(1.00 g, 1.94 mmol) and 1*H*-tetrazole (0.47 g, 6.7 mmol) in 12 mL of dry pyridine was transferred into the reaction vessel, and the mixture was stirred for 3.5 h. ^{31}P NMR indicated the formation of two diastereoisomeric phosphites (^{31}P NMR ($CDCl_3$): δ 140.8 and 140.4), which were readily oxidized through the addition of *tert*-butyl hydroperoxide (2 mL).[13] After evaporation of all volatiles (coevaporation with toluene), the residue was dissolved in 18 mL of dry nitromethane and 0.5 mL of dry methanol. After addition of anhydrous zinc bromide (7 g) the orange suspension was stirred for 4 h. To this suspension 100 mL of a 5% aqueous ammonium acetate solution was added, and subsequently the mixture was extracted with 50 mL of dichloromethane (four times). The combined organic layers were dried on magnesium sulfate. After filtration, the filtrate was concentrated in vacuo, and purification was effected by column chromatography on silica gel with dichloromethane/methanol (92:8 v/v) as eluent (R_f 0.36). This afforded a white solid. (Yield: 1.0 g (48%). ^{31}P NMR ($CDCl_3$): δ −0.1 and −0.2), which was dissolved in 1 mL of dry pyridine. Triethylamine (0.25 mL, 1.8 mmol) was added. After being stirred for 5 h the mixture was evaporated, and the residue was coevaporated with toluene and chloroform, yielding a yellow oil containing **8**. ^{31}P NMR: δ −0.7 and −0.8. The two diastereoisomers (S_p and R_p) of **8** were separated with reversed-phase HPLC. S_p-(**8**). ^1H NMR (D_2O): δ 2.10 (3 H, s, CH_3 of acetyl), 2.36 (1 H, m, $H_{2''}$ of dAp), 2.46 (1 H, m, $H_{2'}$ of dAp), 2.64 (1 H, m, $H_{2''}$ of pdA), 2.89 (1 H, m, $H_{2'}$ of pdA), 3.64 (2 H, d, $H_{5'}/H_{5''}$ of dAp), 3.77 (3 H, d, OCH_3, J = 11.2 Hz) 4.24 (1 H, m, $H_{4'}$ of dAp), 4.40 2 H, m, $H_{5'}/H_{5''}$ of pdA), 4.42 (1 H, m, $H_{4'}$ of pdA), 5.03 (1 H, m, $H_{3'}$ of dAp), 5.47 (1 H, m, $H_{3'}$ of pdA), 6.05 (1 H, dd, $H_{1'}$ of dAp), 6.28 (1 H, dd, $H_{1'}$ of pdA), 7.88 and 8.02 (2 H, s, H_2 of dAp and H_2 of pdA), 8.00 (1 H, s, H_8 of dAp),[19] 8.24 (1 H, s, H_8 of pdA).[19] ^{31}P NMR (D_2O): δ 1.66. Because of the partially demethylated R_p-(**8**) diastereoisomer, it was impossible to determine the complete ^1H NMR spectrum. R_p-(**8**) ^{31}P NMR (D_2O): δ 1.74.

2′-Deoxycytidyl-(3′→5′)-3′-*O*-acetyl-2′-deoxycytidine *O*-(Methyl phosphate) (9). Compound **2a** (1.38 g, 1.91 mmol) was dissolved in 11 mL of dry pyridine. To this solution were added bis(*N*,*N*-diisopropylamino)methoxyphosphine (0.546 g, 2.08 mmol) and 1*H*-tetrazole (0.07 g, 1.02 mmol). After 10 min ^{31}P NMR spectroscopy revealed quantitative conversion into the phosphoramidite structure (δ ^{31}P ($CDCl_3$): 150.0 150.0 and 149.4). A solution of 3′-*O*-acetyl-4-*N*-(9-fluorenylmethoxycarbonyl)-2′-deoxycytidine (0.98 g, 1.99 mmol) and 1*H*-tetrazole (0.29 g, 4.12 mmol) in 12 mL of dry pyridine was added, and the mixture was stirred for 2.5 h. Then, ^{31}P NMR showed complete formation of the 3′–5′ phosphite triester (δ ^{31}P ($CDCl_3$): 140.8 140.8 and 140.5). Subsequently, *tert*-butyl hydroperoxide (1.5 mL) was added. After the mixture was stirred for 15 min, ^{31}P NMR revealed formation of the phosphate triester structure. After thorough evaporation of all volatiles, the residue was taken up in 20 mL of 80% acetic acid and stirred for 15 h. Evaporation of all acetic acid afforded a yellowish viscous substance, which was chromatographed on a silica gel column with 2-butanone as eluent. This yielded a white solid (1.09 g, 56%. Mp: 141 °C. ^{31}P NMR ($CDCl_3$): δ 0.07 and −0.35. Calculated mass: 1016. FAB: $(M + H)^+$ = 1017, $(M + Na)^+$ = 1039). This compound was dissolved in a mixture of chloroform (5.0 mL) and triethylamine (5.0 mL) and stirred for 15 h. During stirring, a white precipitate was formed, which proved to be the base-deprotected compound **9**. The R_p and S_p diastereoisomers of **9** were separated with reversed-phase HPLC. S_p-(**9**). ^1H NMR (D_2O): δ 2.06 (3 H, s, CH_3 of acetyl), 2.28–2.36 (2 H, m, $H_{2'}$ of dCp and pdC), 2.54 (1 H, m, $H_{2''}$ of pdC), 2.59 (1 H, m, $H_{2''}$ of dCp), 3.67–3.77 (2 H, m, $H_{5'}/H_{5''}$ of pdC), 3.80 (3 H, d, OCH_3, J = 11.4 Hz), 4.20 (1 H, m, $H_{4'}$ of dCp), 4.27–4.37 (3 H, m, $H_{4'}/H_{5'}/H_{5''}$ of pdC), 4.97 (1 H, m, $H_{3'}$ of dCp), 5.29 (1 H, m, $H_{3'}$ of pdC), 5.99 (1 H, d, H_5 of dCp), 6.00 (1 H, d, H_5 of pdC), 6.14 (1 H, dd, $H_{1'}$ of dCp), 6.20 (1 H, dd, $H_{1'}$ of pdC), 7.70 (1 H, d, H_6 of dCp), 7.75 (1 H, d, H_6 of pdC). ^{31}P NMR (D_2O): δ 2.03. R_p-(**9**). ^1H NMR (D_2O): δ 2.07 (3 H, s, CH_3 of acetyl), 2.31–2.39 (2 H, m, $H_{2'}$ of dCp and pdC), 2.55 (1 H, m, $H_{2''}$ of pdC), 2.60 (1 H, m, $H_{2''}$ of dCp), 3.67–3.77 (2 H, m, $H_{5'}/H_{5''}$ of dCp), 3.80 (3 H, d, OCH_3, J = 11.4 Hz), 4.23 (1 H, m, $H_{4'}$ of dCp), 4.30–4.41 (3 H, m, $H_{4'}/H_{5'}/H_{5''}$ of pdC), 4.98 (1 H, m, $H_{3'}$ of dCp), 5.30 (1 H, m, $H_{3'}$ of pdC), 5.99 (1 H, d, H_5 of dCp), 6.00 (1 H, d, H_5 of pdC), 6.16 (1 H, dd, $H_{1'}$ of dCp), 6.20 (1 H, dd, $H_{1'}$ of pdC), 7.72 (1 H, d, H_6 of dCp), 7.77 (1 H, d, H_6 of pdC). ^{31}P NMR (D_2O): δ 2.13.

