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Synthetic Approaches to 11-Deoxy-7-oxaprostaglandin Analogues

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A synthesis of 11-deoxy-7-oxa prostanoids is presented. The synthesis of this new series of prostaglandin analogues commences with *cis*-2,3-epoxycyclopentanol (1), protected as an appropriate ether. The key step is the highly regioselective opening of that epoxide with an alkynyl alane reagent. For definition of the scope of that reaction, a brief study of the behavior of other carbon-centered nucleophiles with epoxide 1 was undertaken. It was found that only the alanyl reagent is selective in the desired direction. A rationalization for that selectivity is offered. Following the synthesis herein, over 30 analogues were prepared. Among them are eight optically pure compounds, including four isomers of 11-deoxy-7-oxaprostaglandin E_1.

The great activity in recent years in the synthesis and screening of prostaglandin (PG) compounds has proven the value of using analogues in the attempt to maintain valuable physiological properties while avoiding such undesirable ones as side effects and metabolic deactivation. Many reports describe, for example, the synthesis and activities of 11-deoxy prostanoids.[1] To a lesser extent, 7-oxa analogues have also been investigated.[2] Although both classes exhibit potentially useful activities,[3] no examples have yet emerged that combine those two structural modifications.

Our recent development of a simple, one-pot oxygenation procedure[4] for converting olefins to epoxy alcohols allows, for the first time, the facile preparation of (±)-*cis*-2,3-epoxycyclopentanol (**1a**). This compound, in view of Fried's well-developed technology for the alkynyl alane opening of epoxides,[5] is ideally constituted for elaboration into 11-deoxy-7-oxa PG analogues. We thus undertook the development of an efficient, versatile synthesis for this new class of PGs to allow their screening for various PG-like activities. From this study emerged the general strategy illustrated in Scheme I. In the first stage, the two PG side chains are sequentially attached to the protected epoxy alcohol 1 by using a remarkably regioselective epoxide-opening reaction followed by a Williamson ether synthesis. In the second stage, the protective groups are removed, and the C-9 and C-15 oxidation states are adjusted, providing various 13,14-dehydro analogues. These compounds are either funneled directly into the testing program, or, in a third and final stage, they are converted into other analogues by synthetic modification at the C-13,14 site. This strategy is highly convergent: the obligatory carbon atoms all derive from three approximately equal fragments connected together in the first two synthetic steps. By suitably modifying those three fragments, a large number of different analogues may be assembled in short order.

Scheme I illustrates the early stages of this strategy, where 13,14-dehydro analogues are fashioned with different C-9,15 oxidation states. Many alcohol protective groups for starting material **1a** were examined, including the methoxyethoxymethyl, benzyl, dimethyl-*tert*-butylsilyl, methoxymethyl, and (methylthio)methyl ethers. Most advantageous was the methoxymethyl ether, conveniently affixed to **1a** by using chloromethyl ether (prepared by the method of Amato et al.[6]) and diisopropylethylamine in methylene chloride. (Methylthio)methyl protection[7] was useful in some cases, but yields in subsequent steps were often lower with this group. Silyl ethers were not suitable C-9 protective groups for our synthesis because they suffered migration during the Williamson etherification step.[8]

The attachment of the bottom side chain by a regioselective carbanionic epoxide opening was clearly the most speculative step of the synthesis. Although hydrogen

(1) Bindra, J.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977; p 382.

(2) (a) Fried, J.; Mehra, M. M.; Kao, W. L.; Lin, C. H. *Tetrahedron Lett.* **1970**, 2695. (b) Fried, J.; Heim, S.; Etheredge, S. J.; Sunder-Plassmann, P.; Santhanakrishnan, T. S.; Himizu, J.; Lin, C. H. *J. Chem. Soc., Chem. Commun.* **1968**, 634.

(3) (a) Reference 1, p 449. (b) Ford, S. H.; Fried, J. *Life Sci.* **1969**, *8*, 983. (c) Fried, J.; Mehra, M. M.; Kao, W. L. *J. Am. Chem. Soc.* **1971**, *93*, 5594. (d) Fried, J.; Lin, C.; Mehra, M.; Kao, W.; Dalven, P. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 38.

(4) Mihelich, E. D.; Eickhoff, D. J.; Daniels, K., manuscript in preparation.

(5) (a) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899. (b) Fried, J.; Lin, C.-H.; Ford, S. H. *Ibid.* **1969**, 1379.

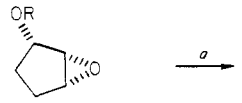
(6) Amato, J. S.; Karady, S.; Sletzinger, M.; Weinstock, L. M. *Synthesis* **1979**, 970.

(7) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

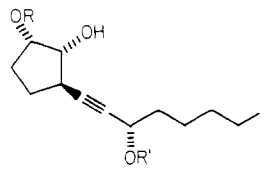
(8) Similar migrations have been reported before. For example, see: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1979**, 1865.

0022-3263/83/1948-0409$01.50/0

Scheme I[j]

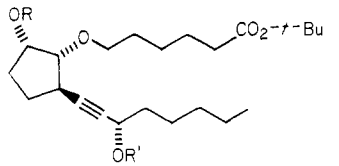


1a, R = H
b, R = CH_2OCH_3
c, R = CH_2SCH_3
d, R = CH_2Ph



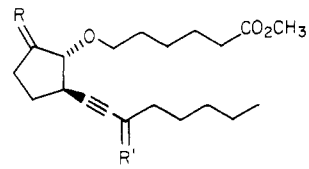
b (for **3a–c**)
b, c (**2a** → **3d**)
b, d (**2c** → **3d**)
b, e (**2b** → **3e**)

2a, R = CH_2OCH_3; R′ = *t*-Bu
b, R = CH_2OCH_3; R′ = $SiMe_2$-*t*-Bu
c, R = CH_2SCH_3; R′ = *t*-Bu



f, g (**3a** → **4**)
h, f, i (**3e** → **5**)
h, f, i (**3d** → **6**)

3a, R = CH_2OCH_3; R′ = *t*-Bu
b, R = CH_2OCH_3; R′ = $SiMe_2$-*t*-Bu
c, R = CH_2SCH_3; R′ = *t*-Bu
d, R = H; R′ = *t*-Bu
e, R = CH_2OCH_3; R′ = H



4, R =  R′ = 

5, R =  R′ = 

6, R =  R′ = 

[a] $Me_2AlC{\equiv}CCH(OR')(CH_2)_4CH_3$. [b] NaH, Me_2SO; $ICH_2(CH_2)_4CO_2$-*t*-Bu. [c] $ClSiMe_3$, Et_4NBr, CH_2Cl_2. [d] MeI, acetone (wet), $NaHCO_3$. [e] $(n\text{-Bu})_4NF$, THF. [f] F_3CCO_2H, CH_2Cl_2. [g] $BF_3{\cdot}Et_2O$, MeOH. [h] CrO_3, pyridine. [i] CH_2N_2, Et_2O. [j] Compounds 2, 3, 4, and 6 are diastereomeric mixtures, as described in the text.

chloride addition to *cis*-1,2-epoxy-3-methoxycyclopentane gives ring opening in the desired sense,[9a] no previous additions of carbon-centered anions to 1 have been reported to our knowledge. The addition of an alanyl reagent to six-membered-ring counterparts of 1 has been shown to be completely regio- and stereoselective;[10] however, these results were interpreted in terms of *trans*-diaxial epoxide opening of a conformationally anchored ring, a rationalization clearly inapplicable to the cyclopentyl case at hand.

Our hopes were based largely on the viewpoint that the high oxygenophilicity of aluminum should favor coordination of the organometallic reagent to 1 (Figure 1) followed by attack by a second equivalent of reagent at the desired site, now assisted in a classical "push–pull" manner[11] by the coordinated aluminum atom.[9b] In the event, alkynyl alane addition in all cases gave very high regioselectivity in the desired direction. In the conversion of **1b** to **2a**, for example, the product consisted of a 15:1 mixture of isomers resulting from attack at the two epoxide carbon atoms of **1b**. The isomers were identified by ^{13}C NMR (particularly the cyclopentane carbon attached to the triple bond, resonating at 37.9 ppm in **2a** vs. 46.3 ppm for the regioisomer). The structural assignments were verified by etherifying both isomers with the same R group used in the epoxy alcohol (**1a**) protection; for the undesired regioisomer, this operation forms a symmetrical bis ether whose ^{13}C spectrum is correspondingly simplified.

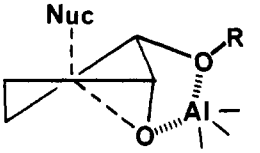
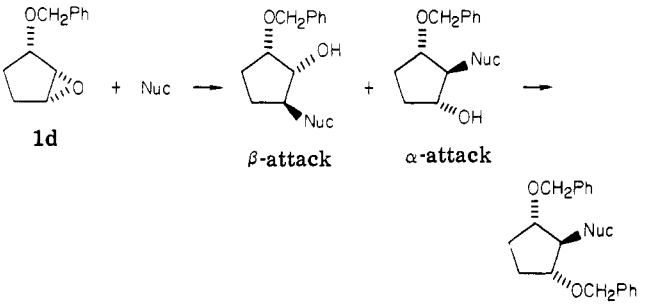
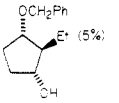
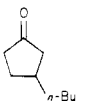


Figure 1. Coordination of organometallic reagent to 1.

Table I



nucleophile	ratio of β attack/ α attack	total yield, %	other products (% yield)
$Et_2AlC{\equiv}CR$	15:1	65–70	
$LiCu(n\text{-Bu})_2$	1:2	45–50	
	1:4	60–80	
$Li^+{}^-CH_2CN$	1:1.2	70	

The crucial role of the organoaluminum species is highlighted by comparison to other carbanionic nucleophiles[9b] (Table I). This brief survey indicates that there is, in fact, a low to modest selection for the undesired regioisomer with the other reagents examined. Again, the products of these reactions were all purified by chromatography and were assigned structures on the basis of ^{13}C NMR; the assignments were verified in each case by making and analyzing the bis ethers as described above.

