ing force constants from *ab initio* calculations on **1a** and bending force constants obtained by interpolation of pertinent empirical data. These force constants (seven in all) lead to calculated frequencies[23] for **1a** (ν_2 = 1236 cm^{-1}, ν_3 = 661 cm^{-1}, and ν_4 = 576 cm^{-1}) and the monodeuterio derivative (*vide infra*), in excellent agreement with the observed bands. We also note that the SCF *ab initio* calculations lead to a predicted square equilibrium geometry (R_e = 1.434 Å) for the triplet state ($^3A_{2g}$) of **1a**[26] similar to Dewar's semiempirical result.[27] Furthermore, calculations using the general valence bond method (GVB)[31] indicate that the singlet lies 7.7 kcal/mol above the triplet at the triplet equilibrium geometry (D_{4h}) and is unstable to a rectangular distortion.

The above discussion has focused on the likelihood of a square geometry for **1a**; we emphasize that any appreciable rectangular distortion of the square would be expected to cause significant splitting of the degenerate 1236-cm^{-1} mode (ν_2). A mild rectangular distortion (R_{CC} and R_{CC} = 1.37 and 1.46 Å, respectively) leads to a predicted splitting of 100 cm^{-1}, if the above force constants are employed, with f_{RR} being allowed to vary with bond length according to Badger's rule.[32] Correspondingly larger splitting would be likely for more pronounced distortions (*e.g.*, the equilibrium singlet geometry of **1a** for which we calculate C–C bond distances of 1.34 and 1.56 Å using the GVB[31] method).

The above assignments receive strong confirmation from the spectrum of monodeuteriocyclobutadiene (**1b**) obtained by photolyzing bicyclo[2.2.0]pyran-2-one-*6-d* (**2b**)[12b,c] in the manner described for **2a** previously. Not surprisingly, the allowed modes of the parent **1a** also show up as strong bands, appropriately shifted and split in the spectrum (Figure 1b) of **1b**, as confirmed by inspection of the location of the bands and by the theoretical calculations. The slight shift in the frequency of the band at 1236 cm^{-1} in **1a** to 1224 cm^{-1} upon isotopic substitution confirms that it is predominantly a distortion of the carbon framework (ν_2).

Assuming that bands at 653, 594, and 540 cm^{-1} arise from the ν_3 and ν_4 modes of the parent **1a**, their location is only consistent (in the harmonic approximation) with the assignment of the band at 540 cm^{-1} to ν_4, and the bands at 653 and 594 cm^{-1} to the two split components (ν_{3a} and ν_{3b}) of the degenerate parent mode (ν_3).[33] The calculations described above are in good agreement with this analysis, predicting only a small splitting of the 1236-cm^{-1} band. (Similar calculations for the 1,2- and 1,3-dideuterio derivatives give splittings of 17 and 32 cm^{-1}, respectively.) A much larger splitting is predicted for the in-plane bending mode (ν_3), with the unshifted line (in which the C–D bend does not participate) assigned to the A_1 component (calcd value, 661 cm^{-1}), and the 594-cm^{-1} band assigned to the B_1 component (calcd, 616 cm^{-1}). The calculations yield a value of 527 cm^{-1} for the remaining parent mode (ν_4), thus completing the confirmation of the above assignment. In addition to the aforementioned intense bands in Figure 1b, arising from the active parent modes, we also note an intense band at 460 cm^{-1} which, from our calculations (477 cm^{-1}), is indicated to be almost a pure CH bending mode of B_1 symmetry. The appearance of spectra **1a** and **1b**, combined with theoretical predictions of the splittings of E_u modes upon descent into C_{2v} symmetry, solidly support assignment of the 1236- and 653-cm^{-1} bands to degenerate modes of square cyclobutadiene.

Although the present results are consistent with a square equilibrium geometry, there remains the possibility of an *effective* square geometry arising, perhaps, from rapid equilibration between slightly distorted squares separated by small barriers. The present *ab initio* calculations rule out such a possibility for any distortion of the triplet; since the equilibrium singlet corresponds to a *strongly distorted* square (a rectangle with normal single and double bond lengths), the larger barrier separating the two rectangular forms should prohibit rapid equilibration between them.

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1a and scaled by the same factor (0.877) which brings the calculated and experimental benzene force constants into agreement; the remaining interaction constant between the C–C bonds was assumed to be zero);[25] $f_{\beta\beta}$ = 0.30 mdyn Å/rad^2 (estimated from standard values[28] on the basis of calculated[29] s character (sp$^{1.6}$) for the C–H bonds); $f_{\alpha\alpha}$ = 1.30 and $f_{\gamma\gamma}$ = 1.30 mdyn Å/rad^2 (based on available data for cyclobutane[30a] and benzene[30b]); $f_{R\beta}$ = 0.36 mdyn/rad (from benzene,[30b] with signs determined by assuming hybrid orbital following); and $f_{\beta\beta}'$ = −0.05 mdyn Å/rad^2 (based on the out-of-plane benzene modes[30c]). This unbiased selection from *a priori* and standard empirical values adequately reproduces the observed bands.

