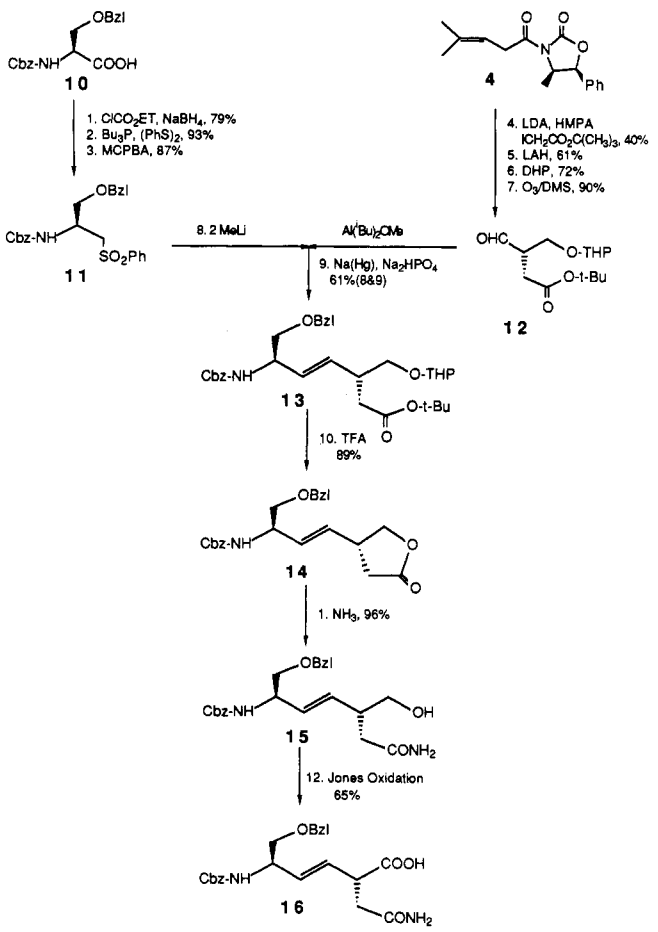
Scheme II. SerAsn *trans*-Alkene Isostere



m, C*H*$(CH_2)_2$), 4.88 (2 H, s, CH_2Ph), 5.95 (1 H, m, NCHAr_2), 6.84, 7.10 (8 H, m, 2 ArOCH_3), 7.36 (6 H, m, *Ph*CH_2, NH), 7.55–7.83 (5 H, m, SO_2Ph), 8.71 (1 H, d, NH). FAB mass spectrum: (M + 1)$^+$ = 603.

Aldehyde 6. Oxazolidinone **4** was alkylated, reduced with lithium aluminum hydride, protected as the THP ether, and ozonolyzed as previously described[2] to give **6**. Successful alkylation required the use of isopropyl triflate and the addition of 1 equiv of HMPA. The isopropyl triflate was prepared according to Beard et al.[7] Purification on short-path chromatography, eluting with EtOAc–hexane (1:9), gave the product as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.01 (6 H, dd, 2 CH_3), 1.41–1.94 (7 H, s, $(CH_2)_3$, C*H*$(CH_3)_2$), 2.40 (1 H, m, C*H*CHO), 3.30–3.95 (4 H, m, 2 CH_2O), 4.61 (1 H, m, OCHO), 9.74 (1 H, m, CHO). FAB mass spectrum: (M + 1)$^+$ = 201.