Registry No. **1a**, 87424-19-9; **1b**, 87424-21-3; **1c**, 87424-20-2; **2a**, 119184-91-7; **2b**, 119184-92-8; **2c**, 119184-93-9; (S_p)-**4**, 119241-83-7; (R_p)-**4**, 119241-84-8; (S_p)-**5**, 119184-97-3; (R_p)-**5**, 119241-85-9; (S_p)-**6**, 119241-86-0; (R_p)-**6**, 119241-87-1; (S_p)-**7**, 119184-98-4; (R_p)-**7**, 119241-88-2; (S_p)-**8**, 119184-99-5; (R_p)-**8**, 119241-89-3; (S_p)-**9**, 119185-00-1; (R_p)-**9**, 119241-90-6; Fmoc-Cl, 28920-43-6; $MeOPCl_2$, 3279-26-3; PCl_3, 7719-12-2; MeOP[N(*i*-Pr)$_2$]$_2$, 92611-10-4; H-dCyd-H, 951-77-9; H-dGuo-H, 961-07-9; H-dAdo-H, 958-09-8; MMTr-dCyd(Fmoc)-Ac, 119184-94-0; H-dCyd(Fmoc)-Ac, 119184-95-1; MMtr-dAdo-H, 51600-10-3; H-dAdo(Fmoc)-Ac, 119184-96-2; H-dThd-Ac, 21090-30-2.

Synthesis of N(1)-Phosphorylated Tryptophan Derivatives[1,2]

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The first synthesis of the *N*(1)-(dimethylphosphono)tryptophan derivatives Z-Trp(PO_3Me_2)-OBzl and Boc-Trp(PO_3Me_2)-ONBzl by reaction of the lithium indolate of protected tryptophan derivatives Z-Trp-OBzl and Boc-Trp-ONBzl with dimethyl phosphorochloridate is described. The *N*(1)-(dimethylphosphono)tryptophan or Trp(Dmop) derivatives are stable to hydrogenation, and to TFA and high HF treatment, and can be fully deprotected with TFMSA/TFA/*m*-cresol/dimethyl sulfide or TFMSA/TFA/*m*-cresol/thioanisole to yield the novel hydrophilic amino acid *N*(1)-phosphonotryptophan quantitatively. Weak base treatment of Trp(Dmop) compounds yields *N*(1)-(methylphosphono)tryptophan derivatives.

The phosphorylation of serine,[3] tyrosine,[4] and threonine[5] residues in biological peptides is well documented, and N_ϵ-phosphoarginine[6] is the only amino acid with an N–P bond that has so far been isolated from biological material. The phosphorylation of these amino acids is known to

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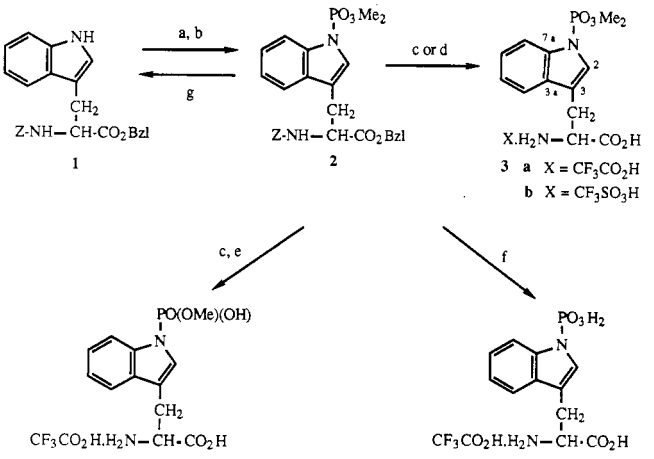
change their physical properties and generally is of major physiological consequence. In recent years, tryptophan metabolites (e.g. serotonin and kynurenine) and indole derivatives have received considerable attention, owing to their physiological significance. Some indole alkaloids (e.g. psilocybin) possess psychomimetic activity, and $N(1)$-acylindole derivatives (e.g. indomethacin) have been synthesized with antihypertensive, antiinflammatory, and tranquilizing activity.[7] In view of the biological significance of the phosphorylation process and of N-acylindoles, it was decided to evaluate the potential physiological activity of N(1)-phosphorylated tryptophan. It is known that N_ϵ-phosphoarginine is not susceptible to the action of arginase until the phosphate is removed,[6] and $N(1)$-phosphotryptophan is a possible inhibitor of tryptophan metabolism and tryptophan-recognizing enzymes, such as chymotrypsin.

