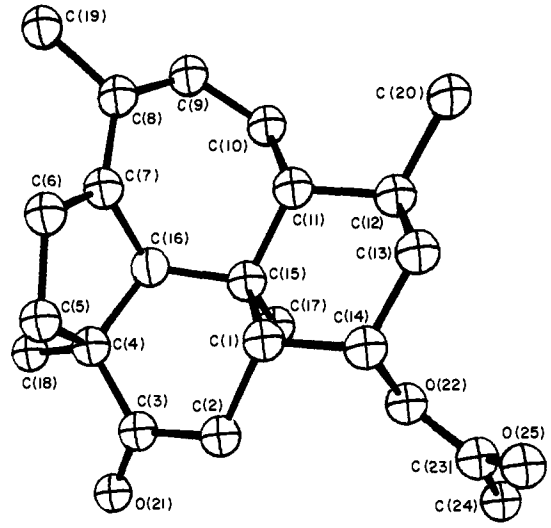

Figure 2. A computer-generated perspective drawing of kempene-2 (**3**). Hydrogens are omitted for clarity.

as the diffraction data were converted to normalized structure factors.[10] Phases were assigned to the 250 largest E values by a multiple-solution weighted tangent formula approach.[11] The resulting E synthesis showed most of the nonhydrogen atoms. The remaining atoms were located by tangent formula refinement with all $|E| \geq 1.00$. Hydrogens were located in difference electron density syntheses.[12] Full-matrix least-squares refinements with anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors for hydrogens have converged to a conventional crystallographic residual of 0.040 for the observed reflections. Tables of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors can be found in the supplemental material.

A perspective drawing of the final x-ray model less hydrogens is given in Figure 2. The absolute configuration was not determined by the x-ray analysis (vide infra). Kempene-2 is a dome-like tetracyclic array of five-, six-, and seven-membered rings. Most of the substituents are on the convex surface, the exceptions being the hydrogens at C-1 and C-11. The bond distances and angles show no pronounced strain effects. The diene system is twisted ~20° out of planarity.

The kempenes are closely related to the trinervitenes, e.g., TG-2 (**1**)[2,3] and hence the absolute configuration should be as drawn in **2** and **3**. However, the configurations of the C-12 methyls are inverted. The absolute configuration shown is corroborated by the positive Cotton effects due to the positively twisted diene system[13] in the kempene skeleton (see stereostructure **5**).

Acknowledgments. We thank the NIH for Grant AI 10187 to K.N. and Fellowship AI 05076 to G.D.P.

Supplemental Material Available: Fractional coordinates (Table 1), important bond distances (Table 2), important bond angles (Table 3), and observed and calculated structure factors (Table 4) (9 pages). Ordering information is given on any current masthead page.

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(6) *Nasutitermes kempae* Harris was collected from arboreal colonies in Kwale, Kenya, East Africa. The termite soldiers were removed, cooled to 0 °C, and decapitated, the heads were crushed under hexane, and the solvent was removed in vacuo. About 100 mg of crude secretion was obtained from 5000 individuals. Chromatography of this crude material over Florisil (100–200 mesh) with increasing percentages of ethyl acetate in benzene afforded two UV-active materials, kempene-1 (R_f 0.41 on silica gel GF254 with 15% ethyl acetate in benzene) and kempene-2 (R_f 0.37). Samples of **2** and **3** for spectroscopic studies (~5 mg each) were further purified by HPLC using a 30 cm × 4 mm μ-Porasil column and eluting at 2 mL/min with 12 and 15% ether in hexane, respectively.
(7) Neither the conditions leading to oxygenation nor the structure of the product were explored further. The EIMS and CIMS both led to a formula containing one extra oxygen.
(8) Details of NMR structural studies will be published separately together with the corresponding data for the trinervitenes.
(9) The very low intensities (ϵ 85) of the diene chromophores around 245 nm in **2** and its 3-epi acetate (see text) are anomalous. The CD $\Delta\epsilon$ values of these two diacetates (+0.058 and +0.069) are slightly stronger than that of kempene-2 (**3** or **5**), and this implies that the diene in the two diacetates is slightly more positlvely twisted. However, this is hardly sufficient to account for the dramatic decrease in the UV peak heights. We tentatively attribute these low ϵ values of the diacetates to the possibility that, when C-3 is sp^3 hydridized as in **2**, the ring strain of the bridged system is released so that the diene moiety approximates an allene-like orthogonality.
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(14) Address correspondence to the Department of Chemistry, State University of New York, Stony Brook, N.Y. 11794.
(15) Camille and Henry Dreyfus Award, 1972–1977.