***trans*-Alkene 8.** A suspension of 0.482 g (0.8 mmol) of **5** in 5 mL of THF at −78 °C was treated with 1.7 mL (2.4 mmol) of 1.4 M MeLi in hexane to form the trianion of **5**. The temperature was raised to −20 °C whereupon the sulfone went into solution; additional cooling was then applied until the temperature returned to −78 °C. In a separate flask, 0.159 g (0.8 mmol) of **6** in 2 mL of THF at −78 °C was treated with 0.7 mmol of diisobutylaluminum methoxide and then cannulated into the solution containing the trianion. The reaction mixture was stirred for 1 h at −78 °C and the solution allowed to warm to room temperature overnight. The reaction was quenched and saturated aqueous NH_4Cl and the product extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. The hydroxy sulfone **7** was purified on short-path chromatography, eluting with EtOAc–hexane (1:1). To the hydroxy sulfone dissolved in 6 mL of MeOH at 0 °C was added 0.5 g (3 mmol) of disodium hydrogen phosphate followed by 5 g (10 mmol) of 5% sodium amalgam. The mixture was stirred for 2 h, diluted with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on short-path chromatography, eluting with EtOAc–hexane (1:1), gave the diastereomeric mixture as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.75–1.91 (6 H, dd, 2 CH_3), 1.41–1.94 (7 H, s, $(CH_2)_3$, C*H*$(CH_3)_2$), 2.10 (1 H, m, C*H*CH_2O), 3.22–3.90 (4 H, m, 2 CH_2), 3.78 (6 H, s, 2 OCH_3), 4.50 (2 H, m, NC*H*CH=, OCHO), 5.04 (2 H, s, CH_2Ph), 5.51 (2 H, m, CH=CH), 5.85 (1 H, m, NH), 6.10 (1 H, m, NCHAr_2), 6.21 (1 H, m, NH), 6.78–7.15 (8 H, m, 2 *Ar*OCH_3), 7.32 (5 H, s, Ph). FAB mass spectrum: (M + 1)$^+$ = 645.

AsnVal *trans*-Alkene[8] Isostere 9. In 5 mL of MeOH, 0.115 g (0.2 mmol) of **8** was stirred with 0.010 g (0.04 mmol) of pyridinium *p*-toluenesulfonate overnight and then the solvent removed in vacuo. The residue was dissolved in 15 mL of acetone, cooled to 0 °C, and treated with 6 mL of 1.92 M Jones reagent. After stirring for 2 h, 100 mL of both saturated aqueous NaCl and Et_2O were added, and the organic layer was washed with additional aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo, to give a clear oil product. ^{1}H NMR ($CDCl_3$): δ 0.77–1.00 (6 H, dd, 2 CH_3), 1.90–2.11 (1 H, m, C*H*$(CH_3)_2$), 2.45–2.75 (3 H, m, CH_2CON, C*H*COOH), 3.80 (6 H, s, 2 OCH_3), 4.50 (1 H, m, NC*H*CH=), 5.05 (2 H, s, CH_2Ph), 5.55–5.74 (2 H, m, CH=CH), 6.08 (1 H, m, NCHAr_2), 6.35 (1 H, m, NH), 6.84–7.11 (8 H, m, 2 *Ar*OCH_3), 7.34 (6 H, m, Ph, NH). FAB mass spectrum: (M + 1)$^+$ = 575.

Lactone 14. The intermediate **13** was obtained similarly as described above, with the exception that the intermediate hydroxy sulfone was not isolated. In 20 mL of CH_2Cl_2, 0.35 g (0.9 mmol) of this tetraprotected *trans*-alkene **13** was treated with 0.5 mL of TFA. After 2 h, the solvent was removed in vacuo. Purification by short-path chromatography, eluting with EtOAc–hexane (1:1), gave the product as an oil. ^{1}H NMR ($CDCl_3$): δ 2.32, 2.65 (2 H, dd, CH_2CO_2 of lactone), 3.20 (1 H, m, CH of lactone), 3.52 (2 H, m, CH_2OBzl), 3.95 (1 H, m, NCH), 4.30–4.45 (2 H, m, CH_2O of lactone), 4.51 (2 H, d, CH_2OCH_2Ph), 5.10 (2 H, s, PhCH_2OCO), 5.20 (1 H, d, NH), 5.61 (2 H, m, CH=CH), 7.26–7.41 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 396.

Alcohol 15. To 0.150 g of **14** was added 5 mL of MeOH saturated with gaseous ammonia. Stirring for 12 h at room temperature yielded the product as a clear oil which needed no further purification. ^{1}H NMR ($CDCl_3$): δ 2.31 (2 H, m, CH_2CON), 3.12 (1 H, m, C*H*CH_2OH), 3.54 (4 H, m, CH_2OBzl, C*H*$_2$OH), 4.30 (1 H, m, NCH), 4.48 (H, d, *J* = 14 Hz, OCH_2Ph), 4.52 (H, d, *J* = 14 Hz, OCH_2Ph), 5.11 (2 H, s, CH_2OCO), 5.35 (3 H, m, 3 NH), 5.59 (2 H, m, CH=CH), 7.36 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 413.

