Acknowledgment. We thank the National institutes of Health (GM 36792) for support.

Supplementary Material Available: Spectral data (IR, MS, ^1H NMR, and ^{13}C NMR) for compounds **1–6**, **9**, **10**, **12–18**, **21**, **22**, and **24** (4 pages). Ordering information is given on any current masthead page.

Novel Stereospecific Silyl Group Transfer Reactions: Practical Routes to the Prostaglandins

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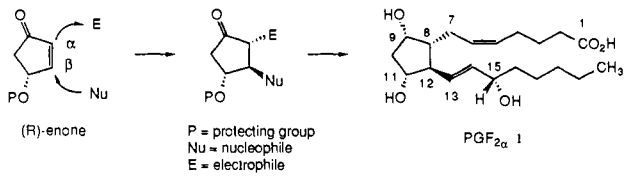
The notion of synthesizing prostaglandins by dialkylation of an α,β-unsaturated ketone goes back to the early days of the field.[1] The first success in a fully functionalized setting was realized by Stork and Isobe.[2] Major advances in conciseness and efficiency have been introduced by Noyori,[3,4] Johnson,[5] and Corey.[6]

While there have been countless variations, a common theme is apparent. Addition of a nucleophilic version of the C_{13}–C_{20} ("lower-chain") to C_{12} generates a C_8–C_9 enolate which is trapped with an electrophile suitable for construction of the C_7–C_1 ("upper") chain. In these schemes, the R enantiomer is employed. The stereochemical rationale of this method is that the organometallic nucleophile (Nu) attacks anti to the OP group and the electrophile attacks C_8 anti to the "lower" chain installed at C_{12}. The proper configuration at C_{15} is achieved either from the use of a suitable educt[7] or by reduction of the C_{15} ketone.[7,8] The general outlines of the previous three-component strategy are implied in Scheme I, where $PGF_{2\alpha}$ is the goal system.

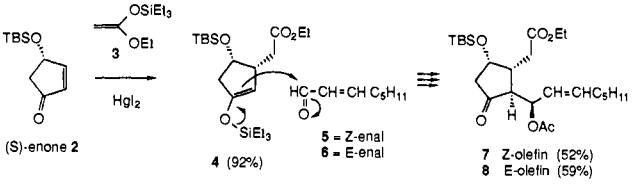
In this paper we disclose a new strategy wherein the C_{12}–C_{13} bond is established from an electrophilic version of C_{13}, and the C_8–C_7 bond is fashioned from a nucleophilic version of C_7. As will be seen, this method has significant advantages in terms of simplicity of building blocks and reactions. Either isomer at C_{15} becomes readily available by stereochemical communication.[9]

The success of the route arises from the confluence of several rather interesting findings. The first is that a group transfer reaction of (*S*)-enone **2** (vide infra) with the silylketeneacetal derivative **3** occurs cis to the OTBS group to produce the specific enolate equivalent **4**.[10,11] This compound reacts with (*Z*)-[12a] or (*E*)-octenal[12b] (**5** and **6**, respectively) under catalysis by $TiCl_4$ to produce the C_{12}–C_{13} syn aldol products.[13,14] In each case, the aldehyde has entered trans to the carbethoxymethyl group at C_8. In each instance, the aldol process involves a second group transfer reaction of the triethylsilyl (TES) unit. Each aldehyde attacks trans to the resident group at C_8, and a syn C_{12}–C_{13} siloxyaldol system is produced in an essentially stereospecific reaction. In each instance selective cleavage of the TES function is achieved with maintenance of the OTBS group.[15] For the product derived