In this paper, we describe an efficient synthetic procedure for the first reported preparation of the novel amino acid $N(1)$-phosphotryptophan. Tryptophan is recognized as imparting added hydrophobicity to peptides, and the introduction of the phosphate moiety was expected to alter the physical and possibly physiological properties of tryptophan.

N(1)-protected tryptophan derivatives currently used in peptide synthesis are prepared by Illi's method[8] of phase-transfer catalysis[9-11] or by generating the indolate anion with sodium hydride or "naked" fluoride ion (generated from KF and crown ethers).[12] In preliminary phosphorylation studies, lithium diisopropylamide (LDA) addition to the protected tryptophan substrate followed by addition of dimethyl phosphorochloridate was found to be more efficient than sodium hydride in THF or DMF, the latter procedures giving the required product in only 23% and 38% yield, respectively. The low yield obtained with sodium hydride abstraction of the indole proton was surprising considering that yields between 62% and 100% have been reported for the sodium hydride initiated sulfonation of Trt-Trp-OBzl.[9] Our studies also demonstrated the necessity of addition of the LDA to the amino acid, the reverse process causing extensive racemization of tryptophan (based on optical rotation measurements of the purified derivatives) and that optimum phosphorylation depended on the accurate determination of the n-butyllithium concentration;[13] excess n-butyllithium gave rise to reduced yields and more byproducts.

In a typical experiment, successive treatment of Z-Trp-OBzl (1) with LDA and dimethyl phosphorochloridate

Scheme I.[a] Synthesis and Reactions of Z-Trp(PO_3Me_2)-OBzl



[a] (a) LDA (1 equiv), −78 °C; (b) $(MeO)_2P(O)Cl$, −60 °C, 10 min; 25 °C, 3.5 h; (c) H_2, 10% Pd/C; (d) TFMSA/TFA/m-cresol, 25 °C; (e) 20% piperidine in DMF, 1 h; (f) TFMSA/TFA/dimethyl sulfide/m-cresol, 1 h, 25 °C; (g) tetra-n-butylammonium fluoride (10 equiv), 5 min.

gave Z-Trp(PO_3Me_2)-OBzl (2) as a pale yellow oil in 68% yield after chromatographic purification. Similar phosphorylation of Boc-Trp-ONBzl (6) gave Boc-Trp-(PO_3Me_2)-ONBzl (7) as a yellow glass in a maximum yield of 66%. Purification of the crude phosphorylated derivatives by silica gel flash chromatography[14] typically gave 10–15% of the starting material; the remaining mass balance (20–25%) consisted of highly polar orange-brown material, possibly a polymerization or oxidation byproduct.

Phosphorylation of the indole nitrogen of derivatives 2 and 7 was readily established by ^{31}P and ^{13}C NMR spectroscopy, the ^{13}C NMR spectrum of 2 displaying characteristic phosphorus-coupled doublets for carbons C2 (J_{CP} = 6.1 Hz), C3 (J_{CP} = 8.6 Hz), C3a (J_{CP} = 9.8 Hz) and C7a (J_{CP} = 3.7 Hz) of the indole moiety. Furthermore, the upfield chemical shift of the C2 ($\Delta\delta$ 4 ppm), C7a ($\Delta\delta$ 1 ppm), C3 ($\Delta\delta$ 5 ppm) and C3a ($\Delta\delta$ 1 ppm) carbon signals (relative to their respective chemical shift in 1) is consistent with the inductive effect caused by phosphorus. The C2 and C3 carbons are more strongly influenced by substitution at N1 than the carbons in the homocyclic ring.

Catalytic hydrogenation of 2 in methanol/water (9:1) containing TFA (1 equiv) with 10% Pd/C readily removed the benzylic protecting groups and gave 3 in quantitative yield (Scheme I). The product was found to be homogeneous by HPLC and ^{13}C NMR, the latter confirming the presence of the phosphate group and that no hydrogenation of the aromatic system had occurred. It was interesting to note that hydrogenation of 2 in methanol containing acetic acid (1 equiv) gave two products, which were shown by ^{13}C and ^{31}P NMR spectroscopy and by HPLC comparison with authentic material to be a mixture of $N(1)$-(dimethylphosphono)tryptophan acetate (3) and $N(1)$-(methylphosphono)tryptophan acetate (4) in a 5:1 ratio. The dealkylation of alkylphosphates by primary and secondary amines is well documented,[15] and it is likely that demethylation occurs intermolecularly by reaction with the α-amino group as it is liberated.

The treatment of 2 with TFMSA/TFA/dimethyl sulfide/m-cresol (2:10:2:1) at 25 °C effected complete removal

(2) A number of abbreviations are used in this paper. The abbreviations for natural amino acids and nomenclature for peptide structures follow the recommendations of the IUPAC–IUB Commission on Biochemical Nomenclature. Other abbreviations used: TFA = trifluoroacetic acid, TFMSA = trifluoromethanesulfonic acid, MSA = methanesulfonic acid, THF = tetrahydrofuran, DMF = dimethylformamide, Dmop = dimethylphosphono, SPPS = solid-phase peptide synthesis, Z = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl.