Although numerous experiments were performed for optimization of the epoxide opening reaction (1 → **2**), no significant improvement was found over the conditions developed by Fried and co-workers;[5] their method was therefore used throughout our study. It should be noted

(9) (a) Langstaff, E. J.; Moir, R. Y.; Bannard, R. A. B.; Casselman, A. A. *Can. J. Chem.* **1968**, *46*, 3649–58. (b) High regioselectivity in the opening of both *cis*- and *trans*-2,3-epoxy-1-(benzyloxy)butane by organoaluminum reagents has recently been reported and rationalized by an identical transition-state model. See: Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71; *Angew. Chem. Suppl.* **1982**, 161–168.

(10) Danishefski, S.; Tsai, M.-Y.; Kitahara, T. *J. Org. Chem.* **1977**, *42*, 394–6.

(11) Eliel, E. L. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 2, p 112.

in the Scheme I example that the alane reagent comes from optically pure (*S*)-octynol.[12] Since the cyclopentenol oxide **1a** is racemic, a diastereomeric mixture arises from the epoxide opening; structures **2–4** and **6** thus represent ca. 1:1 mixtures of two diastereomers. In only one case could we separate the alkynyl diastereomers (by crystallization, discussed below). In every other instance the isomers were indistinguishable by TLC, ^{1}H NMR, and ^{13}C NMR; this is doubtless due to the rigidly linear C-13,14 acetylene unit, which holds the two centers of molecular asymmetry so far apart that very little interaction between them is possible.

The Williamson etherification of **2a–c** with *tert*-butyl 6-iodohexanoate[3d] was quite clean, proceeding in almost quantitative, corrected yield; however, the conversion in early experiments was only about 35%. Even though starting material was easily separated from the product for recycling, the low conversion made large-scale work tedious. In order to improve the yield, the following parameters were examined: solvent, rate and order of addition, amount and choice of base, amount of alkylating reagent, and reaction time. The most dramatic change was observed when the amount of *tert*-butyl 6-iodohexanoate was increased from 3 to 5 equiv (fast addition). Under these conditions, products **3a–c** were isolated in ca. 60% yield, along with 35–40% recovered starting material. Changing the other parameters either had no effect or decreased the yield.

Compound **3** was deprotected in various ways, depending on the 13,14-dehydro analogue required. PGF analogue **4** was most conveniently produced by treating **3a** with trifluoroacetic acid to remove all three protective groups[13] and then esterifying the crude product with boron trifluoride in methanol. The same transformation occurred if the trifluoroacetic acid step was omitted, but in that case the yield was lower due to incomplete deprotection. PGE analogue **6** could be obtained from **3** in several different ways involving selective removal of the C-9 protective group. For example, the (methylthio)methyl ether of **3c** was cleaved with methyl iodide in wet acetone,[7] giving **3a** and leaving the *tert*-butyl groups intact. It was generally more efficient, however, to use **3a** as a common precursor to both E and F series PGs. We found that the methoxymethyl group of **3a** is selectively removed by using the reagent chlorotrimethylsilane/tetraethylammonium bromide[14] to give **3d**. Compound **3d** by either route smoothly oxidized to the ketone under standard Collins oxidation conditions. Treatment of this ketone with trifluoroacetic acid followed by diazomethane produced PGE analogue **6**. It was also of interest to selectively unmask the C-15 hydroxyl group of **3**. This was accomplished by using racemic 3-(dimethyl-*tert*-butylsiloxy)octyne in the epoxide opening of **1b** to yield **2b**. After the normal etherification (giving **3b**), the silyl group was hydrolyzed with fluoride in the usual way;[15] oxidation, deprotection, and esterification as above then provided compound **5**, where the normal C-9/C-15 oxidation pattern of the E prostaglandins has been reversed.

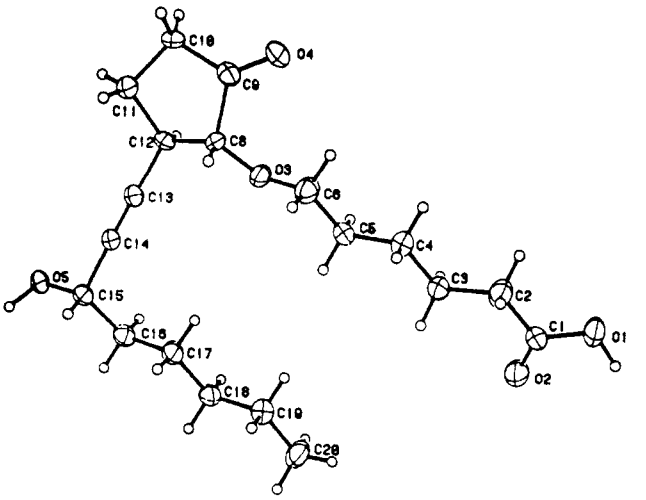


Figure 2. Structure of **6** as the free acid from X-ray crystallography.

As noted earlier, all the C-15 hydroxy analogues described in Scheme I were isolated as inseparable mixtures of two diastereomers. During the preparation of E analogue **6**, however, crystals were obtained when the compound was isolated as the free acid. Careful analytical HPLC indicated that this material was diastereomerically pure. (Although the free acid of the corresponding PGF analogue **4** also crystallized, HPLC analysis gave an isomer ratio that was still 1:1 after several recrystallizations, and so diastereomerically pure **4** could not be obtained.) A single-crystal X-ray analysis of crystalline **6** (as the free acid, illustrated in Figure 2) allowed assignment of the relative stereochemistry at carbons 8, 12, and 15.[16] Since the bottom side chain containing the C-15 chiral center ultimately comes from optically pure (*S*)-octynol, we could assign the absolute stereochemistry for the crystalline isomer as 8*R*, 12*R*, and 15*S* (this is the same as the absolute stereochemistry of the natural prostaglandins). We mention in passing that free acid **6** is not efficiently prepared via saponification of its methyl ester because of epimerization at C-8, which gives approximately a 2:1 mixture of the *trans*/*cis*-cyclopentane compounds.

With routes to the 13,14-dehydro analogues secured, we investigated the conversion of those alkynyl prostanoids into a number of other analogues as shown in Scheme II. The C-13,14 cis olefins were produced in quantitative yield by a standard Lindlar hydrogenation of the corresponding alkynes. Alternatively, hydrogenation with palladium on carbon gave saturated analogues (e.g., **4** → **9**). In the F series, the cis olefins were photochemically isomerized[17] to trans olefins in good yield; however, in the E series (e.g., compound **14a**) the photoisomerization yield was low. We therefore resorted to a sulfoxide rearrangement sequence[18] to effect that transformation and could thus synthesize

(12) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342. Also see ref 3d, p 61.

(13) Deprotection as in ref 3c. Although the trifluoroacetic acid does remove all three protective groups, it is not as efficient at removing the methoxymethyl ether as it is for the *tert*-butyl groups. Thus, the next step (boron trifluoride catalyzed methyl ester formation) serves to complete the removal of the methoxymethyl group as well as to esterify the carboxylic acid.

(14) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Bularam, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3213, ref 2b.

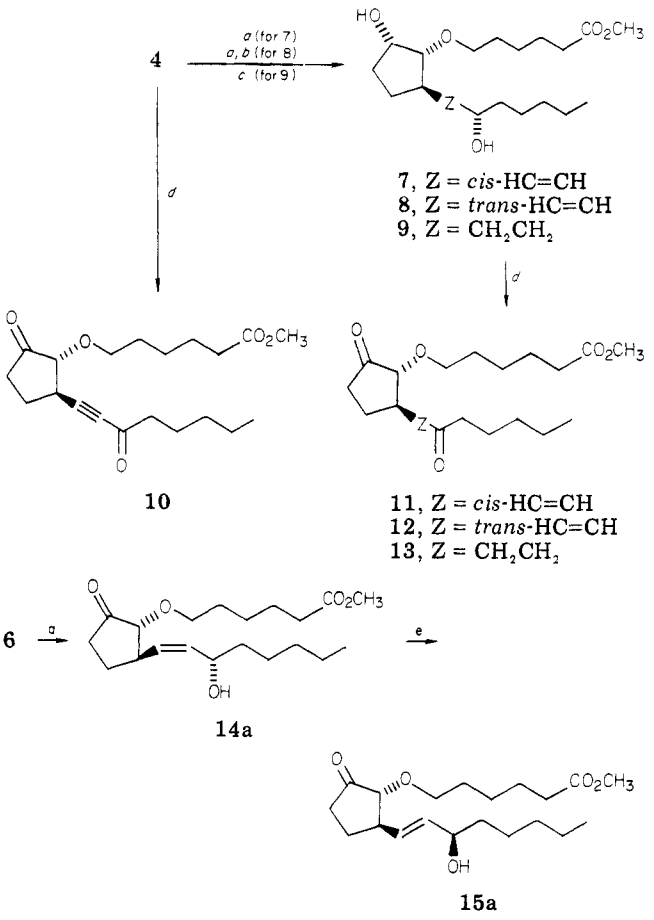
(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(16) The X-ray structure was obtained by Dr. J. D. Oliver and Mr. L. C. Strickland; the details have been submitted for publication elsewhere.

(17) (a) Bundy, G. L.; Daniels, E. G.; Lincoln, F. H.; Pike, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2124. (b) Corey, E. J.; Hamanaka, E. *Ibid.* **1967**, *89*, 2758.

(18) (a) Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *J. Am. Chem. Soc.* **1974**, *96*, 6774. (b) Andrews, G. C.; Evans, D. A. *Acc. Chem. Res.* **1974**, *7*, 147.

Scheme II



[a] H_2, Lindlar catalyst. [b] $h\nu$, PhSSPh. [c] H_2, Pd/C. [d] CrO_3, Pyr. [e] ArSCl; $P(OMe)_3$, MeOH.

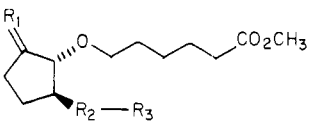
PGE analogues represented by compound **15a** in Scheme II (this sulfoxide route also inverts stereochemistry at C-15).

