(0.045 g, 45%): IR (neat) 3460, 2950, 2920, 2840, 1730, 1645, 1435, 1370, 1270, 1140, 1100, 1070, 980, 955, 915, 805, 775, 760, 730 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) major isomer $\delta$ 5.94 (d, $J$ = 3.3 Hz, 1 H), 4.93 (d, $J$ = 2.6 Hz, 1 H), 4.45–4.52 (m, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.46 (s, 3 H), 2.98 (dd, $J$ = 3.5, 7.8 Hz, 1 H), 2.83–2.90 (m, 1 H), 2.36 (br s, 1 H, OH), 2.07–2.15 (m, 1 H), 1.70–1.94 (m, 1 H), 1.56 (br s, OH); $^{13}C$ NMR ($CDCl_3$, 75 MHz) major isomer $\delta$ 172.84, 162.79, 140.92, 110.25, 100.78, 83.33, 73.93, 56.20, 52.90, 52.33, 42.30, 37.43, 32.08; HRMS $m/z$ calcd for $C_{13}H_{18}O_8$ 302.1002, found 302.1008.

**Conversion of Diol 32 to Monomesylate 33.** To a solution of diol **32** (0.035 g, 0.12 mmol) in methylene chloride (8 mL) at 0 °C was added triethylamine (0.035 g, 0.35 mmol). Methanesulfonyl chloride (3 drops) in methylene chloride (1 mL) was added dropwise at 0 °C until TLC analysis indicated that starting material had disappeared. The solution was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (elution with 80% ethyl acetate/hexanes) to give monomesylate **33** (0.031 g, 71%) as a mixture of acetal epimers: IR (neat) 3470 (br), 2960, 2840, 1730, 1650, 1440, 1370, 1280, 1180, 1150, 1110, 1075, 980, 925, 860, 810, 760 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) major isomer $\delta$ 5.90–5.91 (m, 1 H), 5.24 (dd, $J$ = 6.9, 9.4 Hz, 1 H), 4.95 (d, $J$ = 1.8 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.45 (s, 3 H), 3.05 (s, 3 H), 3.0–3.06 (m, 1 H), 2.95–3.00 (m, 1 H), 2.25 (dd, $J$ = 6.6, 9.4 Hz, 1 H), 2.12–2.23 (m, 1 H), 1.65 (m, 1 H, OH); $^{13}C$ NMR (90 MHz, $CDCl_3$) major isomer $\delta$ 171.21, 162.52, 141.06, 109.00, 100.00, 83.11, 81.25, 56.22, 53.22, 52.44, 42.35, 38.04, 37.40, 30.05; HRMS $m/z$ calcd for $C_{14}H_{20}O_{10}S$ 380.0777, found 380.0807.

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**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR spectra of **7**, **8**, **9**, **11** (major and minor isomers), **12** (major isomer), **21b** (minor isomer), **25**, and **32** (R = H) (18 pages). Ordering information is given on any current masthead page.

# Synthesis, Configuration, and Chemical Shift Correlations of Chiral 1,3,2-Oxazaphospholidin-2-ones Derived from *l*-Serine

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The reaction between (*S*)-methyl *N*-benzylserinoate and phosphorous oxychloride leads to the diastereomeric chloro-1,3,2-oxazaphospholidin-2-ones. Reaction of the chloridates with alcohols or phenols in the presence of base affords the corresponding alkoxy (or aryloxy) derivatives (66–94%), which were readily separated by standard chromatographic methods. The stereochemical arrangement of these compounds was established by NMR chemical shift correlations (carbon-13 and phosphorus-31) and single-crystal X-ray analysis. The trans geometry of the carbomethoxy and exocyclic phosphorus ligand resulted in approximately a 1 ppm upfield shift in the phosphorus-31 spectra relative to the cis isomer. The carbon-13 NMR spectra revealed an opposite trend in the heteroatom-bound alkyl region with most of the trans isomer signals appearing downfield (0.2–1.2 ppm) from the corresponding cis isomer.

## Introduction

The past two decades have witnessed explosive growth in the preparation, reactivity, and utility of the carbon-based chiral center. By comparison, our understanding of events involving the corresponding chiral phosphorus atom remains in its infancy. To a large extent, this is due to a paucity of methods available for preparing chiral phosphorus molecules. Two representative examples include (a) reaction of a racemic phosphoryl halide with a suitably substituted chiral amine,[1] separation of the diastereomeric amides, and displacement of the auxiliary by acidic alcohol solutions and (b) reaction of a phosphoryl dihalide with a bifunctional chiral auxiliary to afford cyclic diastereomers[2] capable of undergoing a series of specific displacement reactions. In the latter instance, Inch and co-workers have elegantly extended this methodology to a wide variety of substrates utilizing ephedrine, pseudoephedrine, and sugars as the chiral appendage.[3,4] Interest in chiral phosphorus molecules, in part, emanates from their known utility as insecticides and nerve gas agents where specific interactions with biomolecules may be dependent upon the configuration at phosphorus.[5,6] Despite the fact that many of these compounds contain a center of asymmetry at phosphorus, little work has been conducted to determine the contribution of the individual antipodes to the toxic event.[7] To understand better the stereochemical implications at phosphorus upon these events, it would be advantageous to construct and examine reactions of chiral phosphorus molecules appended to amino acid residues. This study outlines our preliminary approach to this problem and characterizes the stereochemistry of cyclic chiral phosphorus intermediates obtained from a suitably substituted serine derivative.