SerAsn *trans*-Alkene[8] Isostere 16. The isostere **16** was prepared by the oxidation of **15** to the acid as described for the preparation of **9** and was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.22–2.70 (2 H, m, CH_2CON), 3.51 (3 H, m, C*H*CO_2H, CH_2OBzl), 4.33 (1 H, m, NCH), 4.49 (2 H, dd, OCH_2Ph), 5.09 (2 H, s, CH_2OCO), 5.43 (3 H, m, 3 NH), 5.71 (2 H, m, CH=CH), 7.30 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 427.

(7) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3073.

(8) Trans stereochemistry in these highly functionalized dipeptide isosteres was confirmed after their incorporation into pentapeptide target molecules. ^{1}H NMR spectra recorded at 400 MHz in DMSO-d_6 and MeOH-d_4 gave vicinal coupling constants of the olefinic protons measured as *J* = 10–14 Hz, consistent with the desired stereochemistry.

Synthesis and Novel Properties of *N*-Phosphoryl Peptides

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Introduction

Since N-phosphorylated proteins and amino acids play important roles in the regulation of enzyme activity, protein biosynthesis, etc.,[1,2] it is of great significance for us

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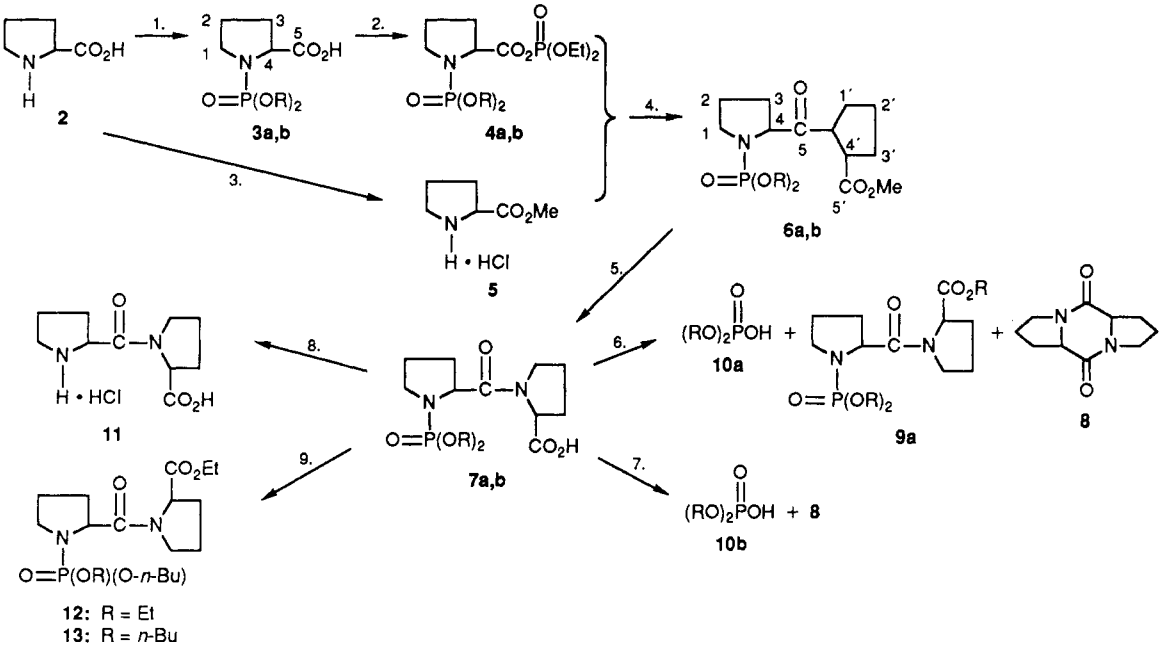
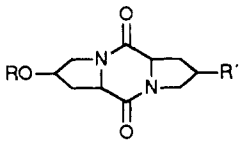
Scheme I[a]



[a] (1) $(RO)_2P(O)H$, CCl_4, Et_3N, $EtOH/H_2O$; (2, 4) $(EtO)_2P(O)H$, CCl_4, Et_3N, CH_2Cl_2; (3) MeOH, $SOCl_2$; (5) LiOH, $THF/MeOH/H_2O$ (3:1:1); (6) *n*-BuOH, 105–110 °C; (7) toluene, 105–110 °C; (8) HCl, −5 to 0 °C; (9) EtOH, 20 °C, 10 days; **a**, R = $C_\alpha H_2C_\beta H_2C_\gamma H_2C_\delta H_3$; **b**, R = $C_\alpha H(C_\beta H_3)_2$.