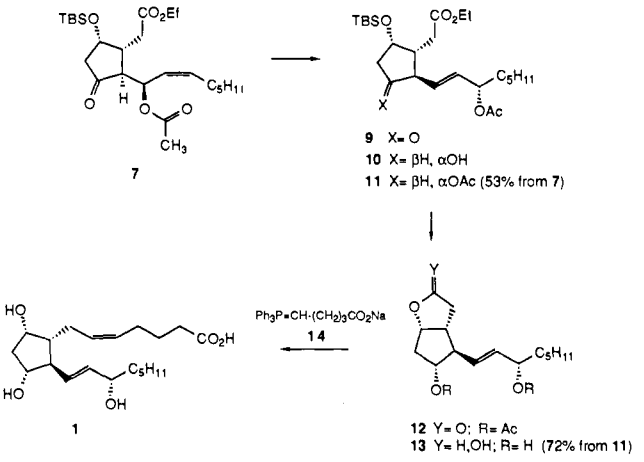
Scheme I



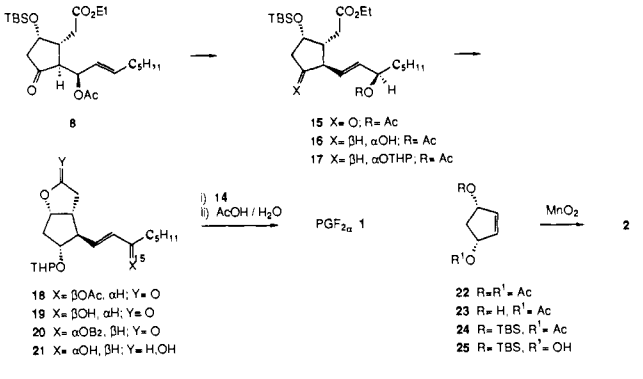
Scheme II



Scheme III



Scheme IV



(1) For comprehensive reviews of prostanoid syntheses, see: (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (b) Mitra, A. *Synthesis of Prostaglandins*; Wiley-Interscience: New York, 1977. (c) Garcia, G. A.; Maldonado, L. A.; Crabbe, P. *Prostaglandin Research*; Crabbe, P., Ed.; Academic Press: New York, 1977; Chapter 6. (d) *New Synthetic Routes to Prostaglandins and Thromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic Press: London, 1982.

(2) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(3) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.

(4) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.

(5) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726.

(6) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(7) Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.

(8) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616.

(9) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.

(10) This phenomenon which awaits full explanation is restricted to Lewis acid catalyzed additions (as opposed to cuprate additions which occur anti to the OTBS group). It has also been extended to $TiCl_4$ mediated addition of allyltrimethylsilane to **2** (Chow, K. Yale University unpublished results). For similar results using 4-OTBS cyclohexenone, see: a) Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1555. b) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, 0000.

(11) All new compounds were characterized by ^1H NMR, IR, mass spectrometry, HRMS, and/or elemental analyses.

(12) (a) Byrne, B.; Lafleur-Lawter, L. M.; Wengenroth, K. J. *J. Org. Chem.* **1986**, *51*, 2607. (b) Commercially available from Aldrich Chemical Company.

(13) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(14) Masamune, S.; Ali, Sk. A.; Snitmann, D. C.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

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from **4** + **5** (*Z*-series), this selective desilylation is accomplished upon exposure of the system to the aldol reaction conditions ($TiCl_4$–CH_2Cl_2, −85 °C, 30 min). For the product derived from **4** + **6** (*E*-series), a subsequent reaction of the siloxy transfer product with aqueous AcOH–THF achieves the same result. The resultant alcohols are acetylated (Ac_2O; Py; DMAP) to afford acetates **7** and **8** in the indicated yields.

The pathways from compound **7** and **8** to $PGF_{2\alpha}$ were very direct indeed. *Reaction of compound 7 with $Pd(MeCN)_2Cl_2$ led to allylic transposition of the acetate with the formation of the $E_{13,14}$ double bond and installation of the required 15S stereochemistry (see compound 9) in 72% yield.*[16-19] At this stage[20] reduction of the C_{11} ketone with sodium borohydride is stereospecific in the desired sense. Acetylation provided compound **11** in 74% yield (53% overall yield from **7**). Cleavage of the TBS group and lactonization was accomplished through the action of TBAF. Reaction of **12** with DIBAL resulted in formation of the lactol with deacylation to give compound **13** in 72% overall yield from **11**. Reaction of **13** with phosphorane **14** under the usual conditions gave, in 53% yield,[21] $PGF_{2\alpha}$ (**1**) whose infrared and NMR spectra as well as optical rotation and chromatographic properties were identical with those of an authentic sample.[22]

The same type of allylic transposition occurred even more rapidly[23] with the *E* isomer **8**. The rearrangement is unidirectional,[24] and the C_{13}–C_{14} double bond emerges cleanly trans. The stereochemistry at carbon 15 is of course *R*. Again, reduction of the C_{11} ketone with sodium borohydride is stereospecific affording compound **16** which was protected as its tetrahydropyranyl ether **17** (69% overall yield from **8**). Desilylation as above is accompanied by lactonization, and compound **18** is obtained in 84% yield. This substance is clearly a very valuable intermediate for preparing prostaglandins of the 15*R* series. We have used it to cross over to the natural series by inverting the stereochemistry at carbon 15. This was accomplished as follows. Deacylation of the **18** epiacetate afforded (98%) the 15*R* alcohol **19**, which was inverted in a standard Mitsunobu reaction[25] to the 15*S* benzoate **20** in 73% yield. Treatment of this compound with diisobutyl aluminum hydride resulted in reduction of the lactone and debenzoylation, affording compound **21**. Reaction of this compound with Wittig reagent, **14**, followed by cleavage of the THP protecting group (aqueous acetic acid), again afforded $PGF_{2\alpha}$ (**1**), this time in 46% yield from **20**.[21]

These routes offer major advantages in terms of conciseness, availability of all the building blocks, and simplicity of the reactions. Not the least advantage is the ready access to the required (*S*)-enone **2**. The diacetate **22**, available in multigram scale from cyclopentadiene,[26] is converted through the action of acetylcholinesterase[27] in 89% yield and, essentially total optical purity, to the monoacetate **23**. Protection of the alcohol as its TBS derivative through the action TBSCl and imidazole in DMF affords **24** which on simple hydrolysis (sodium methoxide) leads to **25**. The latter is oxidized with manganese dioxide to the optically pure (*S*)-enantiomer **2**. The overall conversion of **22** to **2** is achieved in 70% yield. *This chemistry provides an eminently practical route for the total synthesis of prostaglandins and congeners thereof.*[28] Experiments directed toward taking advantage of this new capability will be described in due course.