## Results and Discussion

**Synthesis.** Initially, amide (benzoyl) and sulfonamide (toluenesulfonyl) nitrogen protecting group derivatives of (*S*)-methyl serinoate were examined. Unfortunately, these derivatives could not be induced to cyclize in good conversion and mostly polymeric material was obtained. The *N*-benzyl derivative **2** was chosen owing to its structural similarity to previously reported 1,3,2-oxazaphosphorus cyclic systems prepared from ephedrine.[3] A somewhat surprising drawback to this approach was a paucity of

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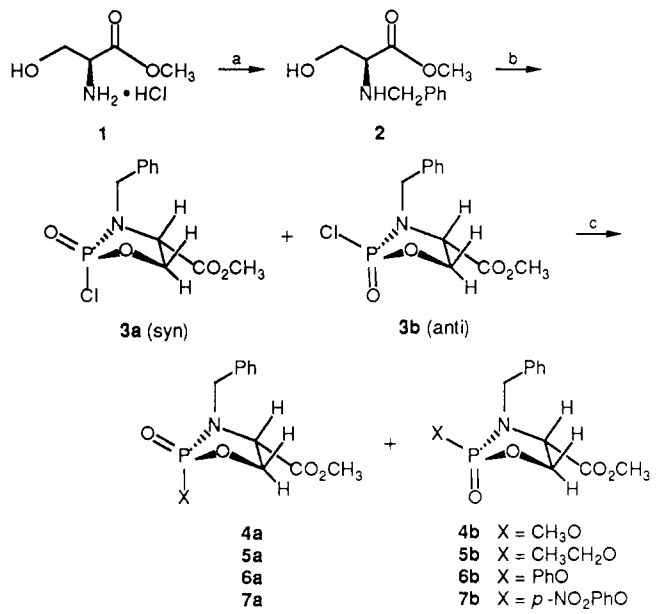
0022-3263/90/1955-0111$02.50/0 

**Scheme I. Synthesis of Chiral Oxazaphospholidin-2-ones**[a]




[a] (a) PhCHO, $Et_3N$, $NaBH_4$; (b) $POCl_3$, 200 mol % of $Et_3N$, toluene; (c) ROH, $NaHCO_3$, acetone.

methods available for the preparation of methyl *N*-benzylserinoate.[8,9] Reductive amination ($NaCNBH_3$) under acidic conditions[9] was successful but the yields on a scale greater than 20 g were low (35–50%) and, further, chromatography was required. Slight modification to a $NaBH_4$ reductive amination under basic conditions (triethylamine, benzaldehyde) worked well with yields of 66–70% after simple bulb-to-bulb distillation and of sufficient quality after the extraction to proceed to the next step.

Reaction of methyl *N*-benzylserinoate with phosphoryl chloride provided the diastereomeric 1,3,2-oxazaphospholidin-2-ones (OAP's; Scheme I) in 94% yield. The chloridates were isolated but found to be quite unstable, decomposing in about 2 days at room temperature. Refrigeration of these intermediates extends the lifetime to about a week. Crude isolation and reaction of the diastereomeric mixture of chloridates with the appropriate alcohol or phenol affords **4–7** presumably via retention of configuration at phosphorus,[2,10] although no attempt was made to characterize this transformation. These R groups were chosen to represent a variety of insecticide leaving groups. A number of variations were attempted to optimize the yield of these compounds. Implementing a one-pot, two-step synthesis of OAP's **4–7** from **2** dropped the yield considerably. Separation of the chloridate stereoisomers and subsequent esterification also led to significant decreases in yield. Esterification conditions were also examined and it was found that the reaction could proceed in either aromatic solvents with organic base or acetone with inorganic base. The use of ether solvents was also successful but yields were slightly lower. The elevated temperatures required for the acetone–sodium carbonate esterification were of concern for fear of loss of stereochemical integrity; however, no racemization was noted as compared to the other method. In summary, crude isolation of the chloridates is recommended with immediate esterification. The resultant 1,3,2-OAP esters **4–7** were chromatographed to purity, resulting in crystalline (with the exception of **5**), stable materials.

**Table I. 1,3,2-Oxazaphospholidin-2-ones Physical Data**

| compd | mp (°C) | $[\alpha]^{23}_D$[a] | $^{31}P$ (ppm) | $^{13}C$ (ppm)[b] | yield (%) |
|---|---|---|---|---|---|
| **3a** | *d* | *d* | 23.92 | 169.38 | 94 |
| **3b** | *d* | *d* | 23.68 | 169.46 | |
| **4a** | 77–78 | −26.0 (1.75) | 22.19 | 170.23 | 68[c] |
| **4b** | 64–66 | −90.2 (0.62) | 21.14 | 170.69 | |
| **5a** | oil | −23.9 (2.31) | 20.83 | 170.04 | 87[c] |
| **5b** | oil | −56.1 (1.09) | 19.89 | 170.78 | |
| **6a** | 92–94 | −29.3 (0.96) | 16.38 | 170.08 | 96[c] |
| **6b** | 83–85 | −70.2 (1.12) | 15.01 | 170.45 | |
| **7a** | 91–92 | −4.5 (1.18) | 15.85 | 169.93 | 78[c] |
| **7b** | 101–102 | −27.5 (0.94) | 14.91 | 170.12 | |

[a] (g/100 mL $CHCl_3$). [b] Carbomethoxy carbonyl. [c] Yield from **3a/3b**. [d] Not determined due to instability.

The ester OAP's were all isolated in optically active form in a near 1:1 diastereomeric ratio with the purity confirmed by high performance liquid chromatography and spectral analyses (Table I) (vide infra). This diastereomer ratio is interesting in light of many related studies reporting a clear preference for one of the cyclic isomers (i.e., exocyclic ligand pseudoaxial or pseudoequatorial relative to ring substituents).[3,4,11] In fact, a diastereomeric excess of 12:1 was used to advantage in a chiral cyclophosphamide synthesis.[12] Although we have not examined the exact nature of this balanced mixture, it is presumed that the added conformational flexibility of the serine derivative, as compared to ephedrine and pseudoephedrine, may play a major role. Fortunately for this study, this lack of stereoisomer bias was not of major concern (and indeed was an unexpected benefit as both isomers would be needed in a related study).

