(5, 79%, eq i).[11] Also, 4 is readily oxidized by static air (THF, 21 h) to (η^5-C$_5$H$_5$)Re(NO)(PPh$_3$)(PPh$_2$O) (6, 71%).[11]

In view of the numerous common transition-metal ligands with lone pairs on the ligating atoms (OR, SR, SR$_2$, NR$_2$, etc.), we believe that the ideas set forth above will prove useful in interpreting a large body of structural and reactivity data. Our results also suggest several reasons for the ease of formation and stability of *bridging* phosphide[16] ligands and may bear on the extremely low phosphorus inversion barriers observed with 4 and related complexes.[17]

Supplementary Material Available: Tables of analytical (3–6) and crystallographic (4) data (31 pages). Ordering information is given on any current masthead page.

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An Extremely Short Way to Prostaglandins[1]

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Among various strategies for prostaglandin (PG) synthesis, the three-component coupling process[1] is one of the ideal approaches in view of the directness and synthetic flexibility. Obviously, the ultimate goal along this line is, as illustrated by eq 1 (M = metal, X = halogen), the single-pot construction of the whole frameworks
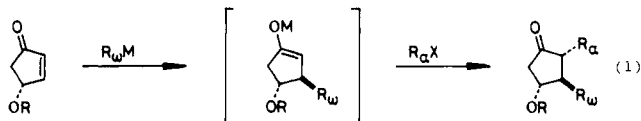
via organometallic-aided conjugate addition of the ω side-chain unit to 4-oxygenated 2-cyclopentenones followed by trapping of the regiochemically defined enolate species by *organic halides* having α side-chain structures. However, Syntex groups[2] among others, after pioneering, extensive study on this possibility, noted extreme difficulty in achieving the direct alkylation.[3] Here we wish to announce the realization of this earnestly desired convergent synthesis. The success relies simply on the lithium (or copper) to tin transmetalation in the enolate stage, a technique elaborated earlier by Tardella (simple alkylation)[4] and Itoh et

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al. (vicinal carba-condensation).[5]

The requisite optically active cyclopentenone and ω side-chain blocks are now accessible in various ways.[1,6] An organocopper reagent was prepared under our standard conditions[7] by mixing the vinyllithium derived from 2a[6,8] in ether and a THF solution containing copper(I) iodide (1 equiv) and tributylphosphine (2.6 equiv). Sequential treatments of the enone 1 with this copper
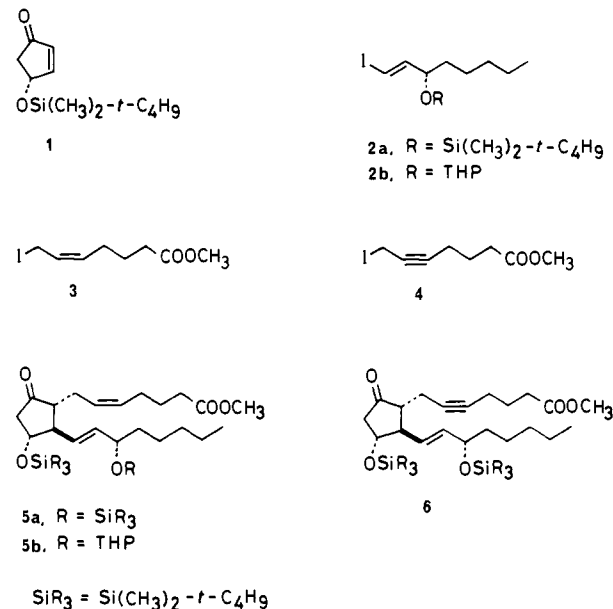
reagent (1:1 molar ratio, –78 °C, 1 h),[9] hexamethylphosphoramide (11 equiv, –78 °C, 30 min), triphenyltin chloride (1 equiv, –78 °C, 10 min), and the allylic iodide 3[10] (5 equiv, –30 to –20 °C, 17 h) afforded stereoselectively the PGE$_2$ derivative 5a in 78% yield,[11–13] [α]^{19}$_D$ –49.9° (c 1.02, CH$_3$OH). No PGA derivatives were detected. Natural PGE$_2$ can be obtained from 5a by removal of the silyl protective group with HF–pyridine[3b] followed by enzymatic ester hydrolysis.[14] In a like manner, 5b (a versatile precursor of D series of PGs), [α]^{16}$_D$ –60.0° (c 1.02, CH$_3$OH), was prepared in 77% yield by the one-pot condensation of 1, 2b, and 3.[13] Use of methyl 7-iodoheptanoate, a saturated alkylating agent (–20 °C, 16 h), gave the corresponding PGE$_1$ derivative in only 20% yield.[13]

