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A NEW APPROACH TO PROSTANOIDS

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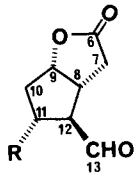
Abstract: A new asymmetric approach to 11-deoxyprostanoids is presented.

The vast majority of prostaglandin syntheses proceed through a "Corey lactone" intermediate 1 to establish both the relative and absolute stereochemistry of the ring substituents.[2] The lower side-chain is usually attached using the Horner reaction while the upper side-chain is subsequently attached via the Wittig reaction on the reduced lactone. The oxidation at the 9-position must then be adjusted for most prostaglandins. Recently, more convergent approaches



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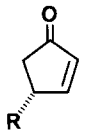

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involving conjugate addition of vinyl organometallics to cyclopentenones 2 have appeared.[3] The upper side-chain may be introduced either prior or subsequent to the lower one. In these two basic strategies, the substituent "R" at the 11-position is critical for establishing the stereochemistry at the 8- and 12-positions. We needed to prepared optically active prostanoids devoid of functionality at the 11-positon (R = H), and thus have developed a method for establishing the stereochemistry of the two side-chains without resolution. Furthermore, the correct oxidation state at the 9-position is maintained throughout the synthesis.

The masked cyclopentenone carboxaldehyde **3** needed for this approach is readily obtained from cyclohexenone via ketalization with (2R,3R)-2,3-butanediol using oxalic acid as a catalyst.[4,5] The resulting ketal is ozonized with reductive workup (Me_2S) and immediately subjected to a piperidinium acetate catalyzed aldol condensation (90% overall yield). The aldehyde **3** is asymmetrically allylated using (l)-B-allyldiisopinocampheylborane at -78°C[6]. Analysis of the MPTA derivative[7] indicated a diastereofacial selection of 90%.[8] Treatment of the alcohol with potassium hydride in refluxing glyme effected the anionic oxy-Cope rearrangement in high yield. The degree of chirality transfer in the rearrangement was conveniently determined on **7a** to be 56% by GC analysis.

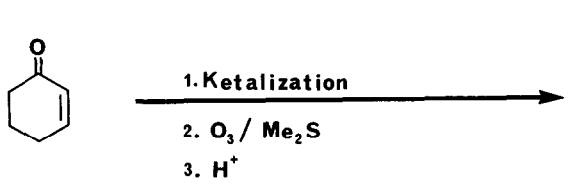
Based on Evans' work,[10] it was reasoned that a more stable chair conformation would improve the degree of chirality transfer in the anionic oxy-Cope rearrangement. The adducts derived from two additional allyl boranes, **4b** and **4c**, were examined to test this hypothesis.[11] Both reagents showed high diastereofacial selection for the aldehyde as well as high diastereomeric excesses for the two new chiral centers. Compound **5b** underwent a remarkably facile anionic oxy-Cope rearrangement at 0° whereas **5c**, like **5a**, required refluxing glyme for 40 hrs. There also was a dramatic difference in the optical purity of the rearranged products; the phenyl substituted system afforded racemic product while the alkyl substituted one afforded product in 58% ee (see Table).

Several important conclusions can be drawn from these results. First, the diastereofacial selectivity for the addition of allylboranes to α,β-unsaturated aldehydes is routinely similar to that for aliphatic aldehydes.[6] Secondly, with regards to the anionic oxy-Cope, our system is acyclic whereas Evans' system has three of the carbons constrained in a ring. In the acyclic cases, the number of low energy conformations increases thus making it difficult to predict the degree of chirality transfer. Furthermore, the great ease with which the phenyl substituted system **5b** rearranged suggests a change in mechanism to possibly one with a transient diradical intermediate.[13] Lastly, **7c** has been converted to **8**, the carboxyl masked $\Delta^{5,6}$-trans-11-deoxy PGE_2.

The novel approach reported herein allows one a moderate degree of control in establishing the absolute stereochemistry of prostanoid side-chains without depending on a C-11 substituent. The aldehyde carbon in **3** serves not only as a building block for the lower side-chain, but as a handle for introducing the upper side-chain.

TABLE

R	ee at hydroxyl center of **5**	de of **5**	de of **7**
H	90%	---	56%
C_6H_5	89	96%	0
$(CH_2)_3C(OADM)$	95	95	58



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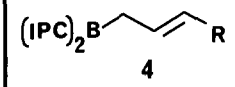

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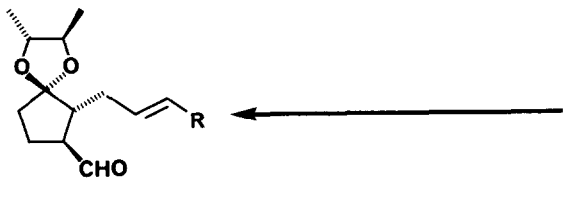

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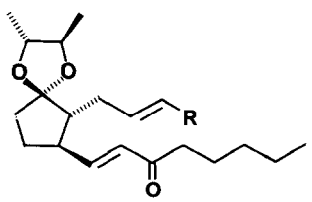
a) R = H

b) R = Ph

c) R = $(CH_2)_3$



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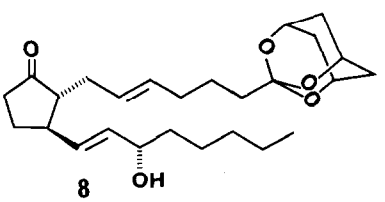

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Footnotes

1. Address correspondence to Hyperion Catalysis International, 128 Spring St., Lexington, Massachusetts 02173.

2a. A. Mitra, "The Synthesis of Prostaglandins," John Wiley & Sons, Inc., 1977;
b. J. S. Bindra and R. Bindra, "Prostaglandin Synthesis," Academic Press, 1977.

3a. S. M. Roberts and F. Scheinmann, "New Synthetic Routes to Prostaglandins and Thromboxanes," Academic Press, 1982;
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4. All new compounds afforded satisfactory spectral and combustion analysis.

5. The choice of acid and diol minimized olefin isomerization to less than 2%. The optical activity of the ketal does not effect the subsequent chemistry. Molecular models show the methyl group to be too far from the β-position of the unsaturated aldehyde to bias the approach of nucleophiles as large as diethyl malonate anion which does form a racemic Michael adduct with **3**.

6a. H. C. Brown and P. K. Jadhav, J. Amer. Chem. Soc., 105, 2092 (1983);
b. H. C. Brown and B. Singaram, J. Org. Chem., 49, 945 (1984).

7. J. A. Dale and H. S. Mosher, J. Amer. Chem. Soc., 95, 512 (1973).

8. The absolute stereochemistry of compounds 5-8 have not been correlated with a known compound. However, the addition of the alkyl group to the aldehyde takes place in a predictable stereochemical sense based on the chirality of the pinene.[6] Likewise, the diastereomeric sense (erythro vs threo) of the addition is also predictable.[9]

9a. M. M. Midland and S. B. Preston, J. Amer. Chem. Soc., 104, 2330 (1982);
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11. Hydroboration of phenylallene generated 4b while 4c was obtained by hydroborating the allene derived from coupling allenyl lithium with the appropriate ortho ester derived from 4-bromobutyronitrile.[12]

12a. J. M. Osbond, P. B. Philipott, and J. C. Wickens, J. Chem. Soc., 2779 (1961);
b. G. Voss and H. Gerlach, Helv. Chim. Acta, 66, 2294 (1983).

13. Preliminary MNDO calculations are in agreement with such a conclusion. Unpublished results Dr. C. M. Cook, Hoffmann-La Roche, Nutley, NJ.

14. A de of 96% corresponds to a 98:2 mixture.

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