to study the chemical properties of the phosphoryl group in the phosphorylated amino acids. In addition, many of the peptide antibiotics discovered so far belong to the class of cyclic peptides, and few methods for their synthesis are known.[3] The simplest cyclic dipeptide is 2,5-dioxopiperazine. Both natural product and artificially synthesized analogues of this compound are known.[4] For instance, 2,5-dioxopiperazine derivative **1** was prepared by the reaction of proline with proline derivatives in $(CH_2O)_2$ at 180 °C for 3 h in 40% yield[5] or by the hydrogenation of 4-alkoxy-*N*-carbobenzoxyproline benzyl ester as trace product.[6] Our interest in this aspect prompted us to synthesize the N-phosphorylated dipeptide **7** and to investigate its chemical reactivity, seeking a new synthetic route to cyclic dipeptides.



1

R = Et, R′ = OEt; R = H, Me, $PhCH_2$, Ac, R′ = H

Results and Discussion

The synthetic route to *N*-phosphoryl dipeptide **6** is described in Scheme I. N-Protected amino acid **3** was reacted with diethyl phosphite and carbon tetrachloride to form the mixed anhydride **4**[7] followed by the nucleophilic substitution reaction of the amino acid ester **5** to give the dipeptide ester **6** in 70% yield under mild conditions. No reaction took place if dibutyl phosphite was used instead of diethyl phosphite. The optimum amount of diethyl phosphite was 1.05 equiv. Excess reagent led to formation of N-phosphorylated amino acid ester and decreased the yield of **6**. The reaction temperature must be maintained at −10 to −5 °C. Regarding the hydrolysis of the dipeptide ester **6**, we found that the best yield, 76%, was obtained when lithium hydroxide was used in a mixture of tetrahydrofuran/methanol/water (3:1:1) at 60 °C for 5 h (Table I). Dry hydrogen chloride was used for the dephosphorylation of *N*-phosphoryl dipeptide **7** below 0 °C in 71% yield.

Table I. Hydrolysis of Dipeptide Ester 6

base (mol)	time, h	temp, °C	solvent	yield, %
KOH (1)	48	20	H_2O	30
	10	60	THF/H_2O (1:1)	44
NaOH (1)	48	20	H_2O	30
	10	60	THF/H_2O (1:1)	38
KOH (3)	48	20	H_2O	50
	10	60	THF/H_2O (1:1)	69
LiOH (3)	5	20	$THF/MeOH/H_2O$ (3:1:1)	70
	5	60	$THF/MeOH/H_2O$ (3:1:1)	76

As the ^1H NMR and EI high-resolution MS indicated, ester exchange reaction on the phosphorus atom and esterification occurred when *N*-phosphoryl dipeptide **7a** was dissolved in ethanol at the ambient temperature for about 10 days to yield the compounds **12** and **13**. No obvious change occurred when the *N*-phosphoryl dipeptide **7a** was heated below 60 °C in toluene. When the compound **7a** was stirred in butanol and **7b** in toluene, respectively, at 105–110 °C for 6 h, a tricyclic fused compound **8** was formed in 42–48% yields. As in butanol, in addition to the formation of compound **8**, a second product, *N*-[*N*′-[bis(butyloxy)phosphinyl]prolyl]proline butyl ester **9**, was also isolated in 28% yield.

The formation of compounds **8–10**, **12**, and **13** might be explained by the self-activation of compounds **7a,b** via the pentacoordinate phosphorus intermediate **14** with an