Glenn D. Prestwich*[14]
The International Centre of Insect Physiology and Ecology
P.O. Box 30772, Nairobi, Kenya

Barbara A. Solheim, Jon Clardy*[15]
Ames Laboratory—USERDA and Department of Chemistry
Iowa State University, Ames, Iowa 50011

Frank G. Pilkiewicz, Iwao Miura
Steven P. Tanis, Koji Nakanishi*
Department of Chemistry, Columbia University
New York, New York 10027

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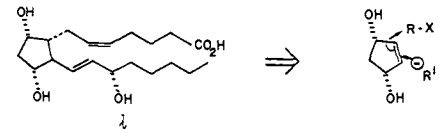
Prostaglandin Synthesis via Carbopalladation

Sir:

Synthesis of the primary prostaglandins has been a focal point for organic chemists for almost 10 years; during this time several elegant total syntheses have been achieved by a variety of workers.[1] We wish to report a different approach to this problem which has now led to the development of an exceptionally efficient and short conversion of cyclopentadiene into prostaglandin.

Our general strategy for synthesis of, for example, $PGF_{2\alpha}$ (**1**) initially involved the development of methods for the direct



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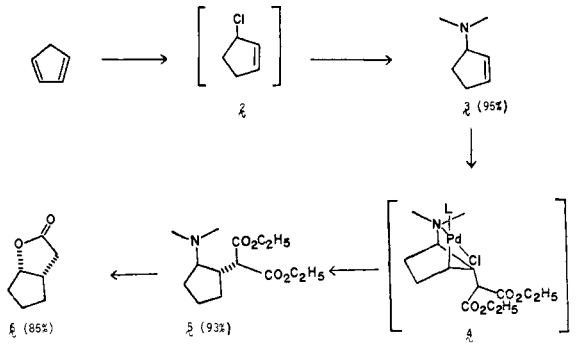
attachment of two side-chain fragments R and R′ to the *unactivated* double bond of an appropriately substituted cyclopentene derivative. To this end, preliminary studies in our

laboratory have produced methodology permitting regiospecific attachment of stabilized enolates at either C-2 or C-4 of simple olefinic amines or sulfides leading, after reduction of intermediate palladium complexes, to γ- and ϵ-amino- and alkylthio esters in high yield.[2,3] Furthermore, we have demonstrated that the intermediate palladium complexes may be easily converted to enones in the presence of an appropriate vinyl ketone.[2,4]

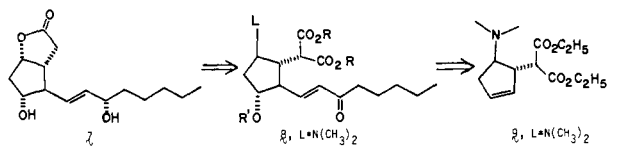
Application of this methodology to prostanoid synthesis required that carbopalladation proceed with complete stereospecificity as well as regiospecificity. Indeed, there exists literature precedent[5] which allows one to predict exclusive trans addition of malonate and palladium to the olefinic linkage. Verification of this postulate has been provided in the following way. Addition of hydrogen chloride gas to cyclopentadiene gave the very reactive chloride **2**[6] which was added directly without isolation to a solution of excess anhydrous dimethylamine in tetrahydrofuran (THF) at −78 °C. After the solution was warmed to room temperature over a 12-h period, cyclopentenylamine **3**[7] could be isolated in 95% yield:[8] bp 35 °C (20 mm); NMR ($CDCl_3$) δ 1.60–2.30 (m, 4), 2.20 (s, 6), 3.67 (m, 1), 5.83 (m, 2); IR ($CHCl_3$) 3.45, 6.85, 7.34, 9.65 μ. Carbopalladation of **3** with sodium diethyl malonate in THF at 0 °C for 2 h proceeded smoothly to afford a palladium complex, presumably **4,** which deteriorated sufficiently rapidly so as to preclude isolation and characterization. However, introduction of a stream of hydrogen gas directly into the THF solution at 0 °C rapidly gave a precipitate of metallic palladium[9] and amino diester **5**:[7] bp 117–120 °C (1 mm, Kugelrohr); NMR ($CDCl_3$) δ 1.27 (t, 6, J = 8 Hz), 2.19 (s, 6), 3.32 (d, 1, J = 7 Hz), 4.13 (q, 2, J = 8 Hz), 4.20 (q, 2, J = 8 Hz); IR ($CHCl_3$) 3.44, 5.78, 6.89, 7.32, 9.5 μ; 93% yield.[8] The trans stereochemistry assigned to **5** was unambiguously demonstrated by conversion to the methiodide, which was treated directly with aqueous KOH in dimethylformamide,



