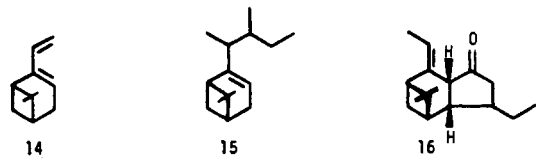

14 15 16

The present study adds to the growing list of highly stereoselective methods for preparing exocyclic alkenes.[9] Finally, we made an erroneous claim that the reaction of 1,3-butadiene with n-Bu_2ZrCp_2 gave (1,3-butadiene)$ZrCp_2$.[2] In the light of the results presented herein, we wish to correct this error with apology.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8842237) and the National Institutes of Health (Grant GM36792) for support. We acknowledge that this study was triggered by an observation in 1987 by Dr. Y. Zhang of our laboratory that the reaction of 1-vinyl-1-cyclohexene with n-Bu_2ZrCp_2 produced an n-Bu-incorporated product **4b**. We also thank Dr. G. Wu for technical assistance in obtaining some NMR spectra.

Total Synthesis of 13-Oxygenated Prostanoids Derived from Arachidonate: An Instance of Extraordinary Variability in the Stereochemical Sense of a Mukaiyama Aldol Reaction

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Received September 18, 1989

Summary: A complete reversal of stereochemical outcome in the Mukaiyama reaction of oct-2-ynal as opposed to either (*E*)- or (*Z*)-oct-2-enal with a common enoxysilane has been noted and applied to a very straightforward synthesis of the titled series.

Sir: The principal 9α,11α-endoperoxides arising from the in vivo oxidation of arachidonate, in the presence of PGH synthase, contain a trans 13,14-double bond and either 15(*S*)-hydroperoxy (PGG_2) or 15(*S*)-hydroxy (PGH_2) functions.[1,2] Surprisingly, it was recently shown that this process also produces isomers of the above, bearing oxygen substitution at C_{13} (Scheme I). Reduction of this endoperoxide gives rise to the allylic isomer of $PGF_{2\alpha}$.[2,3] That this prostaglandin is properly represented by structure 1 was demonstrated by Hofmann and colleagues. The four permutants bearing a 13-hydroxy group and a Δ^{14} double bond were synthesized.[4] A minor synthetic product, shown to be compound 1, corresponded to the naturally derived product.

It was our intention to provide the difficulty accessible compound 1 through total synthesis. Recently we described two concise syntheses of $PGF_{2\alpha}$[5] (Scheme II). Each synthesis involved a stereospecific aldol-like reaction,[6] catalyzed by titanium tetrachloride, between enoxysilane **4**[7] and the α,β-unsaturated aldehydes (*Z*)- and (*E*)-2-octenal. Each aldol reaction occurred with transfer of the triethylsilyl group to afford **5** and **6**, respectively, wherein, in each case, the configuration at C_{13} is *R*.[8] In principle, one could envision one of several protocols to bring about an overall inversion at C_{13} with preservation of the *Z*-Δ^{14} unsaturation for the conversion of compound **4** to **1**. In practice a much simpler route was discovered.

The key reaction was that of enoxysilane **4** with oct-2-ynal (**7**).[9] As in the previous work,[5] the reaction was carried out in methylene chloride in the presence of titanium tetrachloride (1 equiv). There was thus obtained an acetylenic alcohol. Unlike the reactions with the two enals, we could not observe any of the silyl group transfer product. At this stage, it was not possible to determine the stereochemistry at C_{13} in this product. Semihydrogenation of the triple bond (H_2; Lindlar catalyst; 50 min) afforded a *Z*-allylic alcohol, which, upon acetylation (Ac_2O, Py, DMAP), afforded a *Z*-allylic acetate in 50% overall yield from **3**. This compound did not converge with any transformation products of **5**. *Our suspicion that the noncorrespondence arose from a differing configuration at C_{13}[8] was confirmed.* The allylic acetate, thus formulated as **9**, upon treatment with $PdCl_2(MeCN)_2$[10] afforded compound **11**. The same compound was obtained from the allylic transposition carried out in the same way on the 13-acetate derived from **6**.[5] The structure of **11** is secure in that it had been converted to $PGF_{2\alpha}$[5] by a sequence that