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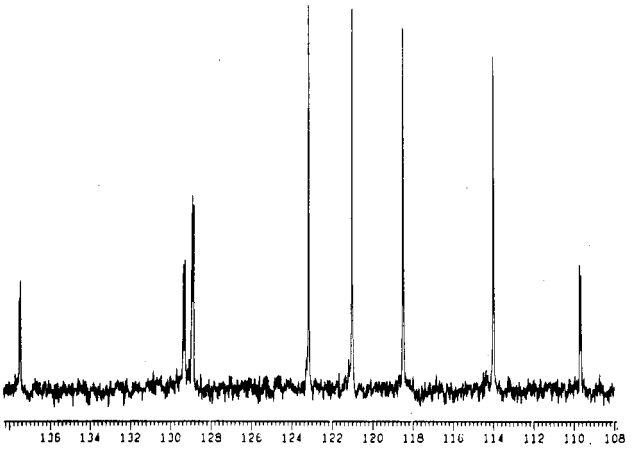


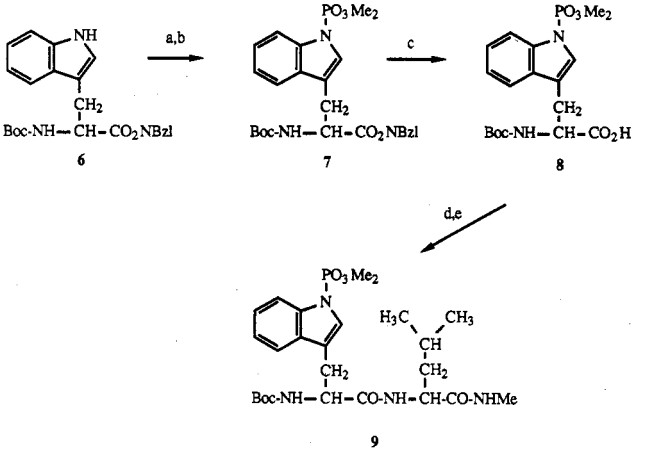
Figure 1. 400-MHz ^{13}C NMR spectrum of aromatic region of **2** displaying phosphorus-coupled doublet signals.

of both the methyl phosphate ester groups and the benzylic protecting groups and gave **5** in quantitative yield as judged by ^{13}C and ^{31}P NMR spectroscopy. The stability of the P–N bond in strongly acidic but poorly nucleophilic media has been reported.[16] The presence of the thioether mediates dealkylation,[17] and **3b** is obtained quantitatively if TFMSA/TFA/*m*-cresol is used. The dealkylation reaction, which is readily monitored by ^{31}P NMR spectroscopy, proceeds more slowly with thioanisole (2–3 h) than with dimethyl sulfide (45 min). The amino acid **5** was also produced by the use of bromotrimethylsilane in TFA,[18] although the reaction was very slow and needed heating (55 °C, 77 h) to proceed to completion.

Structural characterization of both **3** and **5** was established by the combined use of ^{13}C NMR spectroscopy and FAB mass spectrometry. The FAB mass spectra of **3**, **4**, and **5** gave high intensity [M^+] ions at m/z 313, 299, and 285, respectively, and contained fragmentation ions consistent with N-substitution of the indole nitrogen. The ^{13}C NMR spectra of these derivatives all displayed characteristic phosphorus-coupled doublet resonances for carbon atoms 2, 3, 3a, and 7a in the aromatic region (Figure 1). In the ^1H NMR spectra of **3**, **4**, and **5**, phosphorus-induced splitting was observed only for the proton attached to C2 (J = 2.2–2.4 Hz).

Despite the reported acidolytic lability of the P–N bond in phosphoramidates,[19] the P–N linkage of *N*(1)-(dimethylphosphono)tryptophan (Trp(Dmop)) derivatives was found to be stable under acidolytic conditions, compound **3a** being recovered unchanged after a 7-h treatment with TFA/1,2-ethanedithiol/anisole/ethyl methyl sulfide[20] (93:1:3:3). In addition, the P–N bond of **2** was completely stable under high HF[21] conditions, but partial cleavage occurred under low HF[22] conditions, derivatives **3–5** and tryptophan being produced as determined by ^{13}C and ^{31}P NMR spectroscopy and HPLC. The *N*(1)-(dihydrogen phosphonate) derivative is more acid labile than the *N*-(1)-(dimethyl phosphonate) derivative, and fully protonated **5** slowly dephosphorylates to give tryptophan (15% tryptophan was observed by amino acid analysis of **5** after 2 weeks in 0.1% aqueous TFA solution, and 1% tryptophan by ^{13}C NMR after 2 weeks in the solid state).

Scheme II.[a] **Synthesis of Boc-Trp(PO_3Me_2)-Leu-NHMe**



[a] (a) LDA (1 equiv), −78 °C; (b) $(MeO)_2P(O)Cl$, −60 °C, 10 min; 25 °C, 3.5 h; (c) H_2, 10% Pd/C, 2 h; (d) NMM, IBCF, −20 °C, 3 min; (e) H-Leu-NHMe HCl, NMM, −20 °C, 2 h.

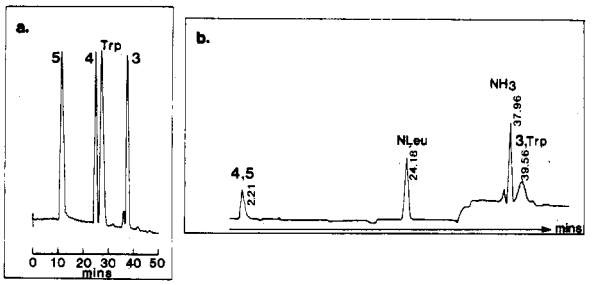


Figure 2. HPLC and amino acid analyzer profiles of **3–5** and Trp (a) C_8 RP HPLC; buffer A, 0.1% aqueous TFA; buffer B, 0.1% TFA in CH_3CN; 0% B for 5 min and then 0–30% in 40 min. (b) Amino acid analyzer column, 45–65 °C, sodium citrate buffer.