The versatility of our overall synthetic plan is apparent from the variety of alkynyl reagents that may be used to open epoxide **1b**, leading to PG analogues with different substitution patterns on the bottom side chain and with different oxidation states at the C-9 and C-15 hydroxyls and at the C-13,14 position. A list of the analogues thus prepared is presented in Table II. In each case, the synthesis closely parallels the chemistry already described.

All the analogues above were isolated as diastereomeric mixtures (with the aforementioned exception of **16a**). We needed optically pure versions of certain of these analogues for our biological testing program, since it has been established in similar cases that the absolute configurations at prostanoid chiral centers can strongly affect activity, in some cases even making the difference between agonism and antagonism.[3c] Two series of optically pure compounds were therefore synthesized, as illustrated in Schemes III and IV, involving 13,14-dehydro analogues and analogues having the natural 13,14-trans double bond.

Scheme III outlines the synthesis of the optically pure alkynes **16a,b** and **18a,b**. The two optically pure antipodes of octyn-3-ol[12] were separately converted to diastereomeric mixtures (**16** and **17**) of the E series prostanoids by using the chemistry in Scheme I (methoxymethyl ether route). Multiple recrystallizations then gave the optically pure mirror images **16a** and **16b**, that cleanly oxidized to diketones **18a** and **18b**. The optical rotations of **18a** and **18b** were nearly equal and of opposite sign. Since C-15 in the diketones is no longer a chiral center, **18a** and **18b** must

Table II

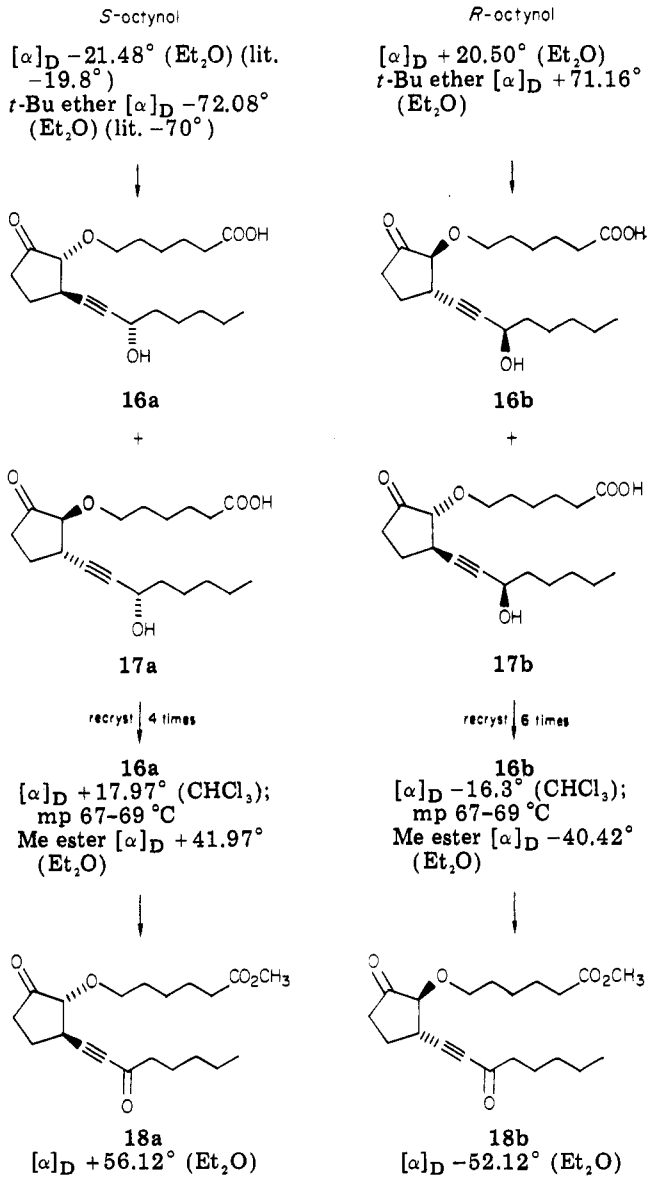


compd	R_1	R_2	R_3
4	α-OH	C≡C	$CHOH(CH_2)_4CH_3$
5	α-OH	C≡C	$CO(CH_2)_4CH_3$
6	=O	C≡C	$CHOH(CH_2)_4CH_3$
7	α-OH	*cis*-CH=CH	$CHOH(CH_2)_4CH_3$
8	α-OH	*trans*-CH=CH	$CHOH(CH_2)_4CH_3$
9	α-OH	CH_2CH_2	$CHOH(CH_2)_4CH_3$
10	=O	C≡C	$CO(CH_2)_4CH_3$
11	=O	*cis*-CH=CH	$CO(CH_2)_4CH_3$
12	=O	*trans*-CH=CH	$CO(CH_2)_4CH_3$
13	=O	CH_2CH_2	$CO(CH_2)_4CH_3$
14	=O	*cis*-CH=CH	$CHOH(CH_2)_4CH_3$
15	=O	*trans*-CH=CH	$CHOH(CH_2)_4CH_3$
21	α-OH	C≡C	$CH_2(CH_2)_4CH_3$
22	=O	C≡C	$CH_2(CH_2)_4CH_3$
23	=O	C≡C	$CH_2C(CH_3)$-$OHCH_2(CH_2)_2CH_3$
24	α-OH	C≡C	$CH_2C(CH_3)$-$OHCH_2(CH_2)_2CH_3$
25	=O	*trans*-CH=CH	$CH_2C(CH_3)$-$OHCH_2(CH_2)_2CH_3$
26	=O	CH_2CH_2	$CH_2C(CH_3)$-$OHCH_2(CH_2)_2CH_3$
27	α-OH	*trans*-CH=CH	$CH_2C(CH_3)$-$OHCH_2(CH_2)_2CH_3$
28	=O	C≡C	$COC(CH_3)_2$-$CH_2(CH_2)_2CH_3$
29	α-OH	C≡C	$CHOHC(CH_3)_2$-$CH_2(CH_2)_2CH_3$
30	=O	C≡C	$COH(CH_3)$-$CH_2(CH_2)_3CH_3$
31	α-OH	C≡C	$COH(CH_3)$-$CH_2(CH_2)_3CH_3$
32	H_2	C≡C	$CO(CH_2)_4CH_3$
33	H_2	C≡C	$CHOH(CH_2)_4CH_3$

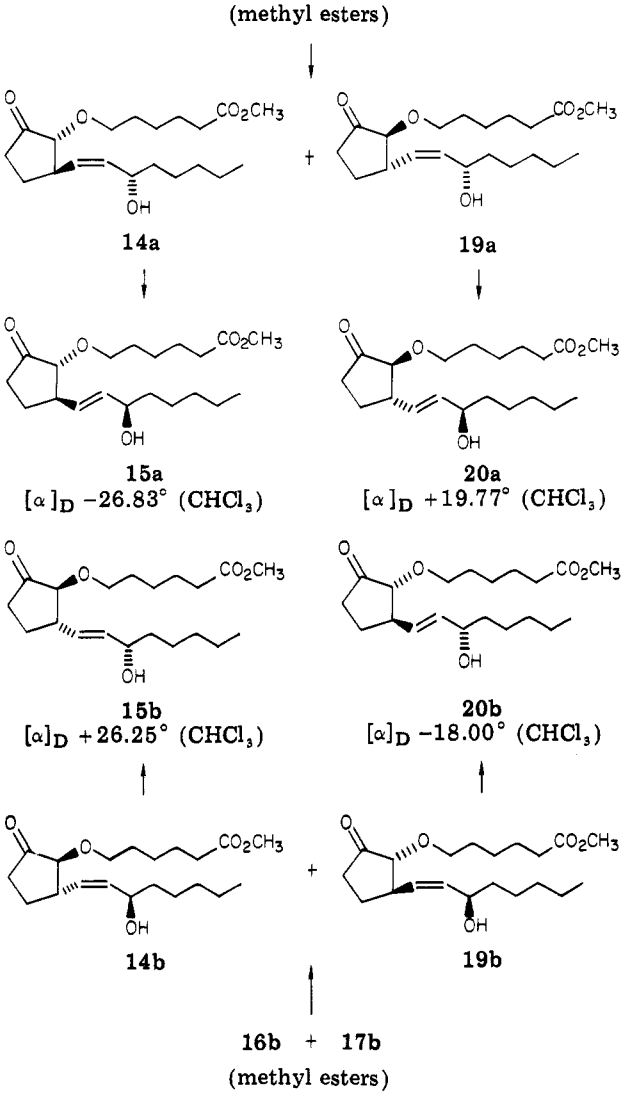
be enantiomers; this, in turn, validates the assignment of **16b** as the enantiomer of **16a**. The absolute configurations of all four isomers thus follow by correlation with the X-ray structure of **16a**.