**Spectroscopy.** Individual stereoisomers were examined by $^1H$, $^{13}C$, and $^{31}P$[13] NMR spectroscopy in an attempt to develop trends in stereochemistry and perhaps gain insight into any conformational preferences. Cooper et al.[14] used $^1H$ NMR spectroscopy to assign the configuration of 1,3,2-oxazaphospholanes and, recently, Setzer[15] developed an elegant proton NMR analysis (coupling constants) of conformational differences among related ephedrine and pseudoephedrine OAP's. Efforts to assign completely the stereochemistry of compounds **4–7** by proton NMR were thwarted by overlapping ring and *N*-benzyl $CH_2$ coupling patterns. Moreover, the spectrum of the slow ("slow" and "fast" indicating the order of elution during flash chromatography) isomer appeared as a mixture of half-chair conformers, consistent with other reports,[16] which further complicated assignment. In most cases, the H(C-4) proton ($\delta$ = 3.9) was the only clearly resolved absorbance. In some instances, the fast (cis) isomer did not appear to be conformationally flexible (assuming the isomers prefer the half-chair conformation). This is illustrated by comparison of the Karplus proton couplings of H(C-4) of **7a** and **7b**

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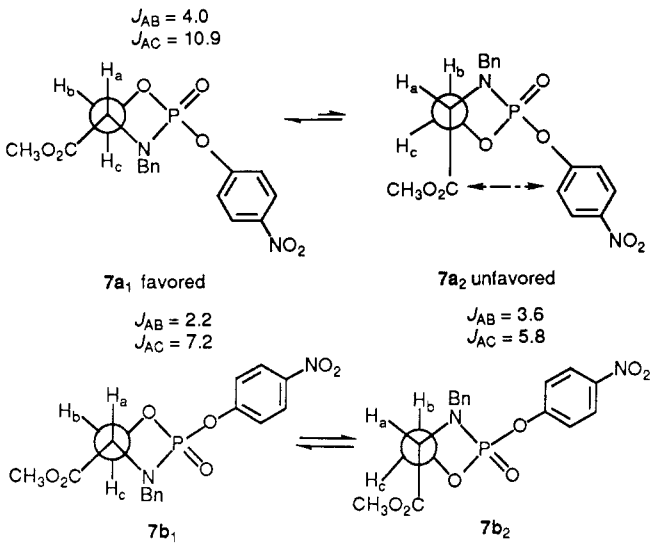
Table II. Tabulation of Alkyl $^{13}C$ Chemical Shifts

| compd | $NCH_2$- | $POCH_2$- | C-4 | $POCH_3$ | -(O)$COCH_3$ | C-5 | $POCH_2CH_3$ |
|---|---|---|---|---|---|---|---|
| **3a** | 66.60 | | 55.57 (19.1) | | 52.71 | 46.98 (5.9) | |
| **3b** | 66.85 | | 56.78 (17.8) | | 52.75 | 47.50 (3.1) | |
| **4a** | 65.38 | | 56.70 (18.6) | 54.40 (6.8) | 52.32 | 47.78 (5.8) | |
| **4b** | 65.86 | | 57.26 (17.6) | 54.75 (6.3) | 52.57 | 47.19 (6.2) | |
| **5a** | 65.27 | 63.94 (6.9) | 56.67 (18.2) | | 52.27 | 47.56 (5.3) | 16.04 (6.6) |
| **5b** | 66.12 | 64.25 (6.6) | 57.67 (17.6) | | 52.55 | 47.04 (5.9) | 16.37 (5.9) |
| **6a** | 65.63 | | 55.92 (19) | | 52.49 | 47.83 (5.6) | |
| **6b** | 66.66 | | 57.15 (17.6) | | 52.69 | 47.36 (6.1) | |
| **7a** | 66.12 | | 56.26 (18.7) | | 52.72 | 47.99 (5.7) | |
| **7b** | 66.97 | | 57.31 (18.1) | | 52.93 | 47.46 (5.5) | |

**Chart I. Newman Conformations of 7a/7b**




with the vicinally oriented ring protons (Chart I). The proton spectrum of **7a** reveals a coupling pattern that can be explained, in part, by a predominant population of the **7a**$_1$ ($J_{HaHb}$ = 4; $J_{HaHc}$ = 10.9) conformer due to buttressing of the carboxy ester and *p*-nitrophenol ligand (**7a**$_2$), which would be expected to be unfavored. By comparison, the slow isomer **7b** (trans) population appears as a mixture of conformers with distinctly different couplings to the vicinal protons. As shown by **7b**$_1$ and **7b**$_2$ there is no apparent steric interaction, suggesting an equal mixture of conformers. The disparate couplings may be accounted for by the gauche/anti orientation **7b**$_1$ and the gauche/gauche orientation **7b**$_2$. Similar proton coupling results for **5b** (2.3/7.2 and 3.3/6.4 Hz) were also noted. Unfortunately, the spectra of **4** and **6** were unsuitable for a comparative analysis.

Somewhat frustrating was the finding that the chemical shift and coupling pattern of the C-4 proton did not correlate well with the stereochemistry at phosphorus. It has been demonstrated that hydrogens cis to the phosphoryl oxygen tend to be deshielded.[17] Unfortunately, no such correlation was uncovered for the C-4 proton in compounds **4–7**. This may be due either to shielding by the nitrogen atom or insufficient P=O $\pi$ cloud interaction with this proton. Comparison of proton NMR patterns of **4–7** to the structurally similar 1,3,2-dioxaphosphorane heterocycles also proved ineffective largely due to hidden multiplicities by other resonances and contributions from the respective conformers. Part of the problem in comparative NMR evaluation presumably resides in the *N*-benzyl moiety, which may also be affecting the ring conformation. In summary, extension of literature proton NMR patterns (e.g., ephedrine/pseudoephedrine type) to compounds **4–7** are not clear cut and, at this point, we remain cautious in assigning the solution conformation of compounds **4–7**.