(1) Samuelsson, B. *Angew Chem., Int. Ed. Engl.* **1983**, *22*, 805.
(2) Hecker, M.; Hatzelmann, A.; Ullrich, V. *Biochem. Pharmacol.* **1987**, *36*, 851.
(3) Hecker, M.; Ullrich, V.; Fischer, C.; Meese, O. C. *Eur. J. Biochem.* **1987**, 113.
(4) Hofmann, U.; Meese, C. O.; Hecker, M.; Ullrich, V. *Tetrahedron Lett.* **1985**, 5655.
(5) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.
(6) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. (b) Kobayashi, T.; Mukaiyama, T. *Ibid.* **1986**, 1805.
(7) As shown, this compound is prepared from a group transfer Michael reaction of a suitable silylketene acetal. Cf: Webster, O. W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. B.; Rajan Babu. *J. Am. Chem. Soc.* **1983**, *105*, 5706.
(8) The reader will not be confused at the fact that the *R* and *S* descriptors for compounds **6**, **7**, and **8** (13*R* in each case) fail to communicate the fact that the relative configuration at C_{13} is opposite in **8** from that of **5** and **6**. This situation is better captured by focusing on the C_{12}–C_{13} relationship, which may be said to be syn in **5** and **6** (in the zig-zag conformer shown) and anti in **8**.
(9) Prepared by acid-catalyzed hydrolysis of the corresponding dimethyl acetal. Bryne, B.; Lafleur Lawter, L. M.; Wengenroth, K. J. *J. Org. Chem.* **1986**, *51*, 2607.
(10) (a) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

