^{-1}, *F*(000) = 1120, *T* = 295 K, R_F = 0.059 for 3714 unique observed reflections with $I \geq 2.5\ \sigma(I)$ and 453 parameters. Two crystallographically independent molecules are present in the asymmetric unit.

Compound (2*S*,4*S*)-(–)-**1a** was prepared as described above for (±)-**1a** from (2*S*,4*S*)-(+)-**7** (3.5 g, 12.4 mmol) in 31% yield (1.0 g, 4.0 mmol), m.p. 133°C. – $[\alpha]_{578}^{20}$ = –46.4 (*c* = 0.5, $CHCl_3$). – X-ray structure (Figure 2): M_r = 265.25, monoclinic, $P2_12_12_1$, *a* = 5.646(1), *b* = 9.354(1), *c* = 25.105(1) A, *V* = 1325.9(3) A^3, *Z* = 4, D_x = 1.329 g cm^{-3}, (Mo-K_α) = 0.71073 A, μ = 2.07 cm^{-1}, *F*(000) = 560, *T* = 130 K, R_F = 0.031 for 1611 unique observed reflections with $I \geq 2.5\ \sigma(I)$ and 229 parameters. The absolute configuration is determined by refinement of the Flack parameter.

trans-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane [(2R,4S)-(–)-**1b**]: A solution of (2*S*,4*S*)-(–)-**1a** (265 mg, 1.00 mmol) and KF (25 mg, 0.4 mmol) in DMSO (4 ml) was heated at 100°C for 4 h. After cooling to room temp., H_2O (20 ml) was added and the mixture was cooled in ice. The solid was collected and dried to give 250 mg (94%) of a solid mixture of **1a** and **1b** (1:3). The mixture was separated by column chromatography (SiO_2, $CHCl_3$/hexane, 1:2) and the first fraction (R_f = 0.6) gave, after three crystallizations from hexane/Et_2O (2:1), solid (2*R*,4*S*)-**1b** (160 mg, 60%), m.p. 155°C, which was pure according to NMR. – $[\alpha]_{578}^{20}$ = –38.2 (*c* = 0.5 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 3 H, CH_3); 1.16 (s, 3 H, CH_3); 3.99 (AA′X, J_{PH} = 16 Hz, $J_{AA'}$ = 16.8 Hz, 2 H, CH_2); 4.24 (dd, J_{AB} = 11 Hz, J_{PH} = 18.8 Hz, 1 H, 6-H_{eq}); 4.71 (d, J_{AB} = 11 Hz, 1 H, 6-H_{ax}); 5.68 (dd, J_{PH} = 0.7 Hz, 1 H, 4-H); 7.36 (s, 5 H, Ar H). – ^{13}C NMR ($CDCl_3$): δ = 17.0 (CH_3); 21.0 (CH_3); 36.8 (C5); 37.7 (CH_2); 81.7 (C6); 91.9 (C4); 127.1, 128.0, 128.8, 134.9 (Ar C); 162.0 (N=C). – ^{31}P NMR ($CDCl_3$): δ = 2.3. – IR: ν = 2153 cm^{-1} (N=C); 1291/1278 (P=O).

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