We attempted using the shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III)[18] in an effort to diagnose the isomers. However, no further details could be obtained, presumably owing to complexation of the reagent with the less encumbered carboxy ester moiety.

Due to these difficulties, we focused our efforts upon carbon and phosphorus NMR spectroscopy. Initial $^{13}C$ NMR inspection revealed a modest correlation ($\Delta\delta$ = 0.2–0.7) in the chemical shift of the carboxy ester carbonyl absorption (Table I) with the slow eluting isomer (trans stereochemistry) appearing slightly downfield. To our surprise, we also found some correlations existing in the heteroatom-bound alkyl region (40–70 ppm) (Table II). The methoxy (**4a**/**4b**) and ethoxy (**5a**/**5b**) exocyclic absorbencies were clearly discernable from the other common structural features. It is worthy to note that the coupling constants for the exocyclic alkoxy ligands (cases **4** and **5**) were all approximately 6–7 Hz. The four signals, due to $NCH_2Ph$, $POCH_2$ (ring), $NCHCO_2CH_3$ (ring), and $NCHCO_2CH_3$ carbons, required a proton-coupled spectrum for absolute assignment. It was initially assumed that the two coupled lines (57 and 47 ppm) were probably due to the ring carbons (following Karplus P–X–Y–C angle dependence[19]) since the methyl carboxy ester and N-benzylic carbon (conformationally flexible) would not be expected to couple to the phosphorus. The coupled spectrum (Single Frequency Off-Resonance Decoupling, 200-Hz decoupler offset: SFORD) of **7b** shows a quartet for the absorbance appearing at 52.8 ppm and a triplet at 66.5 ppm, consistent with the carboxy ester $CH_3$ moiety and benzylic carbons, respectively. More interesting is the comparative ring carbon assignment. The upfield absorbance exhibits a much smaller phosphorus coupling (approximately 6 Hz as compared to 18 Hz), which should be consistent with modified Karplus angle dependence. We once again relied upon the coupled spectrum, which reveals a doublet of doublets for the downfield absorbance and the expected triplet of doublets for the upfield line (47 ppm). These data relate the rather large coupling constant to the methine (amino acid chiral center) position, implicating an angle dependence for P–O–C5–C4 of approximately 30°.[19] The methylene ring carbon coupling of 6 Hz probably reflects either the geminal $^2J$ (PC) coupling or $^3J$ (PNCC) vicinal coupling although the latter seems unlikely. Slight modification of the Karplus angle dependence to coupling intensity is expected due to the rigid five-membered ring. These correlations are further

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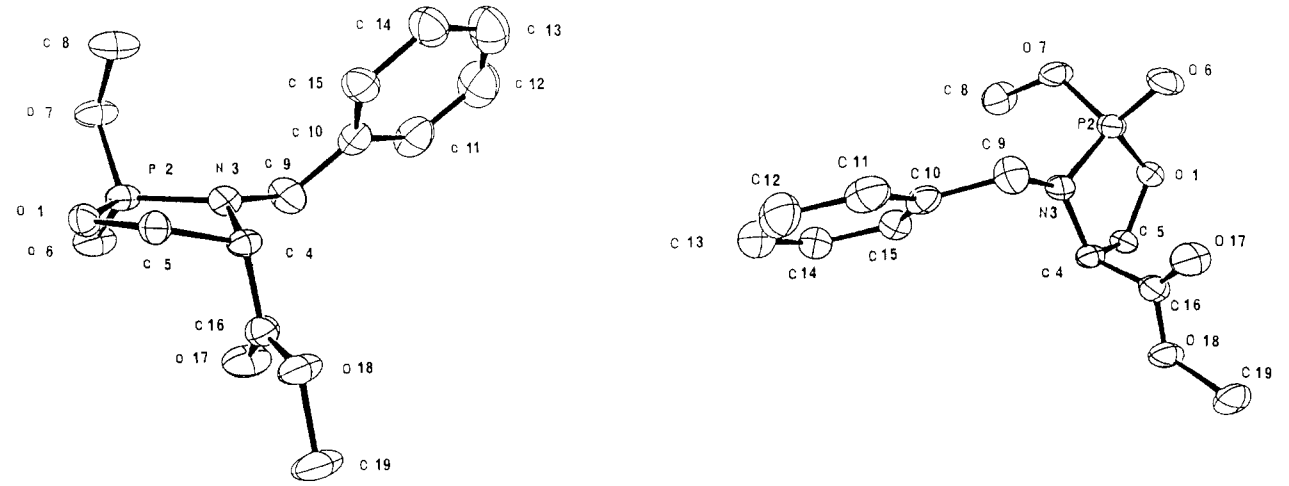


**Figure 1.** ORTEP representations of **4b**.

supported by the X-ray data (vide infra), which show the OAP ring as an envelope.

The carbon spectra for derivatives **3–7** (Table II) show some interesting correlations. In all cases, trends among the fast (**a** series: cis) and slow (**b** series: trans) were apparent. The effect of the stereoisomer orientation is aptly noted in the 1 ppm chemical shift for the benzylic and methine (C-4) carbons with the cis isomer appearing upfield. Somewhat smaller shift correlations were observed for the C-4 and carboxy ester methyl group, indicative of the diminished interaction with the phosphorus center. Interestingly, the C-5 chemical shifts were reversed with the cis isomer appearing, in general, about 0.5 ppm downfield. This feature may reflect compensation for steric compression. The C-4 chemical shift is the most distinctive and readily assigned feature of the carbon-13 spectrum. The large coupling constant and significant chemical shift downfield for the trans isomer would be expected to serve as a guide for future assignments of stereochemistry.