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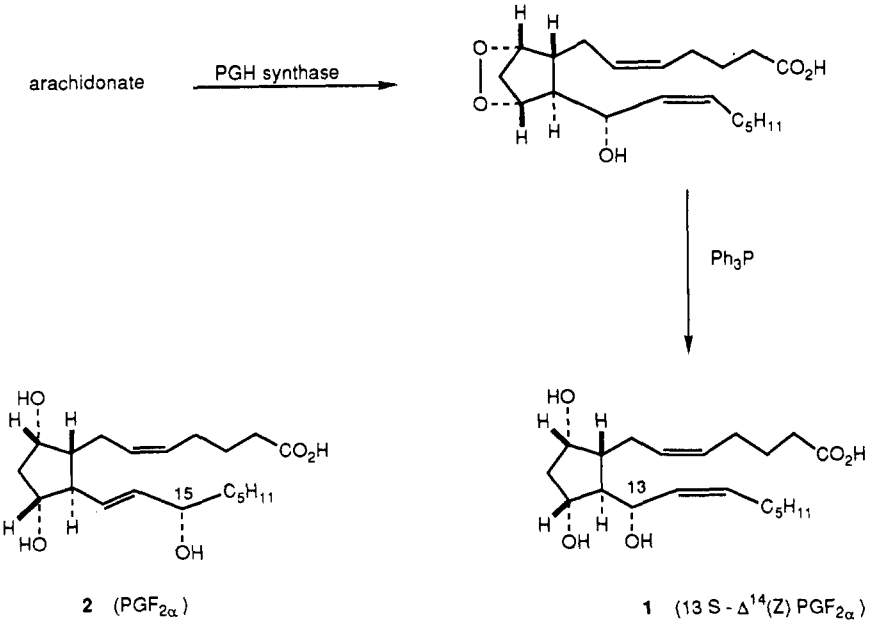
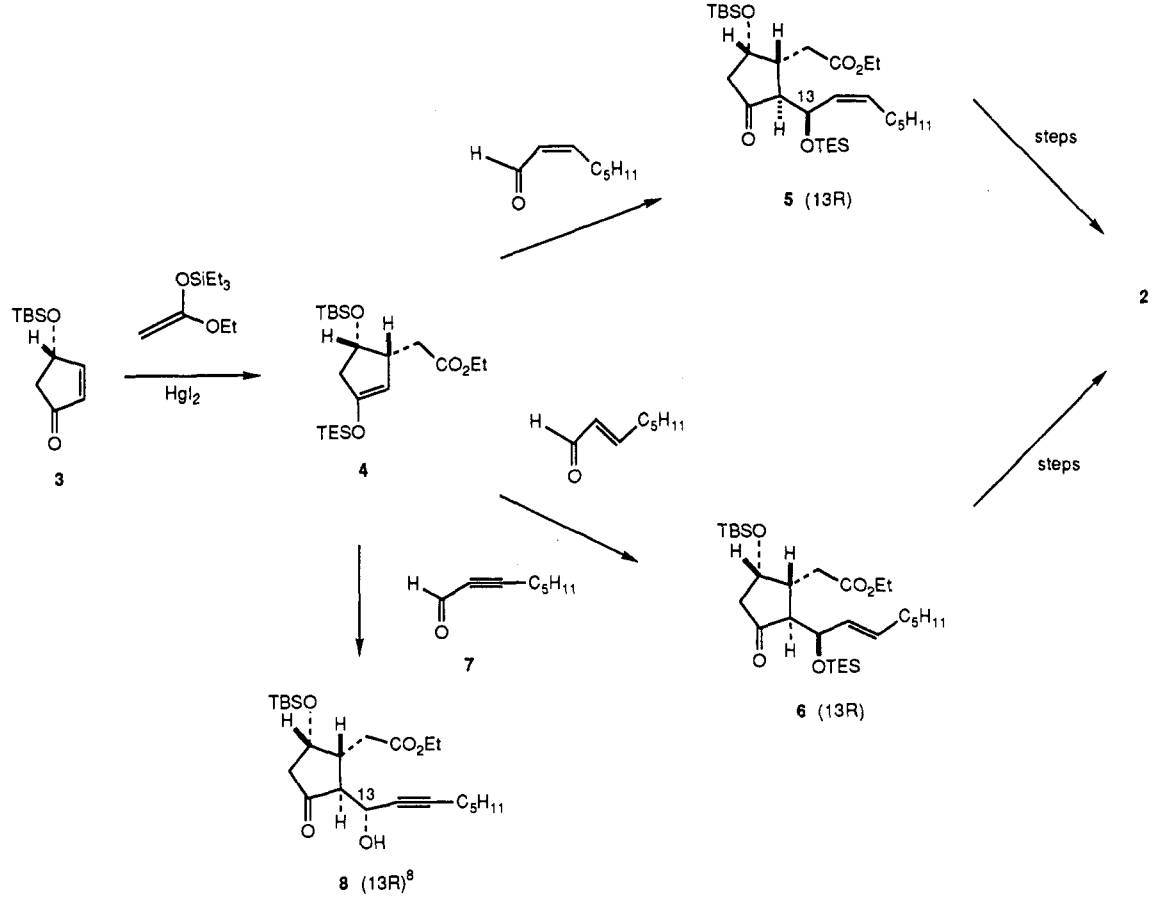
Scheme I