The Trp(Dmop) derivatives undergo the usual reactions of dimethyl phosphates, such as monodemethylation by piperidine or dimethylamine[15] or by sodium iodide.[23] Complete deprotection of Trp(Dmop) to tryptophan is effected rapidly by strong bases such as NaOH (1 h) or tetra-*n*-butylammonium fluoride (5 min), or by prolonged treatment (>3 days) with strong acids (e.g. TFMSA, MSA, 33% HBr in acetic acid). Derivatives **2–5** and **7–9** are Ehrlich[24] positive, indicating cleavage of the P–N bond occurs in concentrated HCl. The purple color takes 0.5–2 min to develop, but is almost instantaneous for **5**, owing to its increased acid lability.

The lack of racemization of the phosphorylated derivatives under the strongly basic conditions of synthesis was established by a modified Manning and Moore procedure.[25] Catalytic hydrogenolysis of the nitrobenzyl ester from **7** yielded the free acid **8**, which was readily incorporated into a dipeptide by solution-phase synthesis using isobutyl chloroformate and *N*-methylmorpholine to generate the mixed anhydride. Coupling to leucine *N*-methylamide was achieved in 91% yield, and the optical purity of the dipeptide was ascertained to be >99% by HPLC and ^{13}C NMR comparison with a similar peptide synthesized from racemic **8**; the diastereoisomeric peptide exhibits two resonances for the nonequivalent β-methylene carbons and

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one of the δ methyl signals of leucine in its ^{13}C NMR spectrum.

Dmop-protected derivatives are freely soluble in most organic solvents, and their stability under peptide synthesis conditions makes them useful and versatile new synthons for use in peptide synthesis with potential applications in the design of peptide drug analogues and in structure–function relationship research. Compound **5** shows greatly enhanced hydrophilic character; it is freely water soluble and elutes very rapidly from C_8 RP HPLC and amino acid analyzer columns relative to Trp (Figure 2).

Studies into the potential biological activity of this novel amino acid and the synthesis of Trp(Dmop) peptides are currently in progress and will be reported on later.

Experimental Section

Dimethyl phosphorochloridate was prepared by a synthetic procedure described elsewhere.[26] Acetic acid, TFA, and TFMSA were of AR grade. Thioanisole and dimethylsulfide were used as provided; *m*-cresol was redistilled. ^{13}C NMR spectra were obtained on a JEOL-FX90Q Fourier transform (FT) instrument operating at 22.5 MHz or on a JEOL-GX 400 FT operating at 100.4 MHz, referenced to internal $CDCl_3$ (77.0 ppm), CD_3CN (1.3 ppm), or dioxane (66.5 ppm), ^{31}P NMR spectra on a JEOL-FX100 FT instrument operating at 40.26 MHz, referenced to external 85% H_3PO_4, and ^1H NMR spectra on a JEOL JMN-PMX60 operating at 60 MHz, referenced to internal TMS or on a JEOL-GX 400 FT operating at 399.65 MHz, referenced to internal dioxane (3.7 ppm). Melting points were determined on a Reichert hot stage melting point apparatus and are uncorrected. TLC was carried out on Merck Kieselgel 60 F_{254} precoated plates with ethyl acetate/petroleum ether (40–60 °C), 40:60, and visualized by UV, iodine, or Ehrlich reagent.[24] FAB mass spectra were obtained on a JEOL-DX 300 mass spectrometer equipped with a FAB source and using glycerol–aqueous HCl as a matrix for samples **3–5** and glycerol–CH_3CO_2H for sample **8**. Amino acid analyses were carried out on a Beckman 6300 ion-exchange amino acid analyzer, and HPLC on a C8 reverse-phase semipreparative column (250 × 4.6 mm), with a UV detector operating at 280 nm.

Z-Trp-OBzl (1). Z-Trp-OH (18 g, 54 mmol) was heated at 80 °C with toluene-*p*-sulfonyl chloride (7.13 g, 65 mmol) in benzyl alcohol (100 mL, 0.96 mol)[27] for 1.5 h. Chloroform was added to the cooled mixture, and the organic phase was washed with 5% $NaHCO_3$ (4 × 100 mL) and water (4 × 100 mL), dried over Na_2SO_4, and filtered, and chloroform was removed under reduced pressure. Z-Trp-OBzl crystallized after silica gel flash chromatography (ethyl acetate/petroleum ether (40–60 °C) 40:60) to remove excess benzyl alcohol: yield 16.5 g, 71%; mp 105–108 °C (lit.[28] mp 105.1 °C); $[\alpha]^{21.5}_D$ +8.84° (*c* 1, $CHCl_3$); R_f 0.47; ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.8, 54.5, 66.8, 67.0, 109.3, 111.2, 118.4, 119.5, 122.0, 122.9, 126.8, 127.4, 128.0, 128.2, 128.4, 135.1, 136.0, 155.7, 171.7; ^1H NMR (60 MHz, $CDCl_3$) δ 3.27 (d, *J* = 6 Hz, 2 H), 4.76 (d, *J* = 8 Hz, 1 H), 5.03 (s, 4 H), 5.67 (d, *J* = 8 Hz, 1 H), 6.60–7.67 (m, 15 H), 8.33 (s, b, 1 H).