A more common method for establishing the stereochemical arrangement about such cyclic phosphorus heterocycles is $^{31}P$ NMR spectroscopy.[13,20] Bentrude et al.[17a] have reported when a exocyclic group on phosphorus resides in the axial position (**a** series) on cyclophosphamide-like molecules, the chemical shift is less than that in the equatorial position (i.e., $\delta$ ($^{31}P_a$) < $\delta$ ($^{31}P_e$)). Although five-membered rings are necessarily less defined conformationally, bias can be introduced by substitution at a ring carbon (e.g. **4–7**) and we can use this knowledge to assign preliminarily the absolute configuration of the two diastereomers obtained in our study. The phosphorus chemical shifts of the slow isomers **4–7** are consistently *1 ppm upfield* from those for the fast band isomer (Table I). Therefore, the slow band isomers are probably the pseudoaxial isomers while the fast correlates with the pseudoequatorial. This trend has been noted in many 2-oxo- and 2-thioxo-1,3,2-oxazaphosphorinane systems[21] as well as with 1,3,2-oxaza- and -thiazaphospholidines.[22] However, it should be noted that 1,3,2-dioxaphospholanes show only small $\Delta\delta$ values and the differences are not uniform.[23] Based upon Bentrude's work,[17a] our initial configuration assignments are as follows: the slow eluting isomer corresponds to the exocyclic alkoxy group trans to the carboxy ester moiety (**b** series) and the fast band corresponds to the ligand cis to the carboxy ester. This correlation is then inversely assigned to the C-4 alkyl carbon NMR spectral data where the slow isomers (trans) appear approximately *1 ppm downfield.* With the appropriate selection of functional group atom, these two NMR nuclei may therefore, serve to identify the stereochemistry of related systems.

**Rotation Correlations.** The rotations of the derivatives **4–7** are tabulated in Table I. In all cases, the slow (trans) isomer exhibited a much larger rotation than the corresponding fast (cis) band. In combination with the aforementioned spectral evidence, this observation is consistent with a report by Cooper[14] that the "axial" isomers of 1,3,2-oxazaphospholanes have a larger absolute rotation. Thus, the larger rotating isomer is correlated with the trans orientation of the exocyclic phosphorus ligand and the carboxy ester moiety.

**X-ray Analysis.** Isomer **4b** formed crystals suitable for single-crystal X-ray analysis.[24] Two ORTEP perspectives resulting from the data collection are shown in Figure 1. Relevant bond lengths and angles are provided in the supplementary material. A prominent feature of the crystalline structure is the five-membered ring conformation, which appears as an envelope. Another interesting feature is the N–P–O bond angle of 96.2°, which illustrates the distortion imparted by the substituents and heteroatom upon the ring system. As shown by Figure 1, and in consort with our spectral data, the slow eluting isomer corresponds to the trans configuration and the fast band with the cis.

**Conversion of 7b into 4b.** In an effort to determine that all the slow band isomers had the same relative configuration we attempted a chemical correlation study. The *p*-nitrophenoxy slow (trans) isomer **7b** was subjected to treatment with catalytic sodium methoxide in methanol.

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Monitoring the reaction by TLC and HPLC determined that **4b** was formed exclusively from **7b**. Therefore, we can conclude that the elution properties correspond to configurationally correlated structures and, as expected, this conversion occurs with retention of configuration.

**Conclusions.** The synthesis and spectral properties of a new class of 1,3,2-oxazaphospholidin-2-ones has been described. The title compounds **4–7** are readily prepared by reaction of an alcohol with the chloridate **3a/3b** derived from phosphorous oxychloride and methyl *N*-benzylserinoate (**2**). The absolute configurations were assigned on the basis of correlations in the phosphorus and carbon NMR spectroscopy in combination with single-crystal X-ray analysis of compound **4a**. The spectral and chromatographic properties were found to be consistent with the relative arrangement of the amino acid ester moiety and the exocyclic phosphorus ligand.

Some conformational preferences were uncovered for **7a/7b** in the proton NMR spectrum but comparison to related systems was ineffective. It was ascertained that the cis isomer **7a** exhibits a preferential conformation with the carbomethoxy pseudoequatorial whereas the trans isomer **7b** exists as a mixture of conformers. We are currently investigating this aspect in more detail.

## Experimental Section

**General Methods.** Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. $^1$H NMR spectra were taken in deuterated chloroform ($CDCl_3$) at 300 MHz. $^{13}$C NMR spectra were taken at 75 MHz. $^{31}$P NMR chemical shifts are relative to phosphoric acid ($H_3PO_4$ in $CDCl_3$). Infrared data were obtained in $CDCl_3$.

Analytical thin layer chromatography (TLC) was conducted with aluminum-backed silica plates (E. Merck). Visualization was accomplished with an ultraviolet lamp and/or anisaldehyde stain (a 2% solution of *o*-anisaldehyde in 95:4:1 absolute ethanol–concentrated sulfuric acid–glacial acetic acid) with heating and/or DBQ (5% 2,4-dibromoquinone 4-chloroimine) stain. Flash chromatography[25] was done on Kieselgel 60, 230–400 mesh (E. Merck).

High performance liquid chromatography (HPLC) was conducted with a variable wavelength ultraviolet detector. Reverse phase chromatography was conducted on a Regis (Morton Grove, IL) 10-$\mu$m ODS (30 cm) column utilizing a 55:45 $CH_3OH/H_2O$ solvent system at a flow rate of 1 mL/min.

