General Procedure for the Ozonolysis–Reduction of 8, 9, 11, 13, and 16. The procedure employed was exactly as previously described.[13] In all cases the alcohols isolated were identical with the known compounds by TLC, ^{1}H NMR, and ^{13}C NMR data, which are included here for those compounds where they are not in the literature.[13]

6a: ^{13}C NMR ($CDCl_3$) δ 24.42, 24.97, 25.99, 26.07 ($4CH_3$), 62.16 (C_6), 68.38, 70.71, 70.85, 71.56 (C_2–C_5), 96.36 (C_1), 108.70, 109.50 ($2C(CH_3)_2$).

12a: ^{13}C NMR ($CDCl_3$) δ 25.24, 26.67, 26.96, 27.01 ($4CH_3$), 62.87 (C_1), 68.01 (C_5), 77.00, 78.86, 80.95 (C_2–C_4), 109.50, 109.91 ($2C(CH_3)_2$).

15b: ^{13}C NMR ($CDCl_3$) δ 55.34, 58.35, 58.98, 61.26 ($4CH_3$), 62.28 (C_6), 70.68, 77.24, 78.11, 80.64 (C_2–C_5), 98.16 (C_1).

Acknowledgment. We wish to thank Professor D. Horton for helpful suggestions. During a portion of the time when this research was conducted S.-R.W. was a Procter and Gamble Fellow (1977–1978).

Registry No.—**6a,** 4064-06-6; **6c,** 4026-28-2; **6d,** 69204-28-0; **8a,** 69204-29-1; **8b,** 69204-30-4; **9a,** 69204-31-5; **9b,** 69204-32-6; **9c,** 69204-33-7; **9d,** 69204-34-8; **10b,** 33985-40-9; **11a,** 69204-35-9; **11b,** 69204-36-0; **12a,** 19139-74-3; **12b,** 13039-93-5; **13a,** 69204-37-1; **13b,** 69204-38-2; **14a,** 69204-39-3; **14b,** 69204-40-6; **14c,** 69204-41-7; **15b,** 22323-68-8; **15d,** 69204-42-8; **15e,** 69204-43-9; **15f,** 69204-44-0; **16a,** 69204-45-1; **16b,** 69204-46-2; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7; *p*-chlorobenzaldehyde, 104-88-1; *n*-pentanal, 110-62-3; 3-phenylpropanal, 104-53-0.

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Prostaglandins and Congeners. 20.[1,2] Synthesis of Prostaglandins via Conjugate Addition of Lithium *trans*-1-Alkenyltrialkylalanate Reagents. A Novel Reagent for Conjugate 1,4-Additions

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A novel method for effecting 1,4-conjugate additions to cycloalkenones using trialkyl-*trans*-1-alkenylalanates is described. The *trans*-1-alkenyl ligand is selectively transferred in preference to the alkyl ligands, and this transfer is accomplished with retention of double-bond configuration. No 1,2-addition is observed. The problems raised by the presence of an oxy function in the alkenyl ligand are discussed. By one or the other adaptations of this procedure, *dl*-11,15-dideoxyprostaglandin E_1, *dl*-15-deoxyprostaglandin E_1, *dl*-prostaglandin E_1, its epimer, their 11-deoxy congeners, and *all-rac*-15-deoxy-16-hydroxyprostaglandin E_2 were synthesized.

As the basis for a convenient and flexible approach to the synthesis of the prostaglandins and their congeners, we have envisioned the stereospecific introduction of the fully elaborated *trans*-1-alkenyl β-chain (C_{13}–C_{20}) into a cyclopentenone nucleus bearing the ω-carboxyalkyl α-chain (C_1–C_7) via the 1,4-addition of an organometallic reagent.[3,4] At the time this study was initiated, there was to our knowledge no reported example pertinent to this concept.[5] In these laboratories we have sought to develop general synthetic procedures to accomplish the conjugate addition step and have discovered that lithium alkenyltrialkylaluminum "ate complexes" are useful reagents for this key operation. We now wish to describe the development of this new methodology and its utility for the synthesis of (±)-prostaglandin E_1 and several prostaglandin congeners.[6]

The most direct conjugate addition approach to the prostaglandins requires the preparation of a *trans*-1-alkenyl organometallic reagent and the stereospecific transfer of the alkenyl ligand to the cyclopentenone nucleus in a manner trans to the ring hydroxyl function, as **1** + **2** → **3.** Hydroalumination of terminal acetylenes with diisobutylaluminum hydride (DAH) readily furnishes *trans*-1-alkenylalanes.[7] Treatment of these alanes with an alkyllithium affords the corresponding lithium "ate complexes", which undergo selective, stereospecific 1,2-addition of the *trans*-alkenyl ligand to carbon dioxide, formaldehyde, and acetaldehyde.[8] We have

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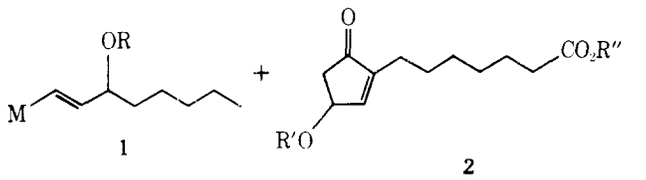

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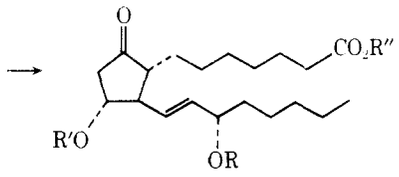

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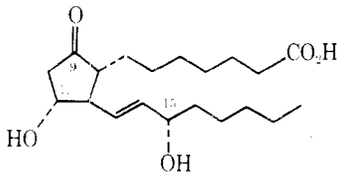