The synthesis of the four optically pure isomers of 11-deoxy-7-oxaprostaglandin E_1 methyl ester, outlined in Scheme IV, follows the Scheme III chemistry to the point where the two diastereomeric mixtures (**16a** + **17a** and **16b** + **17b**) are produced. These two mixtures, as the methyl esters, are separately reduced by Lindlar hydrogenation to give the two corresponding mixtures of olefins **14a** + **19a** and **14b** + **19b**. These 13,14-cis olefinic methyl esters, unlike any of the other compounds in this series, gave clean chromatographic separation into diastereomerically pure isomers. The absolute configurations of **14a** and **19a** could be assigned by correlation with the X-ray structure of **16a** through the following experiment: when the Lindlar hydrogenation was run on the mixture enriched in **17a** (by crystallizing out **16a** as in Scheme III), the product ratio of **19a**/**14a** was found to be 3:1, compared to a normal ratio of 45:55 observed when an unenriched **16a** + **17a** mixture was hydrogenated. It follows that the chiral centers of **14a** must have the same absolute configurations as those of **16a** (the "all natural" isomer); **19a** must then be the other 15*S* diastereomer. By comparison of R_f values, **14b** and **19b** are identified as the enantiomers of **14a** and **19a**, respectively. These four optically pure cis olefins, after double bond isomerization by the sulfenyl chloride method[18] (also causing C-15 inversion), lead to the four optically pure isomers of 11-deoxy-7-oxaprostaglandin E_1 as shown. The optical rotations of these materials are consistent with the

Scheme III



Scheme IV



isomer assignments just described; that is, the rotations of **15a** and **20a** are equal and opposite to the rotations of **15b** and **20b**, respectively.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were run on $CDCl_3$ solutions by using Varian EM-360A and CFT-20 and JEOL FX90Q spectrometers and are expressed as δ values (parts per million downfield from Me_4Si as an internal standard). IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Mass spectra were obtained on an HP 5985B or Kratos MS-30 spectrometer. Exact-mass analytical data for the prostanoids are compiled in Table III. Optical rotations were measured by using a Rudolph Research Autopol III polarimeter. Thin-layer chromatography (TLC) was performed on Analtech Uniplate glass plates bearing a 250-μm layer of silica gel GF. "Flash chromatography" was run according to the method of Still.[19]

***cis*-2,3-Epoxy-1-(methoxymethoxy)cyclopentane (1b).** To a stirred solution of 18.9 g (0.189 mol) of *cis*-2,3-epoxycyclopentanol in 300 mL of dry CH_2Cl_2, under argon, was added 49.4 mL of diisopropylethylamine (1.5 equiv). This mixture was cooled to 5 °C, and 39.4 mL of ca. 6 M chloromethyl methyl ether (in methyl acetate[6]) was added dropwise. The cooling bath was then removed, and the reaction mixture was stirred for 1 h. Analysis by gas chromatography indicated that starting material was consumed. The reaction mixture was added to ether (900 mL) and was washed sequentially with 1 N HCl (300 mL) and 1 N $NaHCO_3$ (200 mL). The aqueous portions were back-extracted twice with 150-mL portions of ether. The combined organic layers were dried (molecular sieves), filtered, and concentrated (at 760 mm through a short Vigreux column) to give the crude product. Distillation gave 18.55 g (68%) of pure **1b**: bp 62–65 °C (2.5 mm); ^{1}H NMR (60 MHz) δ 4.65 (s, 2 H), 4.1 (m, 1 H), 3.55–3.3 (m, 2 H), 3.35 (s, 3 H), 2.45–1.15 (m, 4 H); ^{13}C NMR (20 MHz) 96.19, 78.69, 57.08, 55.26, 55.10, 25.42, 24.07 ppm.

2β-(3-*tert*-Butoxy-1-octynyl)-5α-(methoxymethoxy)-1α-cyclopentanol (2a). To a solution of 3.16 g (17.36 mmol, 2.5 equiv) of 3-*tert*-butoxy-1-octyne in 20 mL of dry toluene at 0 °C under argon was added 10.85 mL of *n*-butyllithium (1.6 M, 2.5 equiv). After 15 min, dimethylaluminum chloride (6.8 mL of a 2 M solution, 2 equiv) was added dropwise via syringe. After 50 min, 1 g of epoxide **1b** (6.94 mmol) was added dropwise, as a solution in 5 mL of toluene. The cooling bath was removed, and the stirring was continued for 4 h. The reaction was then quenched by careful addition of saturated aqueous Na_2SO_4, and the resulting mixture was partitioned between H_2O (200 mL) and ether (100 mL). The aqueous layer was extracted twice more with 150-mL portions of ether, and the combined ethereal portions were dried (molecular sieves), filtered, and concentrated under vacuum to give the crude product. Purification by flash chro-

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(20) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1977**, *42*, 2537.

Table III. Exact Mass Measurements for the Prostaglandin Analogues

compd	calcd	found	mode[a]
4	372.2750	372.2775	CI
5	353.2328	353.2362	EI
6	370.2593	370.2586	CI
7	357.2641	357.2676	EI
8	355.2485	355.2451	EI
9	359.2798	359.2829	EI
10	368.2437	368.2428	CI
11	353.2328	353.2329	EI
12	370.2593	370.2612	CI
13	372.2750	372.2727	CI
14	355.2485	355.2454	EI
15a	372.2750	372.2737	CI
20a	372.2750	372.2766	CI
21	339.2536	339.2504	EI
22	354.2645	354.2610	CI
23	384.2750	384.2766	CI
24	386.2906	386.2913	CI
25	269.2641	369.2636	EI
26	371.2798	371.2837	EI
27	388.3063	388.2937	CI
28	379.2485	379.2471	EI
29	383.2798	383.2804	EI
30	367.2484	367.2523	EI
31	369.2641	369.2628	EI
32	337.2379	337.2364	EI
33	356.2801	356.2836	CI

[a] EI = electron impact mode, MH^+ observed; CI = chemical ionization mode, $(M + NH_4)^+$ observed.

matography with 4:1 hexane/EtOAc gave 1.66 g (73%) of pure **2a**: IR (neat) 3480, 2200(w) cm^{-1}; ^1H NMR (60 MHz) δ 4.6 (s, 2 H), 4.2–3.8 (m, 3 H), 3.35 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (22.5 MHz) 96.15 (OCH_2O), 85.38, 84.40, 79.18, 78.33, 74.28 (CMe_3), 62.14 (C15), 55.55 (OMe), 37.86, 35.77, 31.59 (C18), 28.39 (CMe_3), 28.00, 27.81, 25.33, 22.65 (C19), 14.03 (C20) ppm.

***tert*-Butyl 9α-(Methoxymethoxy)-7-oxa-15-*tert*-butoxyprost-13-ynoate (3a).** A suspension of 0.44 g of sodium hydride (50% dispersion in mineral oil, 3 equiv) in 22 mL of dry Me_2SO was heated in a 70 °C oil bath under argon for 50–60 min, at which time hydrogen evolution stopped. The solution was cooled to 20 °C (under argon) and a solution of 1 g of alcohol **2a** (3.06 mmol) in 3 mL of Me_2SO was added dropwise via syringe. After 5 min, 4.57 g of *tert*-butyl 6-iodohexanoate (15.33 mmol, 5 equiv) was added in a slow stream, via syringe. After being stirred for 3 h, this mixture was added to a separatory funnel containing H_2O (50 mL) and saturated aqueous NaCl (50 mL). The mixture was extracted with three 50-mL portions of ether; the organic layers were combined, dried (molecular sieves), filtered, and concentrated under vacuum to give the crude product. Upon purification by flash chromatography (4:1 hexane/EtOAc) two fractions were isolated. The first (R_f 0.5 with 3:1 hexane/EtOAc) was product **3a**: 0.85 g (56% yield); IR (neat) 1730 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.6 (s, 2 H), 4.2–3.85 (m, 2 H), 3.7–3.3 (m, 3 H), 3.25 (s, 3 H), 2.9–2.55 (m, 1 H), 1.4 (s, 9 H), 1.2 (s, 9 H); ^{13}C NMR (22.5 MHz) 172.98, 95.63, 86.56, 86.36, 83.88, 79.83, 76.64, 74.22, 70.37, 62.14, 55.29, 37.86, 35.51, 32.90, 31.59, 29.70, 28.39 (3 C), 28.13 (3 C), 27.94, 27.74, 25.72, 25.34, 25.00, 22.58, 14.03 ppm. The second fraction was recovered alcohol **2a**, 0.43 g (43%).

***tert*-Butyl 9α-Hydroxy-15(*S*)-(*tert*-butyloxy)-7-oxaprost-13-ynoate (3d).** To a solution of **3a** (0.411 g, 0.829 mmol) in 25 mL of CH_2Cl_2 was added 5.22 g of Et_4NBr and 3.26 mL of chlorotrimethylsilane. This cloudy mixture was stirred at 25 °C for 6 h and then partitioned between 1 N $NaHCO_3$ and CH_2Cl_2. After two more CH_2Cl_2 extractions, the organic layers were combined, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (7:1 hexane/EtOAc) to give 226 mg (60% yield) of pure **3d**: IR (neat) 3500, 2240 (w), 1730 cm^{-1}; ^1H NMR (60 MHz) δ 4.0 (m, 2 H), 3.5 (m, 3 H), 1.4 (s, 9 H), 1.2 (s, 9 H); ^{13}C NMR (22.5 MHz) 172.85, 86.88, 86.03, 83.95, 79.90, 74.22, 71.74, 70.37, 62.08, 37.86, 35.38, 33.09, 31.53, 30.29, 29.57, 28.33 (3 C), 28.13 (3 C), 25.65, 25.26, 24.87, 22.58, 13.97 ppm.

***tert*-Butyl 15-Hydroxy-9α-(methoxymethoxy)-7-oxaprost-13-ynoate (3e).** Silyl ether **3b** (410 mg, 0.74 mmol) was dissolved in 4.4 mL of dry THF and cooled to 0 °C under argon. Tetrabutylammonium fluoride (1 M in THF, 1.48 mL) was added dropwise via syringe. After 5 min the solution was allowed to warm up to 25 °C, and stirring was continued for 40 min. The reaction mixture was then added to a separatory funnel with 100 mL of 1 N $NaHCO_3$ and was extracted with three 40 mL portions of EtOAc. The organic layers were combined, dried (molecular sieves), filtered, and concentrated under vacuum. This crude extract was purified by flash chromatography (3:1 hexane/EtOAc) to give 335 mg (100%) of pure alcohol **3e**: ^1H NMR (60 MHz) δ 4.6 (s, 2 H), 3.8–4.5 (m, 2 H), 3.3–3.7 (m, 3 H), 3.25 (s, 3 H), 2.5–3.0 (m, 2 H), 1.4 (s, 9 H); ^{13}C NMR (22.5 MHz) 173.18 (C1), 95.56 (OCH_2O), 87.21 (C13), 86.69 (C8), 82.77 (C14), 79.96 ($OCMe_3$), 76.37 (C9), 70.37 (C7), 62.40 (C15), 55.29 (OCH_3), 38.19, 35.51, 32.77, 31.59, 29.57, 28.13 (3 C), 27.94, 27.81, 25.65, 24.94, 22.65, 14.03 ppm.