All solvents and reagents were purified when necessary by standard literature methods. Air- or water-sensitive reactions were conducted under a positive argon atmosphere by utilizing standard techniques. Phosphorous oxychloride, benzaldehyde, and *l*-serine were purchased from Aldrich Chemical Co. (Milwaukee, WI).

**(*S*)-*N*-Benzylserine, Methyl Ester (2).** (*S*)-Serine methyl ester hydrochloride (10 g, 0.065 mmol) was dissolved in 50 mL of anhydrous methanol and cooled to 0 °C. Triethylamine (9.0 mL, 0.065 mmol) was added, the reaction was stirred for 10 min, and 6.6 mL of benzaldehyde (0.065 mmol) was added. The reaction mixture was stirred for 2 h, at which time sodium borohydride (4.8 g, 0.13 mmol) was added portionwise to the reaction mixture over a period of 0.5 h. The solution was partitioned between 50 mL of 20% HCl and 50 mL of diethyl ether. The organic phase was extracted twice with 20-mL portions of 20% HCl. The combined aqueous layers were washed with an additional 20-mL portion of diethyl ether and the organic layers were discarded. The aqueous layers were carefully neutralized with solid sodium carbonate and extracted three times with 20-mL portions of diethyl ether. After extraction with brine, the combined ether extracts were dried over $Na_2SO_4$ and evaporated to afford 8.76 g (66–70%) of a yellow oil. The product may be further purified by bulb-to-bulb distillation (110–120 °C, 0.1 mmHg), yielding a waxy solid upon cooling. $R_f$ = 0.28 (100% diethyl ether). $[\alpha]^{23}_D$ +36.5° (*c* 0.395, $CHCl_3$). $^1$H NMR: $\delta$ 2.42 (br s, 2 H), 3.41 (br t, $J$ = 4.8 Hz, 1 H), 3.60 (dd, $J$ = 10.3, 6.7 Hz, 1 H), 3.72 (s, 3 H), 3.75 (dd, $J$ = 10.8, 6.0 Hz, 1 H), 3.78 ($AB_q$, $J$ = 12.4 Hz, 2 H), 7.25–7.32 (m, 5 H). $^{13}$C NMR: $\delta$ 52.08, 61.82, 62.41, 76.59, 127.32, 128.24, 128.51, 139.26, 173.43.

**Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-Chloro-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (3).** (*S*)-*N*-Benzylserine, methyl ester (1 g, 4.78 mmol) was dissolved in 20 mL of distilled toluene and chilled to 0 °C. Triethylamine (TEA; 1.4 mL, 10 mmol) was added, followed by phosphorous oxychloride ($POCl_3$; 0.45 mL, 4.78 mmol). The reaction was monitored by TLC for loss of starting material. At completion, the reaction mixture was diluted with 50 mL of THF, filtered through Celite, and evaporated to yield the crude product as a mixture of diastereomers (94%). The diastereomers were separated by flash chromatography with 100% diethyl ether. [Note: this material is relatively unstable to storage and it is suggested that this compound be immediately converted to the corresponding esters]. Anal. Calcd for $C_{11}H_{13}NO_4ClP$: C, 45.61; H, 4.52; N, 4.83. Found: C, 45.72; H, 4.66; N, 4.79.

**Fast band (3a, cis):** $R_f$ = 0.38 (diethyl ether). $^1$H NMR: $\delta$ 3.75 (s, 3 H), 3.89 (ddd, $J$ = 16.5, 7.4, 4.4 Hz, 1 H), 4.25 (dd, $J$ = 14.4, $J_{HP}$ = 7.5 Hz, 1 H), 4.41–4.48 (m, 2 H), 4.59 (dd, $J$ = 14.4, $J_{HP}$ = 9.0 Hz, 1 H), 7.26–7.33 (m, 5 H). $^{13}$C NMR: $\delta$ 46.98, 52.71, 55.57, 66.60, 128.44, 128.84, 128.90, 134.52, 169.38. $^{31}$P NMR: $\delta$ 23.92.

**Slow band (3b, trans):** $R_f$ = 0.32 (diethyl ether). $^1$H NMR: $\delta$ 3.64 (s, 3 H), 3.79 (ddd, $J$ = 10.9, 7.2, 2.7 Hz, 1 H), 4.28 (dd, $J$ = 14.9, 10.3 Hz, 1 H), 4.44 (dd, $J$ = 14.5, 10.3 Hz, 1 H), 4.44 (dd, $J$ = 9.5, 2.9 Hz, 1 H), 4.56 (dd, $J$ = 9.7, 2.4 Hz, 1 H), 7.26–7.32 (m, 5 H). $^{13}$C NMR: $\delta$ 47.50, 52.75, 56.78, 66.85, 128.31, 128.72, 130.79, 134.27, 169.46. $^{31}$P NMR: $\delta$ 23.68.

**General Procedure for the Preparation of Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-Alkoxy(aryloxy)-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylates 4–7. Method A.** The alcohol (or phenol) (150 mol %) was added to a room temperature solution of methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-chloro-2-oxo-1,3,2-oxazaphospholidine-4-carboxylate (**3**) in toluene (15 mL/g of starting material) followed by the addition of TEA (100 mol %). The reaction was allowed to proceed until TLC indicated consumption of starting material (generally 1–2 h). The reaction mixture was then partitioned between ethyl ether and saturated sodium carbonate and the organic phase was washed twice with sodium carbonate, water, and brine and finally dried over sodium sulfate. The solvent was removed in vacuo to afford the crude product.

**Method B.** A 5% solution of the chloridate in anhydrous acetone was treated sequentially with 100 mol % of anhydrous sodium carbonate and 200 mol % of alcohol (phenol). The reaction was warmed to reflux until TLC indicated complete loss of starting material. The reaction mixture was then cooled, filtered through Celite, and rotary evaporated to afford the crude product, which was purified by flash chromatography. See representative examples below.

**Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-Methoxy-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (4).** Yield: 68%. The diastereomers were separated via flash chromatography using diethyl ether. Anal. Calcd for $C_{12}H_{16}NO_4P$: C, 50.53; H, 5.65; N, 4.91. Found: C, 50.54; H, 5.86; N, 4.84. IR: 1745, 1260.

**Fast band (4a, cis):** $R_f$ = 0.13 (diethyl ether). Off-white crystals developed very slowly from the oil obtained. White crystals were obtained by trituration with diethyl ether; mp = 77–78 °C; $[\alpha]^{23}_D$ –26.0° (*c* 1.75, $CHCl_3$). $^1$H NMR: $\delta$ 3.68 (s, 3 H), 3.71 (d, $J$ = 12.4 Hz, 3 H), 3.83 (dt, $J$ = 8.5, 4.5 Hz, 1 H), 4.15 (dd, $J$ = 14.5, 9.4 Hz, 1 H), 4.22–4.40 (m, 2 H), 4.42 (dd, $J$ = 14.9, 9.6 Hz, 1 H), 7.25–7.39 (m, 5 H). $^{13}$C NMR: $\delta$ 47.78, 52.32, 54.40, 56.70, 65.38, 128.08, 128.51, 128.73, 135.58, 170.62. $^{31}$P NMR: $\delta$ 22.19. HPLC: $t_R$ = 9.5 min.

**Slow band (4b, trans):** $R_f$ = 0.08 (diethyl ether). This diastereomer was recrystallized from methylene chloride/hexane; mp = 64–66 °C; $[\alpha]^{23}_D$ –90.16° (*c* 0.62, $CHCl_3$). $^1$H NMR: $\delta$ 3.72 (s, 3 H), 3.77 (d, $J$ = 11.4 Hz, 3 H), 3.74–3.78 (m, 1 H), 4.16 (dd, $J$ = 15.3, 8.6 Hz, 1 H), 4.26–4.42 (m, 2 H), 4.31 (dd, $J$ = 15.7, 8.4 Hz, 1 H), 7.28–7.32 (m, 5 H). $^{13}$C NMR: $\delta$ 47.19, 52.57, 54.75, 57.26, 65.86, 127.97, 128.25, 128.79, 135.94, 170.67. $^{31}$P NMR: $\delta$ 21.14. HPLC: $t_R$ = 8.8 min.

**Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-Ethoxy-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (5).** Yield: 87%. The

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diastereomers were separated via flash chromatography using diethyl ether. Anal. Calcd for $C_{13}H_{18}NO_5P$: C, 52.18; H, 6.06; N, 4.68. Found: C, 51.99; H, 6.29; N, 4.90. IR: 1375, 1260.

**Fast band (5a, cis)**: $R_f$ = 0.13 (diethyl ether), $[\alpha]^{23}_D$ -23.90° (c 2.31, $CHCl_3$). $^1H$ NMR: δ 1.28 (t, J = 7.1 Hz, 3 H), 3.66 (s, 3 H), 3.82 (dt, J = 8.3, 4.6 Hz, 1 H), 4.01-4.42 (m, 6 H), 7.26-7.39 (m, 5 H). $^{13}C$ NMR: δ 16.04, 47.56, 52.27, 56.67, 63.94, 67.27, 127.83, 128.47, 128.79, 135.63, 170.66. $^{31}P$ NMR: δ 20.83. HPLC: $t_R$ = 12.4 min.

**Slow band (5b, trans)**: $R_f$ = 0.09 (diethyl ether), $[\alpha]^{23}_D$ -56.06° (c 1.09, $CHCl_3$). $^1H$ NMR: δ 1.28 (t, J = 7.0 Hz, 3 H), 3.64 (s, 3 H), 3.72 (ddd, J = 10.8, 6.8, 2.8 Hz, 1 H), 4.02-4.14 (m, 2 H), 4.06 (q, J = 7.0 Hz, 2 H), 4.21-4.36 (m, 2 H), 7.25-7.31 (m, 5 H). $^{13}C$ NMR: δ 16.37, 47.04, 52.55, 57.67, 64.25, 66.12, 127.89, 128.44, 128.62, 135.98, 170.78. $^{31}P$ NMR: δ 19.89. HPLC: $t_R$ = 11.7 min.

**Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-Phenoxy-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (6).** Yield: 96%. The diastereomers were separated by flash chromatography utilizing petroleum ether/ethyl acetate as the eluent. Anal. Calcd for $C_{17}H_{18}NO_4P$: C, 58.79; H, 5.22; N, 4.03. Found: C, 58.75; H, 5.29; N, 4.01. IR: 1745, 1275.

**Fast band (6a, cis)**: $R_f$ = 0.29 (diethyl ether). This diastereomer crystallized as white plates from ethyl acetate/petroleum ether; mp = 92-94 °C, $[\alpha]^{23}_D$ -29.27° (c 0.96, $CHCl_3$). $^1H$ NMR: δ 3.58 (s, 3 H), 3.80 (ddd, J = 9.3, 8.3, 4.7 Hz, 1 H), 4.21-4.40 (m, 3 H), 4.56 (dd, J = 14.5, 8.9 Hz, 1 H), 7.31-7.41 (m, 10 H). $^{13}C$ NMR: δ 47.83, 52.49, 55.92, 65.63, 120.92, 125.12, 128.20, 128.72, 128.91, 129.38, 135.29, 150.68 (d, J = 8.7), 170.06. $^{31}P$ NMR: δ 16.38. HPLC: $t_R$ = 24.4 min.