Utilization of the propargylic iodide[15] as the α side-chain unit allowed the synthesis of 6 in 82% yield, [α]^{17}$_D$ –13.2° (c 0.59,

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(8) For optical resolution of the ω side-chain unit, see: Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* 1972, *94*, 7827.

(9) The conjugate addition proceeds in a completely stereoselective manner to give after aqueous quenching only the C-11/C-12 (PG numbering) trans product.[1]

(10) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* 1975, *97*, 107.

(11) In model vicinal carba-condensation procedures, tributyltin chloride,[4,5] iodide, or fluoride (but not triflate) could also be used, but less effectively. We consider that the alkylation proceeds via the penta- or hexacoordinate stannate species. For alkylation of tin(IV) enolates and related species, see: Odic, Y.; Pereyre, M. *J. Organomet. Chem.* 1973, *55*, 273. References 4 and 5.

(12) In addition, the C-8 epimer[13] was obtained in 2–3% yield.

(13) All products were identified by comparison with authentic samples.

(14) Sih, C. J.; Heather, J. B.; Sood, R.; Price, P.; Perzzotti, G.; Lee, L. F. H.; Lee, S. S. *J. Am. Chem. Soc.* 1975, *97*, 865. Hazato, A.; Tanaka, T.; Toru, T.; Okamura, N.; Bannai, K.; Sugiura, S.; Manabe, K.; Kurozumi, S. *Nippon Kagaku Kaishi* 1983, 1392.

(15) Prepared by treatment of 6-(carbomethoxy)-2-hexyn-1-ol with a mixture of triphenyl phosphite, iodine, and pyridine (3 equiv each) in ether (0 °C, 30 min) in 73% yield.

CH₃OH) (a single stereoisomer as assayed by ¹³C NMR).¹³ The acetylenic compounds of type **6** serve as common intermediates for the general synthesis of the PG family.¹,³ᵇ With this highly efficient chemical operation secured, PGI₂ is now obtainable in only five steps starting from the chiral cyclopentenone **1**.¹⁶

(16) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187.

(I)

Dehydrophenylalanine as the *i* + 2th Residue of a β Turn: Synthesis and Conformational Analysis of *cyclo*(Gly-Pro-Δ²-Phe-D-Ala-Pro) and *cyclo*(Gly-Pro-D-Phe-D-Ala-Pro)