Boc-Trp-ONBzl (6). Boc-Trp-OH (4.75 g, 15 mmol), 4-nitrobenzyl bromide (4.86 g, 22.5 mmol), and triethylamine (3.1 mL, 22.5 mmol) were heated at reflux temperature in ethyl acetate for 3.5 h. Water (10 mL) was then added, the mixture was stirred for 30 min, and the organic phase was washed with 1 M HCl, 5% $NaHCO_3$, and water, dried over anhydrous Na_2SO_4, and filtered. Removal of solvent under reduced pressure and recrystallization of the product from ethyl acetate/petroleum ether (40–60 °C) gave **6** as fine yellow needles: yield 5.97 g, 91%; mp 125.5–126 °C (lit.[29] mp 108–112 °C), $[\alpha]^{14}_D$ +11.0° (*c* 1, $CHCl_3$); R_f 0.37; ^{13}C NMR (90 MHz, $CDCl_3$) δ 28.3, 54.7, 65.4, 80.3, 109.7, 111.4, 118.5, 119.6, 122.2, 123.1, 123.5, 127.5, 128.2, 136.4, 142.6, 147.7, 155.4, 172.2; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40 (s, 9 H), 3.27 (d, *J* = 6.5 Hz, 2 H), 4.65 (m, *J* = 6 Hz, 1 H), 5.08 (s, 2 H), 5.30 (d, *J* = 8 Hz, 1 H), 6.83–8.17 (m, 9 H), 8.68 (b s, 1 H).

General Phosphorylation Procedure: Z-Trp(PO_3Me_2)-OBzl (2). Successive in situ treatment of **1** (2.14 g, 5 mmol) in THF (5 mL, freshly distilled from potassium benzophenone ketal) under dry nitrogen, with LDA (−78 °C, 10 min) (freshly prepared from diisopropylamine (0.80 mL, 5.5 mmol) and *n*-butyllithium (2.86 mL, 5 mmol, 1.75 M in hexane) in THF (1 mL)) and dimethyl phosphorochloridate (1.23 g, 8.5 mmol) in THF (2 mL) (−60 °C, 10 min; 25 °C, 3.5 h) afforded a crude oil after quenching the reaction with 5% $NaHCO_3$ (1 mL), evaporation of THF under reduced pressure, and washing the residual oil dissolved in ethyl acetate (40 mL) with 5% $NaHCO_3$ (3 × 30 mL), 1 M HCl (40 mL), and brine (40 mL), drying over $MgSO_4$, and solvent removal in vacuo; **2** was obtained as a pale yellow oil after flash silica gel chromatography in two batches (Merck Kieselgel 60, 5 × 13 cm) with ethyl acetate/petroleum ether (40–60 °C), 40:60: yield 1.77 g, 68%; $[\alpha]^{21.5}_D$ +15.80° (*c* 1, $CHCl_3$); R_f 0.22; ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.1, 53.2 (d, J_{CP} = 4.9 Hz), 54.0, 66.1, 66.5, 113.1, 115.2 (d, J_{CP} = 8.6 Hz), 118.6, 121.7, 123.4, 126.4 (d, J_{CP} = 6.1 Hz), 127.3, 127.4, 127.8, 130.3 (d, J_{CP} = 9.8 Hz), 134.7, 135.9, 136.6 (d, J_{CP} = 3.7 Hz), 155.4, 171.2; ^{31}P NMR ($CHCl_3$) δ −0.15; ^1H NMR (60 MHz, $CDCl_3$) δ 3.23 (d, *J* = 7 Hz, 2 H), 3.60 (d, *J* = 12 Hz, 6 H), 4.73 (d, *J* = 7 Hz, 1 H), 5.07 (s, 4 H), 5.83 (d, *J* = 9 Hz, 1 H), 6.83–7.93 (m, 15 H).

Boc-Trp(PO_3Me_2)-ONBzl (7). Phosphorylation of **6** (4.39 g, 10 mmol) and purification of the product was carried out as for **2**. Compound **7** was obtained as a yellow foam: yield 3.61 g, 66%; $[\alpha]^{13}_D$ +12.23° (*c* 1, $CHCl_3$); R_f 0.1; ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.5, 53.4 (d, J_{CP} = 4.9 Hz), 64.8, 79.1, 113.0, 115.1 (d, J_{CP} = 8.6 Hz), 118.6, 121.6, 122.9, 123.4, 126.2 (d, J_{CP} = 6.1 Hz), 127.7, 130.2 (d, J_{CP} = 9.8 Hz), 136.5 (d, J_{CP} = 4.9 Hz), 142.0, 146.9, 154.6, 171.2; ^{31}P NMR ($CHCl_3$) δ −0.18; ^1H NMR (60 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 3.30 (d, *J* = 6 Hz, 2 H), 3.83 (d, *J* = 12 Hz, 6 H), 4.80 (d, *J* = 8 Hz, 1 H), 5.23 (s, 2 H), 5.43 (d, *J* = 9 Hz, 1 H), 7.25–8.33 (m, 9 H).

H-Trp(PO_3Me_2)-OH TFA (3a) by Hydrogenation of 2. Hydrogenation of **2** (1.27 g, 2.4 mmol) with 10% Pd/C (0.24 g, 100 mg/mmol) in methanol/water (90:10, 28 mL) containing 1 equiv of TFA (0.27 g, 2.4 mmol) at room temperature and atmospheric pressure for 3 h gave, after removal of catalyst by filtration and removal of solvent under vacuum, **3a** as a glass: yield 0.91 g, 93%; mp 198–202 °C dec; $[\alpha]^{22.5}_D$ −3.05° (*c* 1, H_2O); ^{13}C NMR (400 MHz, D_2O) δ 25.58, 53.07, 54.91 (d, J_{CP} = 5.8 Hz), 113.41, 114.15 (d, J_{CP} = 8.8 Hz), 119.23, 122.93, 124.76, 127.57 (d, J_{CP} = 7.4 Hz), 130.01 (d, J_{CP} = 10.3 Hz), 136.78 (d, J_{CP} = 4.4 Hz), 172.02; ^{31}P NMR (D_2O) δ +0.82; ^1H NMR (400 MHz, D_2O) δ 3.33 (dd, *J* = 15.4 and 7.6 Hz, 1 H), 3.42 (dd, *J* = 15.4 and 5.6 Hz, 1 H), 3.78 (d, *J* = 11.7 Hz, 6 H), 4.28 (dd, *J* = 7.6 and 5.9 Hz, 1 H), 7.32–7.41 (m, 3 H), 7.68–7.70 (m, 2 H); FAB MS (Ar, positive mode) *m/z* (relative intensity) 313 (100, M^+), 296 (27), 236 (45), 225 (22), 130 (28).