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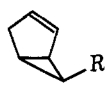
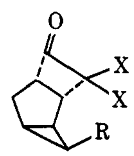
Prostaglandin Synthesis. I. An Improved Synthesis through Bicyclo[3.1.0]hexane Intermediates

Sir:

The potent pharmacological properties of the various members of the prostaglandin family and their limited supply from natural sources have prompted intensive efforts directed at their synthesis.[1–4] In several cases these have resulted in elegant, highly stereocontrolled syntheses.[5–10]

This report details a new, efficient synthesis of prostaglandins. Norbornadiene was oxidized as described by Meinwald, *et al.*,[11] to the bicyclic aldehyde **1**. Treatment of crude **1** with neopentyl glycol and a trace of mild acid in methylene chloride at 25° afforded the crystalline acetal **2**, mp 55–55.5° (61% from norbornadiene).[12] Reaction of **2** with dichloroketene led to the dichlorocyclobutanone **3**, mp 97–99° (81%),[13–16] which on reduction with zinc and ammonium chloride in methanol gave a nearly quantitative yield of cyclobutanone **4** [ir (CH_2Cl_2) 1770 cm^{-1} (C=O)].[17]



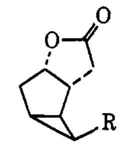


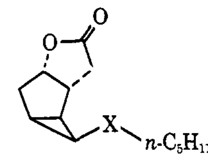
1, R = CHO
2, R = $CH(OCH_2)_2C(CH_3)_2$
3, X = Cl; R = $CH(OCH_2)_2C(CH_3)_2$
4, X = H; R = $CH(OCH_2)_2C(CH_3)_2$

The crude **4** was resolved in the following manner. Treatment of **4** with *l*-ephedrine and a trace of *p*-toluenesulfonic acid in refluxing benzene for 24 hr produced diastereomeric oxazolidines which were purified by crystallization from methanol, mp 159–166° (70% of theory for a resolution from **3**). Hydrolysis with THF–water–HOAc (5:5:1) at 25° afforded the resolved ketone **4**, mp 43–47°.[18]

Oxidation of **4** with *m*-chloroperbenzoic acid produced the lactone acetal **5**, mp 129–131°, αD +9° (*c* 0.9, MeOH) (90% from oxazolidine). Hydrolysis of **5** with 88% formic acid gave a 95% yield of the lactone aldehyde **6**, mp 61–64°, αD −30° (*c* 0.5, MeOH).

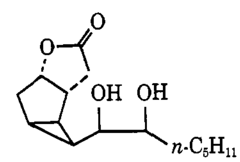
Wittig condensation of aldehyde **6** with *n*-hexyltriphenylphosphonium bromide afforded olefin **7** [nmr ($CDCl_3$) δ 5.7 (d of t, 1, J = 7, 11 Hz)] in 93% yield.



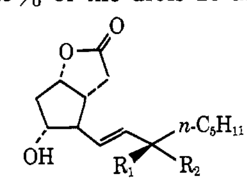


5, R = $CH(OCH_2)_2C(CH_3)_2$
6, R = CHO
7, X = CH=CH—
8, X = CH—CH (epoxide, O bridging)

A number of routes from **7** to diols **10** and **11** were investigated. It was found that the best overall yield was obtained by modification of a previously described method.[19–21] Thus, oxidation of **7** with *m*-chloroperbenzoic acid in methylene chloride containing suspended potassium bicarbonate gave epoxide **8** in nearly quantitative yield. Hydrolysis of **8** in acetone–water–formic acid (65:33:2) produced a mixture containing 75% of the glycols **9** and 25% of the diols **10** and **11**.



9



10, R_1 = H; R_2 = OH
11, R_1 = OH; R_2 = H

Treatment of this mixture with dry formic acid[22,23] at room temperature for 2–3 hr followed by treatment with potassium carbonate and methanol led to a new mixture of glycols and diols.

The desired 15α-diol **10** could be isolated chromatographically from this mixture in 25% yield. The remaining material containing 15β-diol **11** and starting glycols **9** could be reintroduced into dry formic acid for recycle. After two recycles an overall yield of 45% of 15α-diol was obtained from epoxide **7**.

The diol **10** prepared as herein described is identical with that obtained by Corey and coworkers[24] and has been converted to $PGF_{2\alpha}$ and PGE_2 identical with the natural materials.

Thus, an efficient synthesis of $PGF_{2\alpha}$ and PGE_2 through bicyclo[3.1.0]hexane intermediates has been achieved. The most complex step in this synthesis, the opening of the cyclopropylcarbinyl system, is still under investigation and may be the subject of a later publication.

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