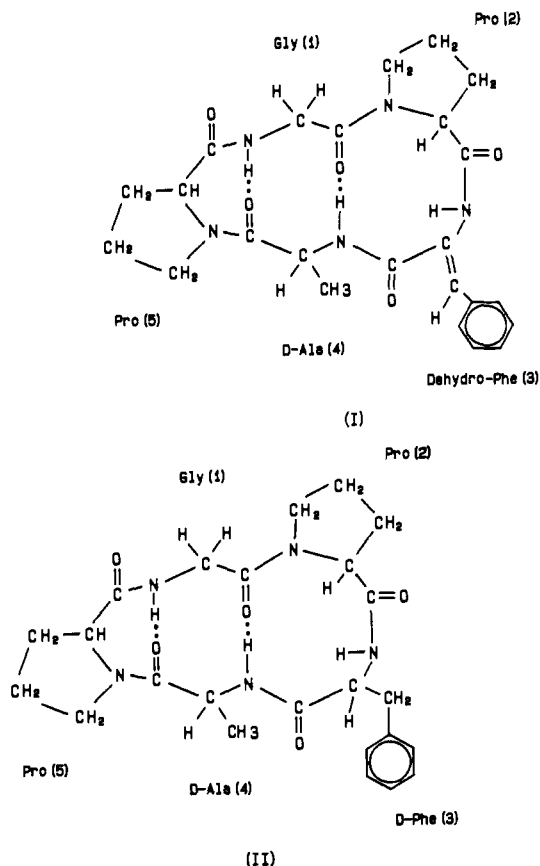Alvin C. Bach, II, and Lila M. Gierasch*

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Analogues of several biologically active peptides, in which *trans*-α,β-didehydrophenylalanine (Δ²-Phe) is substituted for phenylalanine, exhibit high potency¹⁻³ and increased resistance to chymotrypsin degradation.¹ However, in other examples⁴ the Δ²-Phe-containing analogue is markedly less active than the Phe-containing peptide. While the conformational behavior of a Δ²-Phe, with π-bonding between Cα and Cβ, is expected to differ significantly from that of (saturated) Phe, there is as yet no clear understanding of its influence on the available conformations of a peptide.

In both X-ray diffraction analyses and conformational energy calculations of Δ²-Phe-containing peptides the φ angle of the dehydro residue is frequently near 60° and ψ near 0°.⁵ For example, the X-ray crystal structure of *N*-acetyl-Δ²-Phe has φ = 72° and ψ = 13°;⁶ the X-ray crystal structure of *N*-pivaloyl-Pro-Δ²-Phe-methylamide has φ = 63° and ψ = 10° for Δ²-Phe;⁷ energy calculations on *N*-acetyl-Δ²-Phe-methylamide show an energy minimum at φ = 60° and ψ = 10°.⁸ The similarity of the preferred Δ²-Phe conformation to that taken up by a residue in the *i* + 2 position of a type II β turn is noteworthy: average φ and ψ values in type II β turns (from X-ray data) are 80° and 0°, respectively, for the *i* + 2 position.⁹ Substitution of Δ²-Phe for such a residue in a peptide may result in a conformationally homologous *dehydropeptide*.

To test this hypothesis we have synthesized two cyclic pentapeptides: *cyclo*(Gly¹-Pro²-Δ²-Phe³-D-Ala⁴-Pro⁵) I (the cyclic dehydropeptide) and *cyclo*(Gly¹-Pro²-D-Phe³-D-Ala⁴-Pro⁵) II (the

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(II)

cyclic peptide). We anticipated from previous work¹⁰⁻¹² that I would favor a Gly-Pro-D-Phe-D-Ala type II β turn, i.e., with D-Phe in position *i* + 2 of the turn and with a D-Ala-Pro-Gly γ turn (see below). We present evidence that it does. Furthermore, substitution of Δ²-Phe for D-Phe (in peptide I) causes very little conformational change, in keeping with the above hypothesis.

The cyclic peptide II was synthesized by methods previously reported,¹⁰ including cyclization of the pentapeptide *p*-nitrophenyl ester (yield, 37%). An unsaturated azlactone was prepared from Boc-Pro-DL-β-phenyl-Ser-OH by the modified Bergmann synthesis¹³ and was coupled with H-D-Ala-Pro-Gly-OMe giving a Δ²-Phe-containing pentapeptide which was then cyclized as the *p*-nitrophenyl ester (yield, 5%). Since the cyclization conditions were the same for I and II, these different yields reflect the relative ease of forming cyclic product; the required folded conformation may be less accessible to the dehydropeptide. Both I and II are pure by thin-layer and high-performance liquid chromatography, and their monomeric character was confirmed by chemical ionization mass spectroscopy.¹⁴

¹H and ¹³C nuclear magnetic resonance (NMR) data (Figures 1B and 2B) support the proposed conformation of the cyclic peptide II. The resonances of the D-Ala and Gly NH's occur at 7.83 and 7.78 ppm, respectively, typical of NH's involved in intramolecular hydrogen bonds;⁹,¹⁰ᶜ by comparison, the D-Phe NH resonates at higher field (5.89 ppm) as expected for a non-hydrogen-bonded NH in a solvent like CDCl₃, at high dilution (21 mM).⁹,¹⁰ᶜ The D-Ala and Gly NH's also show reduced temper-

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(14) Precise Mass: I, 468.226 (C₂₄H₂₇N₅O₅ + H)⁺; II, 470.241 (C₂₄H₂₉N₅O₅ + H)⁺.