(1) Cohen, P., Ed. *Recently Discovered Systems of Enzyme Regulation by Reversible Phosphorylation*; Elsevier/North Holland: New York, 1980.
(2) Rosen, O. M.; Krebs, E. G. *Protein Phosphorylation*; Cold Spring Harbor Laboratory: Cold Spring Harbor, NY, 1981.
(3) Kopple, K. D. *J. Pharm. Sci.* **1972**, *61*(9), 1345.
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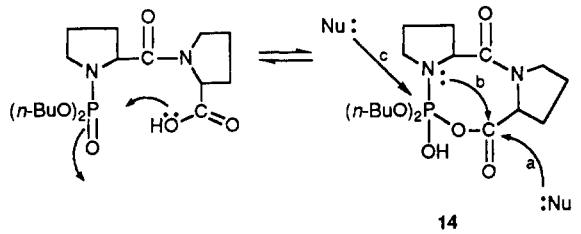
(5) Zoki, N. Pharmaceutical Co. Ltd. Jpn. Kokai Tokkyo Koho JP, 5993, 081, 1962.
(6) Magerlein, B. J. U.S. Patent 3.282, 917, 1966.
(7) Ji, G. J.; Xue, C. B.; Zeng, J. N.; Li, L. P.; Chai, W. G.; Zhao, Y. F. *Synthesis* **1988**, 444.

Table II. ^{31}P NMR, IR, and ^{13}C NMR Spectral Data and Specific Rotation of Compounds 3a and 6–10

compd	^{31}P NMR:[a] δ, ppm	$[\alpha]^{20}_D$ (c = 0.1 $CHCl_3$)	IR: ν, cm^{-1} O=CN	IR: ν, cm^{-1} O=CO	^{13}C NMR ($CDCl_3$): δ (J, Hz)[b] C-α	C-β	C-γ	C-δ	C-1 C-4	C-2 C-3	C-1′ C-4′	C-2′ C-3′	C-5	C-5′
3a	6.18	−100		1720	78.2 (8.9)	31.8 (4.0)	18.5	13.3	46.4 (4.4) 66.1 (6.0)	24.7 (8.8) 30.6 (8.8)				175.0
6a	5.91	−84	1640	1730	78.4 (8.0)	59.4 (5.9)	18.1	12.9	64.8 (8.8) 65.3 (4.4)	31.7 (5.6) 29.9 (8.8)	58.3 57.9	28.0 31.2	171.9 (4.4)	169.1
7a	6.72	−117	1620	1690	65.8 (5.9)	59.4 (7.3)	19.9	12.7	61.9 (4.4) 59.4 (7.3)	31.7 (7.3) 30.6 (8.8)	58.3 52.9	29.9 27.9	174.8 (6.7)	172.0
7b	6.72	−115	1650	1720	76.0 (8.0)	14.2 (4.0)			63.2 (5.1) 60.3 (6.5)	30.6 (6.1) 31.0 (7.0)	59.4 57.8	28.4 30.8	173.7 (4.5)	174.9
8		−165	1660								60.7 53.6	27.8 23.4	175.2	
9a	6.36	−80	1650	1735	67.2 (5.8)	65.9 (4.4)	18.9	13.5	65.5 (6.4) 58.8 (4.4)	32.4 (7.4) 30.3 (5.9)	58.6 56.5	28.6 25.3	172.1 (4.6)	171.5
10a	−1.76				69.2 (5.9)	66.3 (4.4)	19.2	13.7						

[a] ^{31}P NMR spectra were measured in $CDCl_3$ with 85% H_3PO_4 as external reference. [b] For the number on the carbons, see Scheme I. The coupling constant of the carbon as split by the phosphorus atom is given in hertz in parentheses.

Scheme II



14

eight-membered ring. A nucleophile might attack the carbonyl carbon or phosphorus atom through either one of the paths a, b, or c to give the products respectively (Schemes I and II). Studies on the mechanisms of the reaction in more detail are in progress in our laboratory.

Conclusion

Our investigation found that *N*-alkoxyphosphinyl dipeptide **7** was a promising precursor for the synthesis of octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione. Compound **7** possesses novel chemical properties such as the ester exchanging on the phosphorus atom and the self-esterification which might have some implication for the biochemical properties of the phosphorylated protein and peptides. Development of this reaction may provide a method for the synthesis of cyclic peptides.