Scheme II

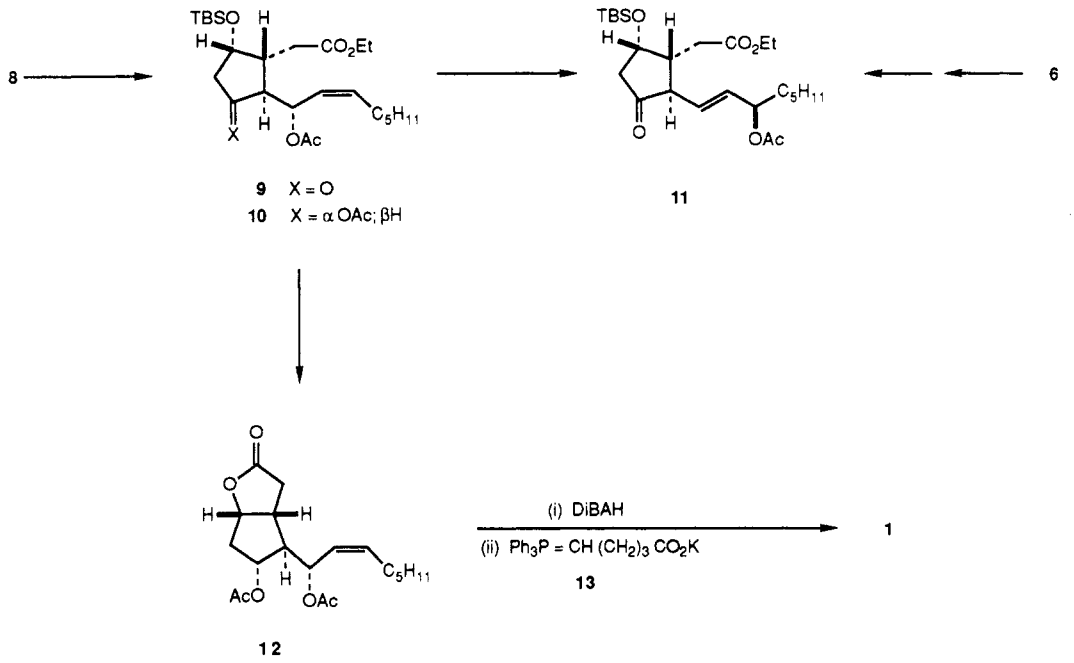


involved inversion at C_{15}. Accordingly, the structures of compounds **8** and **9** are as shown.

With the structure of allylic acetate **9** vouchsafed, the completion of the total synthesis of **1** was a straightforward matter (Scheme III). Reduction of cyclopentanone with sodium borohydride followed by acetylation led to a 79% yield of **10**. Cleavage of the TBS group (TBAF, THF) afforded lactone **12** in 89% yield. Reductive deacetylation was accomplished after exposure of **12** to DIBAH (5 equiv; toluene; −78 °C). Reaction of this hemiacetal diol with the readily available phosphorane **13** afforded **1**[11] in 77% yield

(11) It was not possible to obtain an authentic sample of **1**. The structure is fully proven by the spectral data contained herein. See supplementary material on the free acid, its methyl ester, and the triacetate of the methyl ester.

Scheme III



from **12**. The overall yield of **1** from **3** is 27%. As previously described, **3**[5,12] is readily available in enantiomerically homogeneous form from *cis*-1,4-diacetoxycyclopentene.

The stereochemical outcome at C_{13} arising from the coupling of similar substrates under the same conditions is amazing. In the previously described aldols[5] leading to **5** and **6** no other stereoisomers were observed. Yet when the ynal **7** is employed **8** is the only product observed! Instead of offering ad hoc interpretations that do not flow from sound experimental observations, we prefer to outline an agenda of questions that must be addressed. Why does a particular substitution type on the aldehyde favor or disfavor silyl transfer? Is silyl transfer fundamental or accessory to the stereochemical outcome? Do the sharply differing results arise from a common transition-state alignment differing in the placement of the R and H group of the aldehyde or do the reaction types differ in overall topography (chair vs boat, synclinal vs antiperiplanar)? Answers to these sorts of questions are not readily obtained but are crucial to illuminating this interesting stereochemical finding and extending it to new domains. *In the meantime, we note that the chemistry disclosed here and previously*[5] *provides straightforward access to optically pure prostaglandins with complete control of the configuration at either* C_{13} *or* C_{15} *in any stereochemical sense.*

Acknowledgment. This research was supported by PHS Grant HL25848. NMR Spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

(12) Cf: (a) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, 5615. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Ibid.* **1986**, 1255.

Supplementary Material Available: Experimental procedures and characterization data for all compounds (5 pages). Ordering information is given on any current masthead page.

Rearrangements of Cyclobutenones. Conversion of Selected 4-Allylcyclobutenones to Bicyclo[3.2.0]heptenones

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Received October 9, 1989

Summary: 4-Allyl-4-alkoxy(or hydroxy or (trimethylsilyl)oxy)cyclobutenones are reported to rearrange to bicyclo[3.2.0]hept-2-en-7-ones upon thermolysis in refluxing toluene. The synthetic scope and mechanism of this unusual transformation are discussed. The products are envisaged to arise from an electrocyclic ring opening of the cyclobutenones to the corresponding vinylketenes which then undergo an intramolecular [2 + 2] cycloaddition of the ketene moiety to the nonconjugated allylic double bond.

Sir: Selected 4-alkynyl, 4-alkenyl-, and 4-arylcyclobutenones have recently been shown to undergo facile ring expansion to respectively benzoquinones, hydroquinones,

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