singlet excited state of simple olefins and is thought to involve the promotion of a π electron to a molecular orbital so large that the resulting excited state is expected to display behavior resembling that of a radical cation.[8]

Previous studies on the photoprotonation of olefins have afforded several reactions having important synthetic applicability.[1] The discovery of radical-cation behavior opens yet a new vista of synthetic applications, since trapping of the radical-cation intermediate with any one of a number of nucleophiles should be possible. Moreover, the reaction has the advantage of not being limited to certain cyclic systems. Further work is in progress to explore the full synthetic potential, as well as the mechanistic details, of this new reaction.

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Synthesis of (+)- and (−)-7-Oxaprostaglandin $F_{1\alpha}$ and Their 15-Epimers

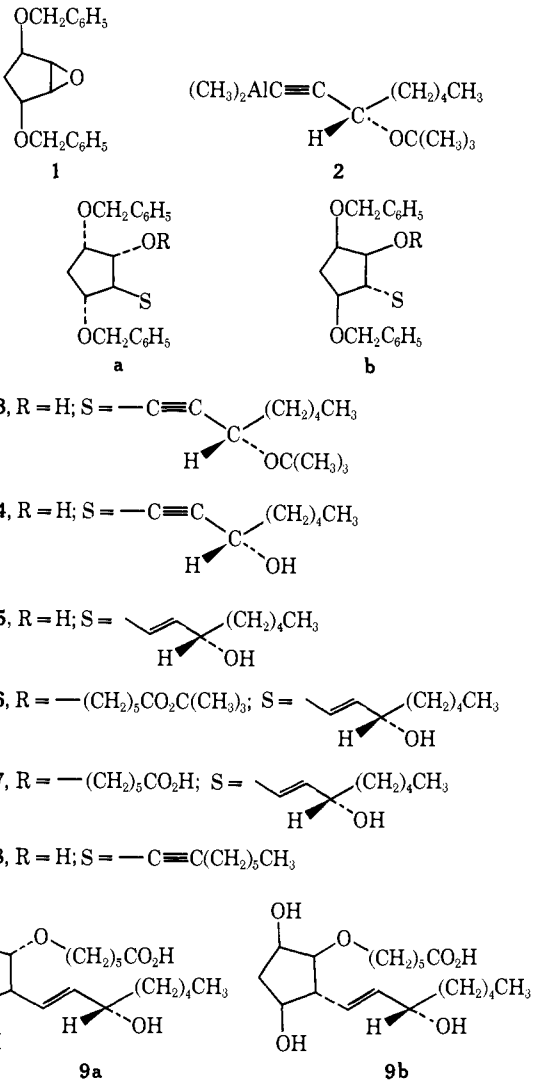
Sir:

We recently reported the synthesis of 7-oxa derivatives of $PGF_{1\alpha}$[1] and PGE_1[2] as well as of skeletally identical but less oxygenated derivatives.[3] Some of these showed prostaglandin-like activity,[4] others were prostaglandin antagonists,[3,5-7] and some combined both activities. The substances originally synthesized and tested were racemic and consisted of mixtures of 15-epimers. The overlap of agonist and antagonistic properties made it imperative that the pure enantiomers of known absolute configuration be available for biological evaluation.

We now wish to report the synthesis of (+)-7-oxa-$PGF_{1\alpha}$ (**9a**)[8] and (+)-7-oxa-15-epi-$PGF_{1\alpha}$ (**9b**) and their enantiomers, as well as preliminary biological data showing that only **9a** possessing the absolute configuration of the prostaglandins exhibits typical prostaglandin-like activities.