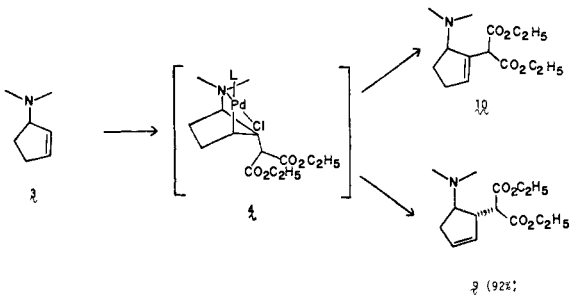
first at room temperature for 18 h, then at ~120 °C (with distillation of water) for 12 h, to produce, after extraction from aqueous acid, the lactone **6**[10] in 85% yield.

With these results in hand, our synthetic strategy focused upon the preparation of Corey lactone diol **7,** an intermediate which has previously been converted to $PGF_{2\alpha}$ in two chemical steps and 80% overall yield.[11] Lactone **7** was envisioned to come from enone **8** via reduction of enone, deprotection, and hydrolysis-lactonization-decarboxylation as above. Amino diester **8** might be prepared by homoallylic alkoxypalladation-ketovinylation[3,12] of **9,** with regiochemistry directed by the sterically shielding diethyl malonate group. We hoped that olefinic amino diester **9** would in turn become available from dehydropalladation of complex **4.**

In the event, addition of potassium *tert*-butoxide to the THF

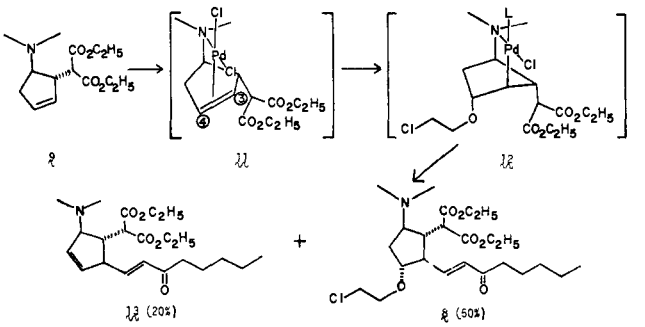


solution of complex **4** at room temperature rapidly gave a mixture of olefinic isomers, with the undesired isomer **10** strongly predominant. However, treatment of **3** with stoichiometric amounts of lithium tetrachloropalladate (LTP) and



sodium diethyl malonate in THF at 0 °C for 2 h, addition of diisopropylethylamine (5 mol equiv), and warming to reflux for 30 min, led, after filtration of palladium, to isolation of isomerically pure desired olefin **9**[7] in 92% yield:[8] bp 117–120 °C (1 mm, Kugelrohr); NMR ($CDCl_3$) δ 1.27 (t, 6, J = 8 Hz), 2.17 (s, 6), 3.30 (m, 2), 4.16 (q, 4, J = 8 Hz), 5.73 (m, 2); IR ($CHCl_3$) 3.43, 5.80, 6.89, 7.34, 8.55, 9.67 μ.