Experimental Section

Methods. ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a JEOL FX-100 spectrometer. Chemical shifts of ^1H NMR are reported in parts per million relative to internal tetramethylsilane (0.00 ppm). Optical rotations were measured with a WZZ polarimeter made by Shanghai Optical Company, China. Positive-ion FAB-MS data and FAB high-resolution mass spectral (FABHRMS) data were obtained on a KYKY Zhp-5 double-focusing mass spectrometer from Scientific Instrument Factory, Beijing, China, equipped with a standard KYKY fast-atom gun. IR spectra were measured as KBr plates or film on NaCl on a Shimadzu 430 spectrometer. Electron-impact high-resolution mass spectra (EIHRMS) were taken on an AEI-50 spectrometer. Column chromatography was performed on 10–40-μm silica gel under 0.8 atm of nitrogen (N_2), and preparative thin-layer chromatography used 10–40-μm silica gel, containing $CaSO_4 \cdot {}^1/_2H_2O$ binder. Both kinds of silica gel were made in the Ocean Chemical Factory, Qingdao, China. Elemental analyses were performed by the Analytical Laboratory, Institute of Chemistry, Academia Sinica, Beijing, China.

Preparation of *N*-(Dialkoxyphosphinyl)proline 3. General Procedure. To an ice-salt-cold solution of proline (1.0 g, 8.7 mmol) in Et_3N (3.1 mL, 22 mmol), H_2O (1.5 mL), and EtOH (1.0 mL) was added dropwise a mixture of dibutyl phosphite (9.0 mmol) and CCl_4 (2.0 mL, 21.1 mmol), and the mixture was stirred at 0 °C for 13–14 h. The reaction mixture was diluted with water (10.0 mL), and the organic solvent was removed by distillation in vacuo. The aqueous phase was washed with EtOAc (2 × 10 mL), acidified to pH 3 with dilute HCl, and then extracted with EtOAc (5 × 10 mL). The combined extracts were washed with 10% citric acid (3 × 5 mL) and saturated aqueous NaCl (3 × 5 mL) respectively, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using 50% MeOH/CH_2Cl_2 as gradient eluent afforded **3a** (2.1 g, 78.6%) as a colorless viscous oil, which solidified on standing below −10 °C. **3a**: ^1H NMR 0.9–1.0 (CH_3, t, 6 H), 1.0–2.2 (CH_2CH_2, m, 12 H), 3.1–3.3 (NCH, NCH_2, M, 3 H), 3.9–4.2 (OCH_2, m, 4 H), 11.4 (OH, s, 1 H). Anal. Calcd for $C_{13}H_{26}NO_5P$: C, 50.81; H, 8.47; N, 4.56. Found: C, 50.68; H, 8.42; N, 4.58.

Proline methyl ester hydrochloride (**5**) was prepared from methanol and thionyl chloride by the method of Gruttmann,[8] in 78% yield.

Preparation of *N*-[*N*′-(Dialkoxyphosphinyl)prolyl]proline Methyl Ester 6. To a stirred solution of *N*-[bis(butyloxy)-phosphinyl]proline (**3a**) (1.0 g, 3.3 mmol) in CH_2Cl_2 (20 mL) at −10 °C was added Et_3N (1.1 mL, 8.2 mmol). A solution of diethyl phosphite (0.44 mL, 3.4 mmol) and CCl_4 (0.95 mL, 9.8 mmol) was added dropwise within 30 min. The mixture was stirred below 0 °C for 8–10 h, and proline methyl ester hydrochloride (**5**) (0.54 g, 3.3 mmol), which was neutralized with excess Et_3N, was added and stirred at 0 °C for 6 h. The resultant mixture was washed with 10% citric acid (3 × 5 mL), saturated $NaHCO_3$ solution (3 × 5 mL), and H_2O (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel using EtOH/EtOAc (3:1) as eluent to afford **6a** (1.0 g, 73.5%) as a colorless oil. **6a**: ^1H

(8) Guttmann, S. T. *Helv. Chim. Acta* **1961**, *44*, 721.

NMR 0.8–1.1 (CH_3, t, 6 H), 3.1–4.0 (NCH, NCH_2, m, 6 H), 1.2–2.2 (CH_2CH_2, m, 16 H), 3.7 (OCH_3, s, 3 H), 3.8–4.6 (OCH_2, m, 4 H); EIHRMS, m/z 418.223 92 ($C_{19}H_{35}N_2O_6P$ requires 418.223 23). Anal. Calcd for $C_{19}H_{35}N_2O_6P$: C, 54.55; H, 8.37; N, 6.70. Found: C, 54.50; H, 8.41; N, 6.63.