The novel feature of this synthesis, which as the key step utilizes the opening of a *meso*-cyclopentene oxide with a dialkylalkynylalane,[1] is the introduction of the completely functionalized eight-carbon side chain in optically active form, leading to two diastereomers, which can be readily separated by chromatography. Such a procedure has the advantage of requiring but one resolution of a simple acetylenic alcohol, which then serves to resolve the remaining chiral portion of the molecule. It also possesses generality in that other analogs can be prepared without additional resolutions. Application of this principle to the synthesis of the prostaglandins themselves will be reported later.

all-cis-Cyclopentene 3,5-dibenzyloxyepoxide (**1**) was condensed with dimethyl (*S*)-(−)-3-*tert*-butyloxy-1-oc-



tynylalane (**2**)[9] (2 equiv) in toluene at 70–80° for 24 hr and the resulting mixture of diastereomeric butyl ethers (**3a** + **3b**, 72%), $[\alpha]D$ −28.6°,[10] debutylated with trifluoroacetic acid at 0° for 2 hr to the acetylenic alcohols (**4a** + **4b**, 98%),[11] $[\alpha]D$ +1.33°, which could

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(9) Prepared from (*S*)-(−)-3-hydroxy-1-octyne (*cf.* ref 5) with isobutylene in methylene chloride in the presence of BF_3–etherate and phosphoric acid, $[\alpha]^{ether}D$ −70°, followed by lithiation (BuLi) and reaction with dimethylchloroalane.
(10) Rotations in chloroform.
(11) All yield figures refer to chromatographically purified fractions.

not be separated by chromatography. Replacing the *tert*-butyl ether (**2**) by the free alcohol (4 equiv) afforded **4a** + **4b** directly (70%). Reduction of the latter with $LiAlH_4$ in THF at 70° for 16 hr produced a mixture of olefins (80%), which was readily separated by tlc on 2-mm silica gel plates with ethyl acetate–chloroform 1:4 into the diastereomeric olefinic alcohols **5a** and **5b** (40% each). The faster moving isomer (**5a**) had mp 45–46°[12] (ether–hexane), $[\alpha]D$ +28.1°, and the slower one (**5b**) mp 89–90° (ether–hexane), $[\alpha]D$ −28.4°. A faster moving fraction (5%) [ir 5.10 μ; nmr τ 4.58 (m) and 4.83 (m)] was assigned the 13,14-allenic structure. Alkylation of the olefinic diols **5a** and **5b** with *tert*-butyl ω-iodohexanoate (4 equiv) using dimsyl anion in DMSO at 25° afforded with remarkable specificity the ring-alkylated products **6a**, $[\alpha]D$ +12.4°, and **6b**, $[\alpha]D$ −6.6°, respectively, both in 30% yield, in addition to 50% of unchanged starting material. Structures **6a** and **6b** were verified by oxidation with DDQ in dioxane to the α,β-unsaturated ketones (λ_{max}^{alc} 233 nm (ε 10,500)). Treatment of the *tert*-butyl esters with 7% KOH in methanol for 20 hr at 25° furnished the corresponding carboxylic acids (95%) **7a**, $[\alpha]D$ +17.2°, and **7b**, $[\alpha]D$ −11.3°. Debenzylation was effected after conversion into the 1,15-dianion with sodium hydride in THF, followed by reduction with excess lithium in ammonia. Column chromatography on silica gel furnished in 50% yield, respectively, crystalline (+)-7-oxa-$PGF_{1\alpha}$ (**9a**), mp 65–67°; $[\alpha]D$ +6.8°, and (+)-15-epi-7-oxa-$PGF_{1\alpha}$ (**9b**), mp 70–72°; $[\alpha]D$ +6.2°. Repeating this sequence of reactions with (*R*)-(+)-3-*tert*-butyloxy-1-octynyldimethylalane instead of its *S* antipode furnished, *via* (−)-**5a** (mp 45–46°; $[\alpha]D$ −29.2°) and (+)-**5b** (mp 89–90°; $[\alpha]D$ +28.6°), (−)-7-oxa-$PGF_{1\alpha}$ ((−)-**9a**, mp 65–67°, $[\alpha]D$ −6.2°) and (−)-15-epi-7-oxa-$PGF_{1\alpha}$ ((−)-**9b**, mp 70–72°; $[\alpha]D$ −5.3°). Co-crystallizing equal amounts of the respective antipodes gave (±)-7-oxa-$PGF_{1\alpha}$, mp 90.5–90.7° and (±)-15-epi-7-oxa-$PGF_{1\alpha}$, mp 72–74°.[13]