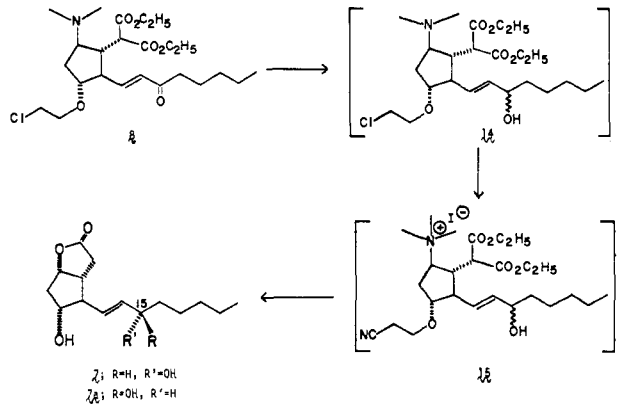
Alkoxypalladation-ketovinylation of **9** proved to be a more difficult proposition. It was necessary to select an alcohol partner for the reaction having (a) sufficient bulk so that interference of the adjacent malony moiety would direct addition to **11** exclusively to position 4, and (b) an alkyl portion which



could subsequently be removed to reveal the free alcohol. We have found β-chloroethanol to be suitable for this purpose. Thus, treatment of **9** with LTP in a mixture of 4:1 β-chloroethanol-Me_2SO containing 5 mol equiv of diisopropylethylamine at 0–5 °C for 18 h gave rise to palladium complex, presumably **12** (isolation and characterization prevented by decomposition), which was immediately treated with *n*-pentyl vinyl ketone[13] in 2:1 dimethylformamide-benzene at room temperature for 24 h.[14] Filtration of palladium metal followed by preparative layer chromatography led to isolation of two enone products, unwanted diene **13** (20% yield from **11**) and the desired enone **8**[7,15] (50% yield[8] from **11**): NMR ($CDCl_3$) δ 2.21 (s, 6), 4.13 (q, 2, J = 8 Hz), 4.14 (q, 2, J = 8 Hz), 6.18 (d, 1, J = 16 Hz), 6.79 (dd, 1, J = 7, 16 Hz); IR ($CHCl_3$) 3.41, 5.77, 5.97, 6.11, 6.86, 7.31, 8.30 μ. We have not yet been able to clearly decipher the origin of **13** nor have we been able to circumvent its formation. We are still attempting to overcome this problem.

Having achieved the synthesis of **8** from cyclopentadiene in three chemical steps and 44% overall yield, we turned to the conversion of **8** into the required lactone **7.** Reduction of enone to allylic alcohol was best accomplished[16] through the use of L-selectride[17] (1.5 mol equiv) in 4:1 ether-THF solution at −115 °C for 2 h. Isolation of allylic alcohol **14** at this stage was hampered by the necessity to remove borane side products, oxidative removal[17] being incompatible with tertiary amino functionality. Therefore, isolation of material was delayed until after deprotection and lactonization; subsequent to reduction,

excess borohydride and lithium alkoxide were quenched by the addition of acetone and ammonium carbonate, and solvent was removed under reduced pressure and replaced with deoxygenated DMF. To this solution was added sodium cyanide (2.0 mol equiv) in DMF and the mixture was warmed to 75 °C for 18 h to allow conversion of chloride to nitrile. The solution was cooled to room temperature and excess methyl iodide was introduced to produce quaternary salt **15**. Volatile material



(methyl iodide, acetonitrile) was removed under reduced pressure and decyanoethylation, hydrolysis, decarboxylation, and lactonization were accomplished through the action of aqueous potassium hydroxide in the same manner as previously described for the **5** → **6** conversion. Extraction from dilute acid afforded, after preparative layer chromatography, the racemic lactone diol **7**[18] along with an approximately equal portion of **7a**, epimeric at C-15, in 75–80% combined yield from enone **8**.

As previously stated, **7** has been converted to a variety of natural prostaglandins in high yield, and synthesis of this material thereby constitutes a synthesis of the natural products. We believe that this synthesis is the simplest and most efficient reported to date, affording **7** in ~35% overall yield in four chemical steps from cyclopentadiene.