Preparation of *N*-[*N'*-[Bis(butyloxy)phosphinyl]prolyl]proline 7. Preparation of 7a as the General Procedure. Lithium hydroxide monohydrate (0.30 g, 2.4 mmol, 3.0 equiv) was added to a solution of **6a** (1.0 g, 2.4 mmol) in 3 mL of THF/MeOH/H_2O (3:1:1) at 20 °C, the resulting reaction mixture was stirred at 60 °C for 5 h, then water (3 mL) was added, and the organic solvent was removed with a rotary evaporator. The aqueous phase was washed with EtOAc (2 × 3 mL), then acidified to pH 3 with 10% aqueous HCl (3 mL) under ice-cold-bath conditions, and extracted with EtOAc (5 × 15 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using ethanol/petroleum ether/HOAc (15:50:1) as eluent afforded **7a** (0.74 g, 76.3%) as a colorless oil. **7a**: ^1H NMR 0.6–1.0 (CH_3, t, 6 H), 1.1–2.2 (CH_2CH_2, m, 16 H), 2.9–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.5 (OCH_2, m, 4 H), 10.7 (CO_2H, s, 1 H). **7b**: ^1H NMR 1.1–1.4 (CH_3, d, 6 H), 1.9–2.3 (CH_2CH_2, m, 8 H), 3.0–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.4 (OCH_2, m, 4 H), 9.5 (CO_2H, s, 1 H). **7a**: EIHRMS, m/z 404.207 ($C_{18}H_{33}N_2O_6P$ requires 404.208), 262.156 68 ($C_{12}H_{25}NO_3P$ requires 262.157 18), 206.0946 ($C_6H_{17}NO_3P$ requires 206.094 58), 150.031 78 ($C_4H_9NO_3P$ requires 150.031 98).

Preparation of *N*-Prolylproline Hydrochloride (11). A solution of 1.0 g (2.48 mmol) of **7a** in 30 mL of dry Et_2O was saturated with dried HCl(g) below 0 °C. After being kept overnight at 0 °C, the precipitate was filtered and washed with petroleum ether. The crude product was recrystallized from ethanol/ethyl ether (1:2), giving colorless needles: mp 89–91 °C[9] (0.44 g, 71%); ^1H NMR (D_2O) 0.8–1.3 (CH_2CH_2, m, 8 H), 2.2–4.1 (NCH, NCH_2, m, 6 H); IR $\nu_{C(O)OH}$ 1735, $\nu_{C(O)N}$ 1665 cm^{-1}.

Thermolysis of *N*-[*N'*-(Dialkoxyphosphinyl)prolyl]proline 7. A solution of **7a** (1.69 g, 4.18 mmol), in 10 mL of 1-butanol was stirred at 105–110 °C for 6 h. After removal of the solvent by distillation in vacuo, an oily residue was obtained. Column chromatography on silica gel using ethanol/petroleum ether/HOAc (15:50:1) as gradient eluent afforded **10a** (0.22 g, 25%) as a colorless oil, compound **8** (0.34 g, 42%) as a crystalline solid, which was recrystallized from CH_2Cl_2/petroleum ether (1:3), giving colorless crystals, mp 142–143 °C,[10] and **9** (0.55 g, 28.6%) as a colorless oil. ^1H NMR 0.8–1.3 (CH_3, t, 6 H), 1.4–1.6 (CH_2CH_2, m, 8 H), 2.0 (OH, s, 1 H), 3.9–4.1 (OCH_2, m, 4 H). **8**: ^1H NMR 1.9–2.3 (CH_2CH_2, m, 8 H), 3.4–3.6 (NCH, NCH_2, m, 6 H); EIHRMS, m/z 194.104 88 ($C_{10}H_{14}N_2O_2$ requires 194.105 50). **9**: ^1H NMR 0.7–1.0 (CH_3, t, 9 H), 1.1–2.1 (CH_2CH_2, m, 20 H), 3.0–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.3 (OCH_2, m, 6 H); FABHRMS, m/z 460.2706 ($C_{22}H_{42}N_2O_6P$ requires 460.2703). The thermolysis of **7b** was carried out in a similar manner as described above, using toluene as solvent instead of 1-butanol. Isolation by preparative TLC using EtOH/petroleum ether/HOAc (15:50:1) as eluent afforded **10b** (0.25 g, 48.7%): ^1H NMR 0.8–1.4 (CH_3, d, 12 H), 3.8–4.2 (CH, m, 2 H), 2.5 (OH, s, 1 H). There was no analogue of **9** formed.