To determine the absolute configuration of this series of compounds the dextrorotatory enantiomer **8a** of known absolute configuration[5] was oxidized with selenium dioxide and the resulting (15*S*) and (15*R*) hydroxy derivatives reduced with $LiAlH_4$ to a mixture of **5a** and its 15-epimer ($[\alpha]D$ +16°). After tlc separation **5a** had mp 41–43°, $[\alpha]D$ +34°, and (+)-**5b** had mp 84–86°, $[\alpha]D$ +26°. Since both **5a** and the antipode of **5b** derived from **8a** are dextrorotatory, **5a** and **5b** obtained by the present procedure must be assigned the absolute configurations shown.

7-Oxa-$PGF_{1\alpha}$, its 15-epimer, and their antipodes were tested for their *in vitro* activities in three widely differing systems with the result that only **9a**, in which *all* chiral centers possess the absolute configuration of the prostaglandins, exhibits typical prostaglandin activity, while the others are either inactive or act as antagonists. Thus, **9a** possessed 5% of the activity of $PGF_{1\alpha}$ in the gerbil colon assay showing a dose response curve (50 ng–10 μg) paralleling that of $PGF_{1\alpha}$. On the other hand, **9b** was inhibitory at the 1 μg/ml level toward $PGF_{1\alpha}$ (250 ng to 2 μg/ml), and (−)-**9a** and (−)-**9b** were without any effect on the gerbil colon at the 1 μg/ml level.[14] Similarly, **9a** at 100 μg/ml stimulated the formation of cyclic AMP in the mouse ovary[6] (activity 0.1 × $PGF_{1\alpha}$), while the remaining three isomers were inactive at the same dose levels.[15] Thirdly, only **9a** proved to be a substrate for the highly specific prostaglandin 15-dehydrogenase from swine lung (K_m 0.4 m*M*; $PGF_{1\alpha}$, 0.02 m*M*)[16,17] while the remaining three isomers were competitive inhibitors of the enzyme (K_i ranging from 0.4 to 0.5 m*M*).[18]

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(12) All new substances, amorphous or crystalline, were characterized by nmr, ir, and mass spectra as well as elemental analyses.

(13) Purification of the mixture of (±)-7-oxa-$PGF_{1\alpha}$ and its 15-epimer, obtained by the procedure of ref 1, *via* the methyl esters gave (±)-7-oxa-$PGF_{1\alpha}$, mp 88.5–88.7° by direct crystallization.

(14) We are indebted to Dr. Jane E. Shaw and Dr. Peter Ramwell of Stanford University for these results.

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Mechanism for the Quenching of Alkanone Singlets by Conjugated Dienes[1]

Sir:

The interactions of electronically excited states with 1,3-dienes have aroused considerable interest and represent an important area of current study, as indicated by numerous reports which have appeared on synthetic,[2] mechanistic,[3] and theoretical[4] studies concerning the chemical basis of these interactions. Recently the risk of using 1,3-dienes as *specific* quenchers of triplet states of ketones has been shown, since at high concentrations (>0.1 *M*) of *trans*-1,3-pentadiene substantial quenching of alkanone singlet states occurs.[5] We report here our work which explores the mechanism of the interaction of dienes with singlet alkanones by introducing variations in both the ketone and diene structures. By examining the quenching of ketone fluorescence we obtain a sensitive and quantitative measure of the rates of interaction.

The data in Table I summarize the effects of systematically hindering the carbonyl function of the

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