Two obstacles remain to be overcome. At this time synthetic **7** consists of a racemic mixture of diastereomers. Although the C-15 epimers are separable by chromatography, and it has previously been established that 15-epi material may be recycled by oxidation–reduction,[19] we find this to be an aesthetically unpalatable procedure. Although we have not yet conducted experiments in this area, we believe that it may be possible to direct the reduction of **8** to the desired isomer[20] by varying either the alkyl portions of the ester or the protecting group attached to the hydroxyl at C-11. Secondly, it should be noted that preparation of optically active materials should present no great difficulty. We believe that resolution of the very inexpensive amine **3** will prove to be an extremely simple task, and from this point no further resolution should be necessary.

A unique feature of this synthesis is the unambiguous establishment of four contiguous stereocenters about a cyclopentane ring from a single amino directing functionality. This sequence of reactions firmly establishes that carbopalladation and alkoxypalladation occur via stereospecific trans addition to the olefinic linkage, and that ketovinylation proceeds with *retention* of configuration of the migrating group attached to palladium. We believe that the principles delineated herein will prove invaluable to organic synthesis; further studies involving carbopalladation and natural product synthesis are in progress.

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(7) Correct exact mass data have been obtained for this compound.

(8) Yields refer to spectrally homogeneous material of >95% purity.

(9) Despite the fact that the reactions described here are not catalytic with respect to palladium, it should be pointed out that palladium may be easily recovered from each of these reactions by simple filtration through Celite and subsequently recycled.

(10) Identified by comparison (TLC, GC, IR, NMR, mass spectrum) with an authentic sample prepared by hydrogenation (H_2, 5% Pd/C, ethyl acetate) of unsaturated lactone i, kindly supplied by Mr. R. J. Pariza.

(11) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971); Dr. G. Bundy, private communication.

(12) Stereochemistry of ketovinylation was predicted to be the same as that of carbonylation; see L. F. Hines and J. K. Stille, *J. Am. Chem. Soc.*, **94**, 485 (1972).

(13) Conveniently prepared from 1,3-diethoxypropene and *n*-pentyl bromide; R. A. Holton, manuscript in preparation.

(14) Ketovinylation of monocyclic complexes similar to **4** requires refluxing benzene or toluene; see ref 4. Presumably the strain inherent in **12** is responsible for this remarkably facile ketovinylation.

(15) Although **8** was a single isomer, unambiguous assignment of stereochemistry at this stage was not possible. The assigned stereochemistry of **8** rests on its ultimate conversion to **7**.

(16) In our hands, neither zinc borohydride (DME, 25 °C) nor sodium borohydride (C_2H_5OH, −78 °C) gave satisfactorily clean 1,2 reduction of **8**.

(17) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

(18) Identical (IR, TLC, NMR, mass spectrum) with an authentic sample kindly supplied by Dr. G. L. Bundy, Upjohn Co. We thank Dr. Bundy and Upjohn for their generosity.

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(21) Du Pont Assistant Professor of Chemistry.

Robert A. Holton[21]

R. B. Wetherill Laboratory of Chemistry
Purdue University, West Lafayette, Indiana 47907

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Mechanism of the Palladium-Catalyzed Synthesis of α-Methylene Lactones from Carbon Monoxide and Acetylenic Alcohols

Sir:

We have found that our palladium-catalyzed synthesis of α-methylene lactones[1] proceeds with kinetic control of the double-bond location, we have proposed a mechanism to explain this and other observations, and we have demonstrated its feasibility by isolating and interconverting the proposed organopalladium intermediates in complexes containing stabilizing ligands.

Although the isomerization of the double bond of damsin during its attempted hydrogenation[2] showed the thermodynamic instability of some α-methylene lactones, we required knowledge of the position of such isomerization equilibria, if established, for the products of our catalytic reactions. We have thus treated the simple fused-ring lactones **1a** and **1b** with $HRh(Ph_3P)_3CO$, known to be an excellent double-bond isomerization catalyst (eq 1).[3] In both cases isomerization to the corresponding butenolides **2a**[4] and **2b** is complete.[5] It is thus apparent that an effective double-bond isomerization