Methyl 9α,15-Dihydroxy-7-oxaprost-13-ynoate (4). To a solution of 1.85 g (3.73 mmol) of **3a** in 8 mL of CH_2Cl_2, stirred at −10 °C under argon, was added 8 mL of trifluoroacetic acid (which had been cooled to 0 °C) in one portion. After 10 min the cooling bath was removed, and the reaction mixture was stirred 60–90 min longer. A vacuum pump was attached, and all volatiles were thus removed. The brown residue was taken up in 75 mL of methanol (anhydrous), and 7.5 mL of BF_3 etherate was added; this mixture was refluxed 10 min on a steam cone and then concentrated under vacuum to remove most of the methanol. The remainder was extracted from 1 N $NaHCO_3$ (100 mL) with CH_2Cl_2. The organic layers were combined, filtered, and concentrated under vacuum to give the crude product. Purification by flash chromatography (1.2:1 hexane/EtOAc) gave 1.16 g (88%) of pure prostanoid **4**: IR (neat) 3480, 2250 (w), 1745 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.5–4.0 (m, 2 H), 3.9–3.5 (m, 3 H), 3.65 (s, 3 H); ^{13}C NMR (22.5 MHz) 174.09 (C1), 87.01 (C8), 82.84 (C14), 77.03 (C13), 71.54, 70.30, 62.40 (C15), 51.50 (OCH_3), 38.12 (C12), 33.88, 32.96, 31.53, 30.09, 29.44, 28.26, 25.65, 24.93, 24.61, 22.58, 13.97 (CH_2CH_3) ppm.

***tert*-Butyl 9α-(Methoxymethoxy)-7-oxa-15-oxoprost-13-ynoate.** A solution of CrO_3 (0.67 g) and pyridine (1.07 mL) in CH_2Cl_2 (17 mL) was stirred 15 min at 25 °C. A solution of alcohol **3e** (325 mg, 0.74 mmol) in 1 mL of CH_2Cl_2 was added, and the resulting mixture was stirred an additional 15 min. After addition of 100 mL of ether the mixture was filtered through a short silica gel column, eluting with 50 mL of EtOAc. The combined eluent was concentrated under vacuum and purified by preparative TLC (4 × 500 μm silica gel plates with 4:1 hexane/EtOAc) to give 260 mg (80%) of product: IR (neat) 2200 (s), 1725 (s), 1670 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.6 (s, 2 H), 4.1 (m, 1 H), 3.4–3.9 (m, 3 H), 3.3 (s, 3 H), 1.4 (s, 9 H); ^{13}C NMR (22.5 MHz) 188.06 (C15), 172.85 (C1), 95.83 (C13), 95.56 (OCH_2O), 86.43 (C8), 81.40 (C14), 79.83 ($OCMe_3$), 76.05 (C9), 70.63 (C7), 55.35 (OCH_3), 45.50, 35.44, 32.83, 31.14, 29.57, 28.07 (3 or 4 C), 27.15, 25.59, 24.87, 23.83, 22.39, 13.84 ppm.

Methyl 9α-Hydroxy-7-oxa-15-oxoprost-13-ynoate (5). *tert*-Butyl 9α-(methoxymethoxy)-7-oxa-15-oxoprost-13-ynoate (220 mg, 0.5 mmol) was dissolved in 1.4 mL of CH_2Cl_2 and cooled to −15 °C under argon; trifluoroacetic acid (1.4 mL, cooled to 0 °C) was then added with stirring. After 10 min the cooling bath was removed, and the reaction mixture was stirred for 90 min more. The reaction mixture was concentrated under vacuum and passed through a silica gel column (elution with 94:3:3 $CHCl_3$/MeOH/HOAc). The 147 mg of crude acid thus obtained was esterified with CH_2N_2 to give the crude methyl ester, which was purified by preparative TLC (3 × 500 μm silica gel plates, developed with 1.8:1 hexane/EtOAc) to give 90 mg of pure ester (65% overall from **3e**): IR (neat) 3500, 2200 (s), 1730 (s), 1665 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.0–4.3 (m, 1 H), 3.5–3.9 (m, 3 H), 3.7 (s, 3 H), 2.8–3.1 (m, 1 H); ^{13}C NMR (22.5 MHz) 188.12 (C15), 173.90 (C1), 95.63 (C13), 86.88 (C8), 81.53 (C14), 71.48, 70.63, 51.44 (OCH_3), 45.50, 33.88, 32.96, 31.14, 29.90, 29.44, 27.68, 25.59, 24.61, 23.83, 22.39, 13.84 ppm.

Methyl 15-Hydroxy-7-oxa-9-oxoprost-13-ynoate (6) and 16a,b. A solution of 1.59 g of alcohol **3d** in 15 mL of CH_2Cl_2 was oxidized by the normal Collins procedure (see procedure for **10**). The crude product was purified by flash chromatography (5:1 hexane/EtOAc) to give 1.40 g of *tert*-butyl 7-oxa-9-oxo-15-(*tert*-butyloxy)prost-13-ynoate: IR (neat) 1750 (s), 1725 (s) 2230

(w) cm^{-1}; ^1H NMR (60 MHz) δ 4.0 (m, 1 H), 3.7 (m, 3 H), 1.4 (s, 9 H), 1.25 (s, 9 H); ^{13}C NMR (22.5 MHz) 213.39, 172.85, 85.71, 85.45, 83.55, 79.77, 74.35, 71.22, 61.95, 37.73, 35.44, 34.40, 34.14, 31.53, 29.50, 28.26 (3 C), 28.13 (3 C), 25.46, 25.20, 24.87 (2 C), 22.58, 13.97 ppm.

Several runs of this oxidation were combined to give 4.18 g of ketone. A solution of this material in CH_2Cl_2 was cooled to −15 °C under argon, and 21 mL of cold (0 °C) trifluoroacetic acid was added dropwise via syringe. After 15 min the cooling bath was removed, and the reaction mixture was stirred for 1 h more. All volatiles were then removed in vacuo, and the dark residue was purified by flash chromatography (94:3:3 $CHCl_3$/HOAc/MeOH). The resulting product partially solidified in the refrigerator over 3 days. One recrystallization from EtOAc/hexane gave impure isomer **16a**: 1.75 g; mp 53–59 °C. Four further recrystallizations gave pure **16a**: mp 67–69 °C; $[\alpha]_D$ +17.97° (*c* 0.48, $CHCl_3$).

Acid **16a** was converted to methyl ester **6** using diazomethane by the usual method. Spectral data for **6**: IR (neat) 3450, 2190 (w), 1730 (br) cm^{-1}; ^1H NMR (60 MHz) δ 4.5–4.15 (m, 1 H), 4.2–3.4 (m, 3 H), 3.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 213.59 (C9), 174.35 (C1), 85.90 (C8), 84.53, 84.21, 71.28 (C6), 62.47 (C15), 51.57 (OCH_3), 37.99, 34.47, 34.01 (2 C), 31.53, 29.37, 25.52, 24.93, 24.67, 22.65, 14.03 ppm.

Compound **16b** was synthesized by exactly the same procedures in the *R* series (see Scheme III).

Methyl 9α-Hydroxy-15-hydroxy-7-oxa-*cis*-prost-13-enoate (7). A solution of 410 mg (1.16 mmol) of diol **4** in 20 mL of absolute EtOH was hydrogenated over 50 mg of Lindlar catalyst at atmospheric pressure. After 1 equiv of hydrogen was consumed, the mixture was filtered, concentrated, and purified (flash chromatography, 1:1 hexane/EtOAc) to give 410 mg (99%) of cis olefin **7** as a 1:1 mixture of diasteriomers: IR (neat) 3450 (s), 1735 (s), 1650 (w) cm^{-1}; ^1H NMR (90 MHz) δ 5.1–5.9 (m, 2 H), 3.7 (s, 3 H); ^{13}C NMR (22.5 MHz) 173.96, 135.78, 134.73, 134.34, 133.36, 87.60, 87.21 (C8), 70.69, 70.43, 70.30, 69.91, 67.95, 66.45, 51.44 (OCH_3), 40.21, 39.88, 37.79, 36.75, 33.88, 32.05, 31.92, 30.16, 29.83, 29.63, 29.18, 27.68, 26.96, 25.65, 25.46, 25.26, 25.13, 24.67, 24.54, 22.65, 14.03 ppm.

Methyl 9α-Hydroxy-15-hydroxy-7-oxaprostanoate (9). A solution of 305 mg (0.86 mmol) of diol **4** in 25 mL of absolute EtOH was hydrogenated over 30 mg of catalyst (5% Pd/C) at 760 mm. After 2 equiv of hydrogen uptake the mixture was filtered and concentrated in vacuo to give the crude product. Flash chromatography (1:1 hexane/EtOAc) gave pure diol **9**: IR (neat) 3450 (s), 1735 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.0 (m, 1 H), 3.6 (s, 3 H), 3.7–2.8 (m, 6 H); ^{13}C NMR (22 MHz) 174.02, 87.60, 71.93, 71.74, 70.83, 69.91, 51.44, 41.32, 41.06, 37.60, 37.40, 35.77, 33.88, 31.92, 30.35, 29.57, 26.57, 26.37, 25.72, 25.33, 24.61, 22.58, 13.97 ppm.

Methyl 9,15-Dioxo-7-oxaprost-13-ynoate (10). A mixture of CrO_3 (2.56 g), pyridine (4.13 mL), and CH_2Cl_2 (65 mL) was stirred 15 min at room temperature. A solution of 500 mg of diol **4** (1.41 mmol) in 2 mL of CH_2Cl_2 was added via pipet, and the resulting heterogeneous mixture was stirred another 15–20 min. After addition of 100 mL of ether, the mixture was filtered through a short silica gel column to remove the chromium salts (the column was then washed with 100 mL of EtOAc). The combined eluant was concentrated under vacuum, and the residue was purified by flash chromatography (3:1 hexane/EtOAc) to give 440 mg (89%) of pure **10**: IR (neat) 2230 (s), 1760 (s), 1730 (s), 1680 (s) cm^{-1}; ^1H NMR (60 MHz) δ 3.85–3.45 (m, 3 H), 3.61 (s, 3 H); ^{13}C NMR (22.5 MHz) 212.15 (C9), 187.74 (C15), 173.96 (C1), 91.97 (C13), 85.19 (C8), 82.18 (C14), 71.67 (C6), 51.44 (OCH_3), 45.50 (C12), 34.40, 34.01 (2 C), 31.14, 29.44, 25.52, 24.74, 24.02, 23.76, 22.39, 13.90 (CH_2CH_3) ppm.