H-Trp(PO_3Me_2)-OH TFMSA (3b) by Acidolysis of 2. Addition of TFMSA/TFA/*m*-cresol (10:50:10, 1.75 mL) to **2** (0.20 g, 0.37 mmol) under dry N_2 at 0 °C followed by reaction at 25 °C for 3 days and precipitation of the product into chilled ether gave **3b** as a white solid: yield 0.079 g, 52%; ^{13}C NMR (90 MHz, D_2O) δ 25.4, 52.7, 54.8 (d, J_{CP} = 4.7 Hz), 98.6, 112.8, 113.8 (d, J_{CP} = 8.6 Hz), 119.3, 123.0, 124.3, 125.1, 126.7, 128.1 (d, J_{CP} = 7.3 Hz), 130.0 (d, J_{CP} = 9.8 Hz), 136.8 (d, J_{CP} = 4.9 Hz), 141.6, 171.38; ^{31}P NMR (MeOH/H_2O) δ −0.15.

H-Trp(PO_3H_2)-OH TFA (5). Treatment of **2** (0.20 g, 0.37 mmol) with TFMSA/TFA/dimethyl sulfide/*m*-cresol (5:25:15:5, 2.5 mL) for 1 h at room temperature under dry N_2, followed by ethereal precipitation and HPLC purification of the product, gave 24 mg of **5**, 16% (reaction yield judged to be 100% by ^{31}P and ^{13}C NMR of the crude product): mp 165–168 °C; $[\alpha]^{22.5}_D$ −11.24° (*c* 1, H_2O); ^{13}C NMR (400 MHz, D_2O) δ 25.66, 53.03, 109.68 (d, J_{CP} = 7.3 Hz), 113.99, 118.47, 121.0, 123.6, 128.91 (d, J_{CP} = 5.9 Hz), 129.33 (d, J_{CP} = 8.8 Hz), 137.94 (d, J_{CP} = 4.4 Hz), 172.05; ^{31}P NMR (D_2O) −5.99; ^1H NMR (400 MHz, D_2O) δ 3.33 (dd, *J* = 15.4 and 7.8 Hz, 1 H), 3.47 (dd, *J* = 15.4 and 5.1 Hz, 1 H), 4.30 (dd, *J* = 7.8 and 5.1 Hz, 1 H), 7.23 (dd, *J* = 7.4 Hz, 1 H), 7.31 (dd, *J* = 7.3 Hz, 1 H), 7.40 (d, *J* = 2.4 Hz, 1 H), 7.64 (d, *J* = 9.5 Hz, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H); FAB MS (Ar, positive mode) *m/z* (relative intensity) 285 (80, M^+), 210 (20), 191 (40), 186 (100), 165 (27), 139 (100).

H-Trp(PO(OMe)(OH))-OH TFA (4). Hydrogenation of **2**

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(0.96 g, 0.18 mmol) in the manner described for **3a** followed by treatment of the product with 20% piperidine in DMF (2 mL) for 30 min, removal of DMF under high vacuum, and HPLC purification of the water-soluble extract of the residue gave **4**: yield 25 mg, 32%; mp 191-192 °C dec; $[\alpha]^{22.5}_D$ -10.9° (*c* 1, H_2O); ^{13}C NMR (400 MHz, D_2O) δ 25.62, 52.71 (d, J_{CP} = 5.9 Hz), 52.93, 110.25 (d, J_{CP} = 7.3 Hz), 113.89, 118.56, 121.36, 123.47, 129.18 (d, J_{CP} = 7.4 Hz), 129.43 (d, J_{CP} = 8.8 Hz), 137.38 (d, J_{CP} = 4.4 Hz), 171.86; ^{31}P NMR (D_2O) δ -3.60; ^1H NMR (400 MHz, D_2O) δ 3.36 (dd, *J* = 15.1 and 7.8 Hz, 1 H), 3.39 (d, *J* = 11.7 Hz, 3 H), 3.46 (dd, *J* = 15.4 and 5.1 Hz, 1 H), 4.33 (dd, *J* = 7.6 and 5.4 Hz, 1 H), 7.25 (ddd, *J* = 7.57 and 0.98 Hz, 1 H), 7.33 (ddd, *J* = 7.69 and 1.22 Hz, 1 H), 7.39 (d, *J* = 2.20 Hz, 1 H), 7.65 (d, *J* = 7.81 Hz, 1 H), 7.76 (d, *J* = 8.30 Hz, 1 H); FAB MS (Ar, positive mode) *m/z* (relative intensity) 299 (100, M^+), 262 (20), 224 (36), 186 (71), 130 (32).

Z-Trp-OBzl (1) by Fluoride Treatment of 2. Compound **2** (0.05 g, 0.14 mmol) was dissolved in THF (2 mL), and a solution of tetra-*n*-butylammonium fluoride trihydrate (0.44 g, 1.4 mmol) in THF (1 mL) was added. After 1 h, the solution was acidified to pH 3 with 1 M HCl, and the THF was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), washed with 1 M HCl (3 × 20 mL), brine (3 × 20 mL), and 5% $NaHCO_3$ (2 × 20 mL), dried over $MgSO_4$, and solvent was evaporated under reduced pressure to yield **1** as an oil: yield 0.037 g, 66%; R_f 0.47; ^{13}C NMR (90 MHz, $CDCl_3$) δ 28.0, 54.7, 66.9, 67.1, 109.6, 111.2, 118.6, 119.6, 122.1, 122.9, 127.5, 128.0, 128.4, 128.5, 135.2, 136.1, 155.7, 171.8; ^1H NMR (60 MHz, $CDCl_3$) δ 3.26 (d, *J* = 5 Hz, 2 H), 4.66 (m, 1 H), 5.07 (s, 4 H), 6.67-7.70 (m, 15 H), 8.17 (s, b, 1 H).