**Slow band (6b, trans)**: $R_f$ = 0.22 (diethyl ether). This diastereomer recrystallized as needles from methylene chloride/ether/petroleum ether; mp = 83-85 °C, $[\alpha]^{23}_D$ -70.22° (c 1.12, $CHCl_3$). $^1H$ NMR: δ 3.70 (s, 3 H), 3.82 (ddd, J = 12.1, 7.4, 2.0 Hz, 1 H), 4.30 (dd, J = 15.6, 8.1 Hz, 1 H), 4.33-4.49 (m, 2 H), 4.52 (dd, J = 15.1, 7.9 Hz, 1 H), 7.14-7.33 (m, 10 H). $^{13}C$ NMR: δ 47.36, 52.69, 57.15, 66.66, 120.27, 125.05, 128.08, 128.58, 128.74, 129.69, 135.55, 151.06 (d, J = 8.1), 170.43. $^{31}P$ NMR: δ 15.01. HPLC: $t_R$ = 23.6 min.

**Methyl (2*S*,4*S*)- and (2*R*,4*S*)-2-(4-Nitrophenoxy)-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (7).** Yield: 78%. The diastereomers were separated via flash chromatography using a gradient from 70:30 diethyl ether–petroleum ether to 100% diethyl ether. Recrystallization was accomplished with methylene chloride/diethyl ether/petroleum ether. Anal. Calcd for $C_{17}H_{17}N_2O_7P$: C, 52.05; H, 4.37; N, 7.10. Found: C, 51.94; H, 4.34; N, 7.10. IR: 1750, 1280.

**Fast band (7a, cis)**: $R_f$ = 0.35 (diethyl ether), $[\alpha]^{23}_D$ -4.49° (c 1.18, $CHCl_3$), mp = 91-92 °C. $^1H$ NMR: δ 3.70 (s, 3 H), 3.91 (ddd, J = 11.0, 8.1, 4.6 Hz, 1 H), 4.23 (dd, J = 14.4, 9.0 Hz, 1 H), 4.30-4.49 (m, 2 H), 4.51 (dd, J = 14.5, 9.8 Hz, 1 H), 7.27-7.36 (m, 7 H), 8.20 (d, J = 7.4 Hz, 2 H). $^{13}C$ NMR: δ 47.99, 52.72, 56.26, 66.12, 121.41, 125.49, 128.41, 128.87, 128.93, 134.91, 155.74 (d, J = 7.3), 169.93. $^{31}P$ NMR: δ 15.85. HPLC: $t_R$ = 28.9 min.

**Slow band (7b, trans)**: $R_f$ = 0.20 (diethyl ether), $[\alpha]^{23}_D$ -27.45° (c 0.94, $CHCl_3$), mp = 101-102 °C. $^1H$ NMR: δ 3.76 (s, 3 H), 3.92 (ddd, J = 12.5, 6.5, 2.9 Hz, 1 H), 4.28 (dd, J = 15.1, 9.9 Hz, 1 H), 4.43-4.53 (m, 2 H), 4.52 (dd, J = 14.6, 7.9 Hz, 1 H), 7.26-7.38 (m, 7 H), 8.19 (d, J = 9.2 Hz, 2 H). $^{13}C$ NMR: δ 47.46, 52.93, 57.31, 66.97, 120.76, 120.83, 125.57, 128.53, 128.90, 135.18, 155.99 (d, J = 7.4), 170.12. $^{31}P$ NMR: δ 14.91. HPLC: $t_R$ = 24.6 min.

**Conversion of 2-(*p*-Nitrophenoxy)- (7b) into Methyl (2*S*,4*S*)-2-Methoxy-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carbxoylate (4b).** The starting phosphorus ester (**7b**; 0.196 g, 0.5 mmol) was dissolved in 10 mL of anhydrous methanol and chilled to 0 °C. A catalytic amount (5 mg) of sodium methoxide was added and the reaction was warmed to room temperature, stirred, and monitored by TLC and HPLC for loss of starting material and appearance of product.

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**Registry No.** 1, 5680-80-8; 2, 123639-56-5; **3a**, 123621-73-8; **3b**, 123672-99-1; **4a**, 123621-74-9; **4b**, 123673-00-7; **5a**, 123621-75-0; **5b**, 123673-01-8; **6a**, 123621-76-1; **6b**, 123673-02-9; **7a**, 123621-77-2; **7b**, 123673-03-0; $^{31}P$, 7723-14-0.

**Supplementary Material Available:** Tables of bond angles and bond lengths of **4b** and details of X-ray analysis for **4b** (3 pages). Ordering information is given on any current masthead page.

# Application of the Dibenzoate Chirality Method To Determine the Absolute Configuration of Glycerols and Related Acyclic Alcohols

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Circular dichroism (CD) and nuclear magnetic resonance spectroscopy (NMR) were applied to the study of various chiral 1,2- (or 2,3)-di-*O*-benzoyl-*sn*-glycerols (substituent at *sn*-C1 or -C3 = cetyloxy, OBn, OMe, hexadecanoyloxy, OAc, penta-*O*-acetyl-β-D-glucopyranosyl, H, $N_3$, Br, OTs, and $OSi(Me)_2{}^tBu$). All compounds gave positive or negative exciton couplet (CD) peaks, reflecting the absolute configuration at C2 and conformational preference about the vicinal di-*O*-benzoates. The results were confirmed by conformational analyses using $^1H$ NMR spectroscopy and led to the proposal of a new method to determine the absolute configuration of asymmetric glycerols.

Glycerol constitutes the backbone of glycerolipids. It has a symmetrical plane centered at C2 and, therefore, is achiral and optically inactive. In biological reactions, however, the prochiral positions at C1 and C3 are differentiated, giving optically active glycerolipids or other natural products.[1] Determination of their absolute con-

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