Methyl 9,15-Dioxo-7-oxaprostanoate (13). Diol **9** was normally not purified before use in this reaction. A mixture of CrO_3 (1.54 g), pyridine (2.48 mL), and CH_2Cl_2 (35 mL) was stirred 15 min at 25 °C. The crude diol **9** was added as a solution in 2 mL of CH_2Cl_2. After 15 min the crude diketone was isolated in the usual way (see procedure for **10**). Purification by flash chromatography (2.5:1 hexane/EtOAc) gave 250 mg (82% overall from **4**) of pure **13**: IR (neat) 1740 (s, br), 1715 cm^{-1}; ^1H NMR (60 MHz) δ 4.0 (m, 1 H), 3.6 (s, 3 H), 3.6–3.1 (m, 2 H); ^{13}C NMR (22.5 MHz) 216.58 (C15), 210.26 (C9), 173.70 (C1), 87.08 (C8), 70.56 (C6), 51.18 (OCH_3), 42.56, 41.19, 39.95, 34.79, 33.75, 31.20, 29.50, 27.55, 25.46, 24.54, 23.30 (2 C), 22.26, 13.71 ppm.

Methyl 15-Hydroxy-7-oxa-9-oxo-*cis*-prost-13-enoates (14a, 19a). A solution of keto alcohol **6** (114 mg, 0.34 mmol) in 10 mL of absolute EtOH was hydrogenated over 20 mg of Lindlar catalyst at 760 mm. After 1 equiv of hydrogen was consumed, the mixture was filtered, concentrated in vacuo, and purified by flash chromatography (1.5:1 hexane/EtOAc) to give 58.3 mg of isomer **14a** [R_f 0.50; IR (neat) 3490, 1750, 1730 cm^{-1}; ^1H NMR (60 MHz) δ 5.3–5.8 (m, 2 H), 2.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 214.82, 174.09, 137.27, 132.57, 85.77, 71.54, 66.65, 51.37, 41.32, 36.68, 34.60, 33.94, 31.79, 29.18, 25.33, 25.13, 24.54, 23.89, 22.58, 13.97 ppm] and 46.2 mg of isomer **19a**: R_f 0.33; IR (neat) same major bands as **14a**, slight differences in fingerprint; ^1H NMR (60 MHz) δ 5.2–5.8 (m, 2 H), 2.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 215.29, 174.02, 135.65, 131.79, 86.75, 71.48, 68.67, 51.44, 41.38, 37.73, 34.66, 33.94, 31.85, 29.50, 25.46, 25.00, 24.67, 24.35, 22.58, 14.03 ppm. The combined yield was 91%.

Methyl 11-Deoxy-7-oxa-15(*R*)-hydroxy-*ent*-prostaglandin E_1 (20a) and Methyl 11-Deoxy-7-oxaprostaglandin E_1 (20b). To a solution of 115 mg (0.325 mmol) of cis olefin **19a** in ether (5 mL), stirred at room temperature under argon, was added 166 μL of triethylamine followed by 122 μL of *p*-toluenesulfenyl chloride dropwise via syringe. After 24 h (in the dark), the ether was removed, and the residue was dissolved in 5 mL of methanol. Trimethyl phosphite (1.1 mL) was added, and the mixture was stirred 48 h at room temperature. The volatiles were all removed in vacuo, and the residue was purified by flash chromatography with 1.5:1 hexane/EtOAc. The product thus obtained was further purified by preparative TLC (2 × 500 μm silica gel plates, 2.7:1 hexane/EtOAc, developed three times) to yield 71.5 mg (62%) of prostanoid **20a**: IR (neat) 3500, 1745 (br), 970 cm^{-1}; ^1H NMR (60 MHz) δ 5.6 (m, 2 H), 4.2–3.2 (m, 5 H), 3.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 215.74, 174.22, 134.92, 131.14, 86.43, 72.65, 71.09, 51.50, 44.98, 37.40, 34.79, 34.01, 31.79, 29.57, 25.59, 25.13, 24.74, 23.63, 22.65, 14.03 ppm; $[\alpha]_D$ +19.77° ($CHCl_3$).

The enantiomer **20b**, prepared in an analogous way from **19b**, had the same spectral properties except for the rotational measurement: $[\alpha]_D$ −18.00° ($CHCl_3$).

The following PG analogues were synthesized by procedures similar to those described above.

Methyl 9,15-dihydroxy-7-oxa-*trans*-prost-13-enoate (8): IR (neat) 3450, 1735 (s), 970 cm^{-1}; ^1H NMR (60 MHz) δ 5.5 (m, 2 H), 4.0 (m, 2 H), 3.6 (s, 3 H), 3.6–3.1 (m, 3 H); ^{13}C NMR (22.5 MHz) 174.09, 133.62, 133.23, 132.97, 86.82, 72.72, 72.91, 70.89, 70.24, 51.50, 44.45, 37.40, 33.94, 31.79, 30.16, 29.57, 26.70, 25.72, 25.20, 24.67, 22.65, 14.03 ppm.

Methyl 7-oxa-9,15-dioxo-*cis*-prost-13-enoate (11): IR (neat) 1750 (s), 1730 (s), 1685, 1620 cm^{-1}; ^1H NMR (90 MHz) δ 6.0 (1 H, dd, J = 11.4, 8.3 Hz), 6.3 (1 H, d, J = 11.4 Hz), 4.2–3.3 (m, 3 H), 3.65 (s, 3 H); ^{13}C NMR (22.5 MHz) 214.30, 201.31, 173.90, 146.94, 128.53, 87.66, 70.11, 51.31, 44.19, 41.65, 34.73, 33.94, 31.33, 29.44, 25.53, 24.67, 23.56, 22.98, 22.45, 13.84 ppm.

Methyl 7-oxa-9,15-dioxo-*trans*-prost-13-enoate (12): IR (neat) 1750 (s), 1740 (s, br), 1690, 1670, 1625, 980 cm^{-1}; ^1H NMR (90 MHz) δ 6.85 (1 H, dd, J = 15.87, 8.79 Hz), 6.24 (1 H, dd, J = 15.87, 0.73 Hz), 4.2–3.3 (m, 3 H), 3.66 (s, 3 H); ^{13}C NMR (22.5 MHz) 214.37, 200.13, 174.02, 145.31, 130.68, 85.77, 71.35, 51.44, 45.11, 40.86, 34.60, 34.01, 31.46, 29.57, 25.59, 24.74, 23.83, 22.78, 22.52, 13.90 ppm.

Methyl (15*R*)-11-deoxy-7-oxa-15-hydroxyprostaglandin E_1 (15a) and methyl 11-deoxy-7-oxa-*ent*-prostaglandin E_1 (15b): IR (neat) 3500, 1745 (br), 975 cm^{-1}; ^1H NMR (60 MHz) δ 6.6 (m, 2 H), 4.2–3.3 (m, 5 H), 3.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 215.68, 174.28, 135.06, 130.95, 86.49, 72.52, 70.96, 51.50, 44.98, 37.34, 34.79, 34.01, 31.79, 29.50, 25.59, 25.13, 24.67, 23.69, 22.65, 14.03 ppm. Rotations: **15a**, $[\alpha]_D$ −26.83° ($CHCl_3$); **15b**, $[\alpha]_D$ +26.25° ($CHCl_3$).

Methyl 9-hydroxy-7-oxaprost-13-ynoate (21): IR (neat) 3500 (br), 2200 (w), 1735 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.1 (m, 1 H), 3.6 (s, 3 H), 3.8–3.3 (m, 4 H); ^{13}C NMR (22.5 MHz) 173.90, 87.27, 82.38, 81.40, 71.61, 70.30, 51.37, 33.94, 33.16, 31.40, 30.29, 29.57, 29.05, 28.59 (2 C), 25.72, 24.74, 22.65, 18.86, 14.03 ppm.

Methyl 7-oxa-9-oxoprost-13-ynoate (22): IR (neat) 2210 (w), 1735 (s, br) cm^{-1}; ^1H NMR (90 MHz) δ 3.9–3.6 (m, 3 H), 3.66 (s, 3 H); ^{13}C NMR (22.5 MHz) 213.91, 173.96, 86.10, 83.10, 79.96, 71.15, 51.37, 34.47, 34.20, 34.01, 31.33, 29.44, 28.85, 28.53, 25.59, 25.26, 24.74, 22.58, 18.73, 14.03 ppm.

Methyl 16-hydroxy-16-methyl-7-oxa-9-oxoprost-13-ynoate (23): IR (neat) 3450 (br), 2220 (w), 1735 (s, br) cm^{-1}; ^1H NMR (60 MHz) δ 4.1 (m, 1 H), 3.8–3.3 (m, 2 H), 3.6 (s, 3 H), 1.2 (s, 3 H); ^{13}C NMR (22.5 MHz) 213.65, 174.02, 86.03, 82.84, 79.44, 71.74, 71.22, 51.37, 40.99, 34.40, 34.07, 33.94, 32.70, 29.44, 26.44, 26.11, 25.52, 25.07, 24.67, 23.17, 14.03 ppm.

Methyl 9,16-dihydroxy-16-methyl-7-oxaprost-13-ynoate (24): IR (neat) 3450 (s), 1735 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.1 (m, 1 H), 3.8–3.2 (m, 3 H), 3.6 (s, 3 H), 2.2 (s, 3 H); ^{13}C NMR (22.5 MHz) 173.96, 87.34, 85.51, 77.68, 71.74, 71.48, 70.37, 51.37, 41.06, 33.94, 33.16, 32.83, 30.22, 29.57, 28.52, 26.44, 26.24, 25.72, 24.67, 23.30, 14.03 ppm.