Boc-Trp(PO_3Me_2)-OH (8). Hydrogenolysis of **7** (3.46 g, 6 mmol) over 10% Pd/C (0.63 g, 100 mg/mmol) in methanol/acetic acid (95:5, 60 mL) at room temperature and atmospheric pressure for 3 h, filtration to remove the catalyst, extraction with 5% $NaHCO_3$ in several portions of an ethyl acetate solution of the residue followed by acidification with concentrated HCl of the aqueous extract, and reextraction of the free acid into $CHCl_3$, drying the organic phase over $MgSO_4$, and removal of solvent in vacuo yielded **8**: 2.12 g, 81%; $[\alpha]^{21.5}_D$ +49.15° (*c* 1, $CHCl_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.9, 53.9 (d, J_{CP} = 4.9 Hz), 79.4, 113.1, 115.9 (d, J_{CP} = 8.6 Hz), 119.1, 122.0, 123.6, 126.5 (d, J_{CP} = 8.2 Hz), 131.1 (d, J_{CP} = 9.8 Hz), 136.7 (d, J_{CP} = 3.7 Hz), 155.2, 173.6; ^{31}P NMR ($CHCl_3$) δ -0.12; ^1H NMR (60 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 3.27 (d, *J* = 6 Hz, 2 H), 3.73 (d, *J* = 12 Hz, 6 H), 4.60 (m, 1 H), 6.80-7.80 (m, 5 H); FAB MS (Ar, positive mode) *m/z* (relative intensity) 413 (15, M^+), 357 (24), 313 (62), 267 (31), 236 (100), 130 (61).

Boc-Trp(PO_3Me_2)-Leu-NHMe (9). *N*-Methylmorpholine (NMM) (0.071 g, 0.7 mmol in 0.5 mL of THF) and isobutyl chloroformate (0.089 g, 0.65 mmol) in 0.5 mL of THF) were added to **8** (0.289 g, 0.7 mmol in 2 mL of THF) at -30 °C under a dry N_2 atmosphere, followed after 3 min by H-Leu-NHMe HCl (0.09 g, 0.5 mmol in 2 mL of THF) neutralized previously with NMM (0.051 g, 0.5 mmol). The reaction was quenched by addition of 5% $NaHCO_3$ (0.5 mL) after 2 h at -20 °C (dry ice/acetone), ethyl acetate (20 mL) was added, the product was washed with 5% $NaHCO_3$ (20 mL) and 1 M HCl (20 mL) and dried over $MgSO_4$, and solvent was removed under reduced pressure to yield **9** as an off-white foam: 0.24 g, 91%; $[\alpha]^{22.5}_D$ -25.25° (*c* 1, $CHCl_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 22.0, 22.7, 24.6, 26.1, 27.6, 28.1, 40.9, 51.7, 54.0 (d, J_{CP} = 4.9 Hz), 54.9, 80.3, 113.4, 115.8 (d, J_{CP} = 8.6 Hz), 119.4, 122.3, 124.0, 126.8 (d, J_{CP} = 6.1 Hz), 130.8 (d, J_{Cp} = 11.0 Hz), 137.0 (d, J_{CP} = 3.7 Hz), 155.7, 171.6, 172.2; ^{31}P NMR ($CHCl_3$) δ -0.12.

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Registry No. 1, 69876-37-5; **2**, 118869-29-7; **3a**, 118869-31-1; **3b**, 118890-31-6; **4**, 118869-33-3; **5**, 118869-35-5; **6**, 57229-69-3; **7**, 118869-36-6; **8**, 118869-37-7; **9**, 118869-38-8; H-Leu-NHMe·HCl, 99145-71-8; Z-Trp-OH, 7432-21-5; BOC-Trp-OH, 13139-14-5; $ClP(O)(OMe)_2$, 813-77-4.

Novel Rearrangement of Tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dienes into 2-Oxatricyclo[6.3.0.$0^{3,7}$]undeca-4,10-dienes by Treatment with Periodic Acid

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Tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dienes **1** on treatment with periodic acid (**6**) in aqueous *tert*-butyl alcohol undergo a novel rearrangement to give 2-oxatricyclo[6.3.0.$0^{3,7}$]undeca-4,10-dienes **7** in fair yields. Hypoiodic acid, IOH, was found to be generated in the course of the rearrangement of **1** into **7**. Independent reaction of **1** with hypoiodic acid derived from iodine and hydrogen peroxide gave the same rearranged product **7** in a yield comparable to that by **6**. The rearrangement of **1** to **7** seems to proceed via an iodonium ion intermediate.

endo-Tricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene (**1a**), readily available from the dimerization of cyclopentadiene, is widely used as a starting material in organic synthesis.[1] The oxidation of **1a** afforded a wide range of compounds depending on the oxidants employed (e.g., allylic alcohol **2** by selenium dioxide,[2] glycol **3** or dialdehyde **4** by permanganate oxidation,[1a,3] and epoxide **5** by peracids[4] or aqueous hydrogen peroxide[5]). On the other hand, periodic acid (**6**), H_5IO_6, or periodates such as $NaIO_4$ and KIO_4 are often used not only as glycol fission reagents but also as the oxidant for a wide range of organic compounds,[6] i.e.,

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