Ester Exchange Reaction of *N*-[*N'*-[Bis(butyloxy)phosphinyl]prolyl]proline (7a). A solution of **7a** (0.5 g, 1.23 mmol) in 10 mL of ethanol was stood at room temperature (20 °C) for about 10 days. Several products were formed as checked by TLC. After removal of the solvent, a light yellowish oil was obtained. **12**: EIHRMS, m/z 404.207 ($C_{18}H_{33}N_2O_6P$ requires 404.208). **13**: EIHRMS, m/z 432.238 ($C_{20}H_{37}N_2O_6P$ requires 432.239).

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Registry No. **2**, 147-85-3; **3a**, 121252-81-1; **5**, 2133-40-6; **6a**, 121252-82-2; **7a**, 121252-83-3; **7b**, 121252-87-7; **8**, 19943-27-2; **9a**, 121252-84-4; **10a**, 107-66-4; **10b**, 1611-31-0; **11**, 76932-06-4; **12**, 121252-85-5; **13**, 121252-86-6; $(BuO)_2P(O)H$, 1809-19-4.

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Synthesis and Structure of 2α-Hydroxytropan-3-one

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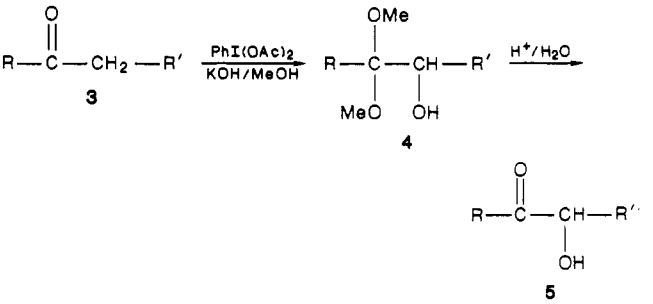
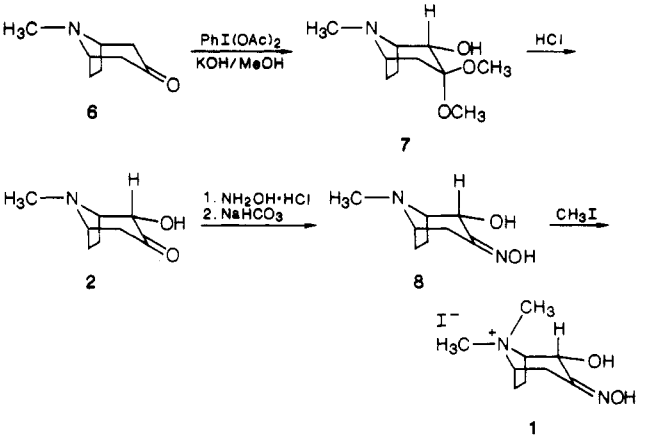
As part of our program directed toward the synthesis of azabicyclo keto oximes as potentially useful acetylcholinesterase reactivators, we synthesized 2α-hydroxytropan-3-one oxime methiodide (**1**). A key intermediate in this synthesis is 2α-hydroxytropan-3-one (**2**), a compound already reported in the literature.[1] Based on our recent work on hypervalent iodine oxidation, it appeared attractive to use this reaction, which entails conversion of enolizable ketones to α-hydroxy dimethyl acetals (**4**) followed by acid hydrolysis (**3** → **4** → **5**).[2]



We have already shown that one of the major advantages of this method is the successful α-hydroxylation of ketones containing an amino functionality, i.e. the nitrogen of the amino group (primary, secondary, or tertiary) is not oxidized under the reaction conditions.[3a,b]

Tropan-3-one (**6**), upon oxidation with iodobenzene diacetate in methanolic potassium hydroxide, afforded 2α-hydroxytropan-3-one dimethyl acetal (**7**), isolated by column chromatography, in 30–35% yield. Hydrolysis of **7**, using 3 N HCl, gave **2**, mp 65–66 °C in 60% yield. Oximation of **2**, followed by quaternization with methyl iodide, resulted in **1**, obtained as a colorless crystalline solid.



The structures of all the products were confirmed by their spectral data and elemental analyses. A determination of the X-ray structure of **1** was undertaken for two reasons. The first was an absolute structural proof, and

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