Methyl 16-hydroxy-16-methyl-7-oxa-9-oxo-*trans*-prost-13-enoate (25): IR (neat) 3500, 1750 (s), 1735 (s), 975 (m) cm^{-1}; ^1H NMR (60 MHz) δ 5.5 (m, 2 H), 4.0–3.2 (m, 3 H), 3.55 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR (22.5 MHz) 215.74, 174.09, 134.40, 127.55, 86.56, 72.26, 71.02, 51.44, 45.50, 44.98, 41.58, 34.73, 34.01, 29.57, 26.76, 26.04, 25.59, 24.74, 23.83, 23.24, 14.10 ppm.

Methyl 16-hydroxy-16-methyl-7-oxa-9-oxoprostanoate (26): IR (neat) 3500, 1740 (s, br) cm^{-1}; ^1H NMR (60 MHz) δ 4.3–3.0 (m, 4 H), 3.6 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR (22.5 MHz) 216.98, 173.76, 87.01, 72.20, 70.63, 51.18, 41.71 (2 C), 41.45, 34.79, 34.20, 33.75, 29.44, 26.63, 25.91, 25.39, 24.54, 23.11, 21.08, 13.90 ppm.

Methyl 9,16-dihydroxy-16-methyl-7-oxa-*trans*-prost-13-enoate (27): IR (neat) 3450, 1735 (s), 975(m) cm^{-1}; ^1H NMR (60 MHz) δ 5.5 (m, 2 H), 4.0 (m, 1 H), 3.6 (s, 3 H), 3.6–3.1 (m, 3 H), 1.1 (s, 3 H); ^{13}C NMR (22.5 MHz) 174.02, 136.56, 125.98, 86.95, 72.20, 70.83, 70.24, 51.44, 45.04 (2 C), 41.58, 33.94, 30.22, 29.63, 26.89, 26.76, 26.11, 25.72, 24.67, 23.30, 14.10 ppm.

Methyl 16,16-dimethyl-7-oxa-9,15-dioxoprost-13-ynoate (28): IR (neat) 2210 (s), 1750 (s), 1730 (s, br), 1670 cm^{-1}; ^1H NMR (90 MHz) δ 3.9–3.5 (m, 3 H), 3.65 (s, 3 H), 1.1 (s, 6 H); ^{13}C NMR (22.5 MHz) 212.15, 193.67, 173.96, 93.15, 85.32, 80.36, 71.67, 51.37, 48.17, 39.49, 34.40, 34.01 (2 C), 29.50, 26.76, 25.59, 24.74, 23.83 (2 C), 23.37, 13.97 ppm.

Methyl 9,16-dihydroxy-16,16-dimethyl-7-oxaprost-13-ynoate (29): IR (neat) 3450, 1735 (s), 2230 (w) cm^{-1}; ^1H NMR (60 MHz) δ 4.0 (m, 2 H), 3.8–3.4 (m, 3 H), 3.6 (s, 3 H), 0.95 (s, 6 H); ^{13}C NMR (22.5 MHz) 174.09, 88.12, 87.14, 81.27, 71.54, 70.43 (2 C), 51.50, 38.32, 38.19, 33.94, 33.03, 30.16, 29.50, 28.33, 26.11, 25.72, 24.67, 23.69, 22.78, 22.52, 14.16 ppm.

Methyl 15-hydroxy-15-methyl-7-oxa-9-oxoprost-13-ynoate (30): IR (neat) 3500, 2220 (w), 1755 (s), 1740 cm^{-1}; ^1H NMR (90 MHz) δ 3.8–3.5 (m, 3 H), 3.6 (s, 1 H), 3.8 (m, 1 H), 1.4 (s, 3 H); ^{13}C NMR (22.5 MHz) 213.51, 174.22, 86.82, 85.97, 83.10, 71.35, 68.15, 51.50, 43.80, 34.47, 34.01, 31.92, 29.90, 29.70, 29.37, 25.52, 24.87, 24.61, 24.48, 22.58, 14.03 ppm.

Methyl 9,15-dihydroxy-15-methyl-7-oxaprost-13-ynoate (31): IR (neat) 3400 (s), 2200 (w), 1730 (s) cm^{-1}; ^1H NMR (90 MHz) δ 4.1 (m, 1 H), 3.6–3.4 (m, 4 H), 3.66 (s, 3 H), 1.4 (s, 3 H); ^{13}C NMR (22.5 MHz) 174.09, 87.08, 85.45, 71.54, 70.37, 68.08, 51.50, 43.93, 33.94, 32.90, 31.98, 30.09 (2 C), 29.50, 28.33, 25.65, 24.61, 24.48, 22.65, 14.03 ppm.

Methyl 7-oxa-15-oxoprost-13-ynoate (32): IR (neat) 2210 (s), 1740 (s), 1675 (s) cm^{-1}; ^1H NMR (60 MHz) δ 3.9 (m, 1 H), 3.6 (s, 3 H), 3.4 (m, 2 H); ^{13}C NMR (22.5 MHz) 188.06, 173.83, 95.83, 86.03, 81.33, 69.26, 51.24, 45.37, 36.63, 33.81, 31.92, 31.20, 31.01, 29.37, 25.65, 24.61, 23.69, 22.78, 22.26, 13.71 ppm.

Methyl 15-hydroxy-7-oxaprost-13-ynoate (33): IR (neat) 3450, 2230 (w), 1735 (s) cm^{-1}; ^1H NMR (60 MHz) δ 4.2 (m, 1 H), 3.8–3.2 (m, 3 H), 3.6 (s, 3 H); ^{13}C NMR (22.5 MHz) 173.90, 87.01, 86.43, 82.38, 68.93, 62.14, 51.24, 37.92, 36.42, 33.75, 31.53 (2 C), 31.33, 29.31, 25.59, 24.74, 24.54, 22.39 (2 C), 13.77 ppm.

Reaction of Various Nucleophiles with Epoxide 1d. Benzyl Ethers 1d. The starting material for this study, epoxide **1d**, was prepared from alcohol **1a** as follows. A 250-mL flask was charged with THF (80 mL, freshly distilled) and cooled to 0 °C under argon. A 4.1-mL portion of potassium hydride (23%, mineral oil dispersion) was added. A solution of 2.0 g of epoxy alcohol **1a** (20 mmol) in 6 mL of THF was then added dropwise with stirring. After 5 min, 3 mL of benzyl bromide was added dropwise via syringe. Ten minutes later the reaction was quenched by dropwise addition of 1 N $NaHCO_3$, and most of the THF was distilled off in vacuo. The residue was added to water (100 mL) and extracted with CH_2Cl_2 to give, after concentration, the crude epoxy ether. Purification by flash chromatography (4:1 hexane/EtOAc) yielded 3.13 g (82%) of pure benzyl ether **1d**: ^1H NMR (60 MHz) δ 7.2 (s, 5 H), 4.5 (s, 2 H), 4.1–3.7 (m, 1 H), 3.4–3.1 (m, 2 H), 2.1–1.1 (m, 4 H); ^{13}C NMR (22.5 MHz) 138.06, 127.87 (2 C), 127.16 (3 C), 79.31, 71.02, 55.62, 54.51, 25.00, 23.24 ppm. The bis benzyl ethers referred to below were all prepared by this general procedure.

(A) Reaction with an Alkynyl Alane Reagent. The reagent was prepared and the reaction run exactly as described above (using Et_2AlCl) in the preparation of **2a**. The yields and product distribution were also the same as those for the **2a** case except that one other minor (5% yield) product was observed, whose structure was tentatively assigned as in Table I: ^{13}C NMR (22.5 MHz) 138.52, 128.47 (2 C), 127.68 (3 C), 84.86, 77.74, 70.89, 55.35, 32.70, 28.79, 24.22, 12.47 ppm.

(B) Reaction with a Cuprate Reagent.[20] Cuprous iodide (762 mg) was slurried with 10 mL of ether and cooled to −45 °C under argon. *n*-Butyllithium (5 mL of a 1.6 M solution in hexane) was added dropwise with stirring. After cooling to −78 °C a solution of 382 mg (2 mmol) of epoxide **1d** in 2 mL of ether was added dropwise over 5–10 min. After 3 h more at −78 °C, the reaction mixture was quenched (saturated NH_4Cl) and extracted with ether. The ether layer was dried (molecular sieves), filtered, and concentrated to give the crude product. Flash chromatography (4:1 hexane/EtOAc) gave 80 mg of "β-attack" isomer: R_f 0.61 (3:1 hexane/EtOAc); ^1H NMR (60 MHz) δ 7.1 (s, 5 H), 4.5 (dd, 2 H), 4.0–3.4 (m, 2 H); ^{13}C NMR (22.5 MHz) 138.26, 128.40 (2 C), 127.61 (3 C), 80.42, 78.20, 71.28, 44.65, 33.75, 30.29, 27.74, 26.50, 22.91, 14.03 ppm. "α-attack" isomer: 154 mg; R_f 0.27; ^1H NMR (60 MHz) 7.15 (s, 5 H), 4.2 (s, 2 H), 3.8–3.3 (m, 2 H); ^{13}C NMR (22.5 MHz) 138.45, 128.33 (2 C), 127.61 (2 C), 127.22, 84.92, 77.74, 70.76, 53.40, 32.51, 31.27, 30.03, 28.66, 22.85, 14.03 ppm; ^{13}C NMR (of α-attack isomer bis ether, 22.5 MHz) 138.91 (2 C), 128.14 (4 C), 127.48 (4 C), 127.22 (2 C), 84.08 (2 C), 70.69 (2 C), 51.05, 32.64, 29.90, 29.18 (2 C), 22.85, 14.03 ppm. Much of the missing mass in this reaction was accounted for by isolation of a relatively volatile component from the early fractions during the flash chromatography (R_f >0.6), tentatively identified as 3-*n*-butylcyclopentanone (see Table I) on the basis of ^{13}C NMR (22.5 MHz): 219.6, 45.2, 38.4, 37.1, 35.4, 30.1, 29.6, 22.8, 14.0 ppm.