Acknowledgment. This research was supported by PHS Grant HL25848. An MEC/Fulbright Fellowship to M.P.C. is gratefully acknowledged. We thank Professor K. C. Nicolaou of the University of Pennsylvania for providing valuable correlation samples for our synthetic intermediates on the way to $PGF_{2\alpha}$. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility of Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Supplementary Material Available: Spectral data (^1H NMR, IR, and MS) for all compounds described herein (5 pages). Ordering information is given on any current masthead page.

(15) A major complication arises if the TBS group is cleaved at this stage. With the C_{11} ketone still in place, β-elimination occurs to give the enone.

(16) For a most interesting precedent for this type of stereochemical adjustment in the [2,3] series, see: Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774.

(17) For the first application of the Pd(II)-mediated allylic acetate transposition to a modified prostaglandin intermediate, see: Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7588.

(18) Pd(II)-catalyzed allylic acetate transposition was first described by: Meyer, K. DOS 2513198 (1975); *Chem. Abstr.* **1976**, *84*, 89629s.

(19) For a full review of Pd(II)-catalyzed [3,3] sigmatropic rearrangements, see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

(20) Attempts to carry out the reduction of the C_{11} ketone before the allylic transposition results, at best, in modest stereoselectivity possibly due to competing directivities from the 13-oxygen function.

(21) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(22) The synthetic material had an optical rotation $[\alpha]_D$ +23.0° (*c* 1.01, THF) which is essentially the same as authentic $PGF_{2\alpha}$ ($[\alpha]_D$ +23.5°, *c* 1.0, THF).

(23) Not surprisingly the rate of transposition of the *Z* isomer is slower than that of the *E* isomer. For compound **7** conditions involved catalytic Pd(II) in THF at room temperature for 4 h. For compound **8**, the equivalent transformation was complete after 2 h.

(24) Compound **9** and **15** failed to show indications of undergoing back rearrangement.

(25) A solution of **19** in THF was treated with triphenylphosphine (2 equiv), benzoic acid (2 equiv), and diethylazodicarboxylate (2 equiv) at room temperature. After 5 min the reaction was quenched with a solution of saturated $NaHCO_3$. See: (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(26) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615.

(27) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

(28) This assessment is not meant by way of a comparison with the efficiency of previous excellent efforts (ref 2-6). A detailed analysis of the implications of our work for commercial production relative to the existing methods has not been undertaken. The attraction of our route stems from the easy availability of all of its components and the ease of their assembly. In that vein we note that, as of this writing, the (*S*)-enone **2** is more readily obtained than is either the (*R*)-enone or, indeed, the racemate.

Hemoglobin Quaternary Structure Change Monitored Directly by Transient UV Resonance Raman Spectroscopy

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We report pulse-probe transient ultraviolet resonance Raman (UVRR) spectra of photolyzed carbonmonoxy hemoglobin (HbCO) which provide direct evidence that the R → T quaternary structure change occurs in ~20 μs. This process coincides with the transition from fast to slow recombining Hb[1] and with the final optical transient of photolyzed HbCO molecules.[2] The UVRR spectra are interpreted as responding to H bonding changes of aromatic groups at the $\alpha_1\beta_2$ interface of the Hb tetramer. The transient signals also indicate the formation of a structural intermediate associated with the R → T transition.

Figure 1 shows a fragment of the UVRR spectra of oxy- and deoxyHb excited at 229 nm with an H_2-Raman-shifted pulsed Nd:YAG laser.[3] The spectra contain bands which are associated with ring modes of tyrosine (Tyr), $\nu_{8a/8b}$ = 1617/1601 cm^{-1}, and tryptophan (Trp), W_3 = 1555 cm^{-1}.[4,5] These spectra have sufficient signal/noise to expose the slight differences between oxy- and deoxyHb. The difference spectrum reveals a downshift (1.5 cm^{-1}) of the Trp band and upshifts (2 cm^{-1}) in the Tyr bands.

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(1) Sawicki, C. A.; Gibson, Q. H. *J. Biol. Chem.* **1976**, *251*, 1533.

(2) Hofrichter, J.; Sommer, J. H.; Henry, E. R.; Eaton, W. A. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2235.

(3) Fodor, S. P. A.; Rava, R. P.; Copeland, R. a.; Spiro, T. G. *J. Raman Spectrosc.* **1986**, *17*, 471.

(4) Rava, R. P.; Spiro, T. G. *J. Phys. Chem.* **1985**, *89*, 1856.

(5) Takeuchi, H.; Harada, I. *Spectrochim. Acta* **1986**, *42A*, 1069.

0002-7863/89/1511-3457$01.50/0