(C) Reaction with the Dithiane Anion. To a solution of 255 mg of dithiane in 10 mL of freshly distilled THF, cooled to −20 °C under argon, was added 1.16 mL of *n*-butyllithium (1.6 M solution in hexane). After being stirred at −20 °C for 2 h the mixture was cooled to −78 °C. The epoxide (336 mg in 1.5 mL of THF) was added dropwise, and the reaction mixture was stored overnight at 3 °C. The crude product was extracted (CH_2Cl_2) from aqueous $NaHCO_3$. Flash chromatography (7:1 hexane/EtOAc) on that extract yielded 82.3 mg (24%) of recovered starting material, 127.6 mg of impure β-attack isomer (R_f 0.31), and 356.2 mg pure α-attack isomer: R_f 0.21; ^1H NMR (60 MHz) δ 7.2 (s, 5 H), 4.4 (s, 2 H), 4.4–3.7 (m, 3 H); ^{13}C NMR (22.5 MHz) 138.58, 128.14 (2 C), 127.61 (2 C), 127.35, 81.60,74.55, 71.15, 58.49, 48.89, 32.38, 30.03, 29.83, 28.98, 25.78 ppm; ^{13}C NMR (of bis ether, 22.5 MHz) 138.84, 128.20 (2 C), 127.61 (2 C), 127.29, 81.20 (2 C), 71.22 (2 C), 56.92, 50.20, 30.74 (2 C), 29.96 (2 C), 25.98 ppm. The β-attack isomer was found to be ca. 75% pure; for characterization, a small sample was purified by preparative TLC (500-μm silica gel plate, 7:1 hexane/EtOAc, three developments) to give pure β-attack isomer: ^1H NMR (90 MHz) δ 7.3 (s, 5 H), 4.5 (dd, 2 H), 4.27 (d, 1 H, J = 5 Hz), 4.2–3.8 (m, 2 H); ^{13}C NMR (22.5 MHz) 138.13, 128.47 (2 C), 127.68 (3 C), 80.29, 74.81, 71.35, 51.18, 49.61, 30.88, 30.35, 27.81, 26.11, 23.43 ppm.

(D) Reaction with the Acetonitrile Anion. To a solution of 3.8 mL of *n*-butyllithium (1.6 M solution in hexane) in 6 mL of toluene, stirred under argon at −78 °C, was added 0.4 mL of acetonitrile (freshly distilled from CaH_2) as a solution in 3 mL of toluene. After 5–10 min a solution of epoxide **1d** (288 mg, 1.51 mmol) in toluene (2 mL) was added dropwise via syringe. The reaction mixture was allowed to warm to 25 °C over 1.5 h. The mixture was then poured into 1 N $NaHCO_3$ and extracted with EtOAc. The combined organics were dried (molecular sieves), filtered, and concentrated in vacuo to give the crude product. Purification by flash chromatography (1.6:1 hexane/EtOAc) produced 100 mg of pure β-attack isomer [R_f 0.39; ^1H NMR (60 MHz) δ 7.2 (s, 5 H), 4.4 (dd, 2 H), 4.0–3.3 (m, 2 H); ^{13}C NMR (22.5 MHz) 137.86, 128.47 (2 C), 127.81, 127.68 (2 C), 118.61, 79.18, 77.16,

71.22, 40.86, 27.28, 25.26, 20.04 ppm] and the α-attack isomer: 123.2 mg; R_f 0.28; ^{1}H NMR (60 MHz) δ 7.2 (s, 5 H), 4.35 (dd, 2 H), 4.0–3.3 (m, 2 H); ^{13}C NMR (22.5 MHz) 138.00, 128.47 (2 C), 127.74 (3 C), 118.41, 81.20, 74.15, 71.48, 49.61, 31.59, 28.00, 17.95 ppm; ^{13}C NMR (for the bis ether, 22.5 MHz) 138.00 (2 C), 128.27 (4 C), 127.55 (6 C), 118.02, 80.55 (2 C), 71.41 (2 C), 47.78, 28.20 (2 C), 18.15 ppm. Also isolated from the column was 15 mg of a mixture of the two isomers, bringing the total yield up to 68%.

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Registry No. **1a**, 25484-62-2; **1b**, 84124-38-9; **1c**, 84131-45-3; **1d**, 62894-14-8; **2a** (isomer 1), 84234-88-8; **2a** (isomer 2), 84234-89-9; **2b** (isomer 1), 84172-91-8; **2b** (isomer 2), 84172-92-9; **2c** (isomer 1), 84131-46-4; **2c** (isomer 2), 84172-93-0; **3a** (isomer 1), 84172-94-1; **3a** (isomer 2), 84172-95-2; **3b** (isomer 1), 84131-47-5; **3b** (isomer 2), 84172-96-3; **3c** (isomer 1), 84131-48-6; **3c** (isomer 2), 84172-97-4; **3d** (isomer 1), 84131-49-7; **3d** (isomer 2), 84172-98-5; **3d** ketone (isomer 1), 84131-50-0; **3d** ketone (isomer 2), 84172-99-6; **3e** (isomer 1), 84173-00-2; **3e** (isomer 2), 84173-01-3; **4** (isomer 1), 84173-02-4; **4** (isomer 2), 84173-03-5; **5**, 84124-51-6; **5** free acid, 84131-51-1; **6** (isomer 1), 84173-04-6; **6** (isomer 2), 84234-78-6; **6** free acid, 84234-80-0; **7** (isomer 1), 84131-53-3; **7** (isomer 2), 84173-06-8; **8** (isomer 1), 84173-07-9; **8** (isomer 2), 84173-08-0; **9** (isomer 1), 84173-09-1; **9** (isomer 2), 84173-10-4; **10**, 84124-49-2; **11**, 84131-54-4; **12**, 84173-11-5; **13**, 84124-52-7; **14a**, 84173-12-6; **14b**, 84173-13-7; **15a**, 84173-14-8; **15b**, 84173-15-9; **16a**, 84131-52-2; **16b**, 84276-40-4; **18a**, 84173-16-0; **18b**, 84172-71-4; **19a**, 84173-17-1; **19b**, 84173-18-2; **20a**, 84173-19-3; **20b**, 84173-20-6; **21**, 84131-55-5; **22**, 84131-56-6; **23**, 84131-57-7; **24**, 84131-58-8; **25**, 84131-59-9; **26**, 84131-60-2; **27**, 84131-61-3; **28**, 84131-62-4; **29**, 84131-63-5; **30**, 84131-64-6; **31**, 84131-65-7; **32**, 84131-66-8; **33**, 84131-67-9; (*S*)-octynol, 32556-71-1; (*R*)-octynol, 32556-70-0; (*S*)-octynol *tert*-butyl ether, 51051-11-7; (*R*)-octynol *tert*-butyl ether, 82311-64-6; *tert*-butyl 6-iodohexanoate, 67899-04-1; *tert*-butyl 9α-(methoxymethoxy)-7-oxa-15-oxoprost-13-ynoate, 84124-46-9; 3-*n*-butylcyclopentanone, 84131-68-0; 2-(benzyloxy)-5-butyl-1-cyclopentanol, 84131-69-1; 1,3-bis(benzyloxy)-2-butylcyclopentane, 84131-70-4; 3-(benzyloxy)-2-butyl-1-cyclopentanol, 84131-71-5; 2-(benzyloxy)-5-(1,3-dithian-2-yl)-1-cyclopentanol, 84143-07-7; 3-(benzyloxy)-2-(1,3-dithian-2-yl)-1-cyclopentanol, 84143-08-8; 3-(benzyloxy)-2-hydroxycyclopentaneacetonitrile, 84131-72-6; 3-(benzyloxy)-5-hydroxycyclopentaneacetonitrile, 84131-73-7; 2,5-bis(benzyloxy)cyclopentaneacetonitrile, 84131-74-8.

Photochemical Synthesis of Some Propellanes through [2 + 2] Cycloaddition of Indeno[2,1-*a*]indene with Several Olefins

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Some interesting propellanes were synthesized by the photochemical cycloaddition of indeno[2,1-*a*]indene, a *trans*-stilbene analogue, with several olefins. Irradiation of indeno[2,1-*a*]indene with electron-rich olefins yielded only two indeno[2,1-*a*]indene dimers without giving cross adducts. While irradiation of the compound in the presence of moderately electron-poor olefins gave propellanes through [2 + 2] cycloaddition reaction, an ene-reaction product was obtained as a major product in the photoreaction of the compound with dimethyl fumarate, an electron-deficient olefin. The fluorescence quenching and kinetic studies indicated the reaction to proceed through a singlet exciplex intermediate.

Photochemical [2 + 2] cycloaddition reactions of *trans*-stilbene with various olefins which are different in electron affinity have been reported and are known to occur via singlet exciplex intermediates.[1] However, relatively little is known about the photochemical cycloaddition reaction of the stilbene chromophore incorporated into a small ring system.

Both direct irradiation and triplet-sensitized excitation of diphenylvinylene carbonate in the presence of dienes results in the formation of mixtures of [2 + 2] cycloadducts[2] in contrast to the failure of excited singlet *cis*-stilbene and triplet *cis*- and *trans*-stilbene to react with olefins. The differences in photochemical reactivity between stilbene and diphenylvinylene carbonate are attributed to the fact that the incorporation of the stilbene chromophore into a small ring increases the lifetime of both the planar singlet and triplet excited state since twisting around the C=C bond is forbidden.

It was reported that indeno[2,1-*a*]indene, a *trans*-stilbene analogue, has similar spectral[3] and photochemical[4] properties with *trans*-stilbene other than the cis ⇌ trans photoisomerization. Kaupp and Stark synthesized several interesting propellanes by trapping electronically excited stilbene and diphenylacetylene with bicyclic alkenes.[5] We report here a synthesis of some interesting propellanes through the [2 + 2] (C_4) photocycloaddition of indeno[2,1-*a*]indene with several acyclic olefins.

Results and Discussion

Characterization of Products. Irradiation of 2,3-dimethyl-2-butene, 1,4-cyclohexadiene, or 1,2-dihydropyran solutions of indeno[2,1-*a*]indene (30 mg/10 mL of indeno[2,1-*a*]indene) gave only two isomeric C_4 cyclodimers of indeno[2,1-*a*]indene without yielding cross-addition products (Scheme I). Reaction mixtures were analyzed by TLC and ^{1}H NMR spectrometry, but there was no product other than two dimers and starting materials in

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