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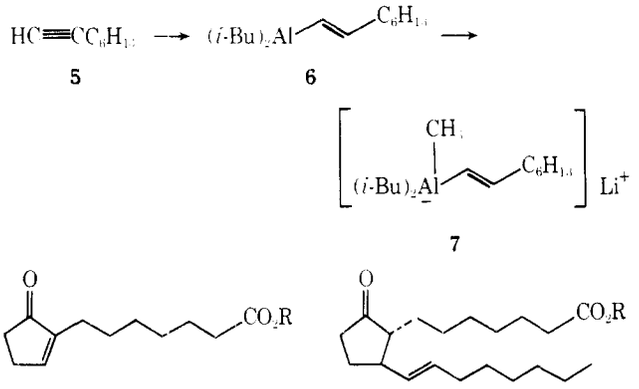
found that these reagents also allow a selective, stereospecific transfer of the alkenyl ligand to cyclopentenones in a 1,4-manner under conditions compatible with the functionalities and stereochemistry found in prostaglandin E_1 (**4**).

In a model experiment, lithium diisobutylmethyl-*trans*-1-octenylalanate (**7**)[9] was treated with cyclopentenone (**8**)[10] at ambient temperatures for 16 h. Upon acidification, the ethyl ester **10** of 11,15-dideoxyprostaglandin E_1 was obtained in 76%



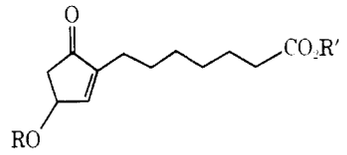
5 6 7

8, R = C_2H_5; **9**, R = CH_3 **10**, R = C_2H_5; **11**, R = H

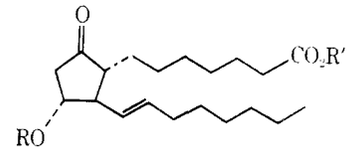
yield. Saponification of **10** provided (±)-11,15-dideoxyprostaglandin E_1 (**11**).[11] By all evidence the transfer of the *trans*-1-octenyl ligand from alanate **7** was effected with complete preservation of its steric integrity. No 1,2-addition to the ketone or ester carbonyl by any of the ligands was observed. Noteworthy is the high degree of selectivity in the transfer of the olefinic ligand relative to the three alkyl ligands.

Octenylalane **6** itself is incapable of conjugatively transferring its ligands to ketone **8** under the reaction conditions employed. Treatment of alane **6** with **8** in ether solvent at room temperature yielded products of apparent 1,2-addition to the ketone carbonyl.[12] Furthermore, complexing alkenylalanes such as **6** with triethylamine failed to yield a reagent capable of conjugate addition to ketone **8**.

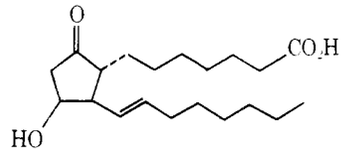
The second problem in this developing scheme was the accomodation of the C-11 hydroxyl function. Several details had to be established: (1) whether the potential C-11 oxy function would allow a conjugate addition; and if so, (2) whether the oxy function would sterically direct the incoming alkenyl ligand to the required trans disposition at C-12; and (3) the compatibility of the blocking groups with the alanate reagent and of the generated β-ketol system to deblocking conditions. Since the free carboxylic acid was also desired, this required a blocking group removable by mild acidic conditions, to which the β-ketol system would be stable. All of these requirements were satisfied by the tetrahydropyranyl group, which was employed to protect both the alcohol and carboxylic acid functions of cyclopentenone **12**.[13,14]



12, R = R′ = H
13, R = R′ = THP
14, R = $-COCH_3$; R′ = C_2H_5



15, R = R′ = H
16, R = $-COCH_3$; R′ = C_2H_5



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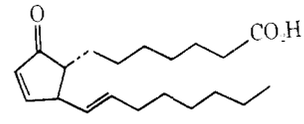

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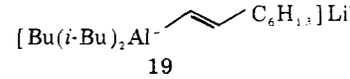

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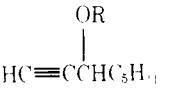
Treatment of bis(tetrahydropyranyloxy)cyclopentenone **13** with alanate reagent **7** for 20 h at ambient temperatures gave upon cold mineral acid workup a conjugate addition product in which both THP groups were intact. Deblocking with 4:2:1 acetic acid–tetrahydrofuran–water at 45 °C[15] for 3.5 h gave, after silica gel chromatography, (±)-15-deoxyprostaglandin E_1 (**15**) in 40% yield.[16] The assignment of the trans C-11/C-12 configuration follows from the ^1H NMR chemical shift of the C-11 carbinolic proton at δ 4.08 as opposed to a lower field signal typical of cis stereochemistry.[17] No 11-*epi*-15-deoxyprostaglandin E_1 (**17**) was found in the reaction product nor any 15-deoxyprostaglandin A_1 (**18**). Assignment of the trans stereochemistry at C-8/C-12 in **15** was established by recovery of **15** in high yield and without change in its ^1H NMR spectrum and TLC behavior after treatment with alcoholic potassium acetate under conditions known to equilibrate the C-8 epimer of prostaglandin E_1 (**4**).[18] Reaction of alanate **19**, prepared from octenylalane **6** and butyllithium, with acetoxycyclopentenone **14**[19] produced (±)-11-*O*-acetyl-15-deoxyprostaglandin E_1 ethyl ester (**16**) in 53% yield as the sole isolable product. The ^1H NMR spectrum of **16** exhibited a single acetate peak at δ 1.98, the C-11 proton as a quartet at δ 4.93 with J = 8 Hz, indicating a coupling to the two C-10 protons and the C-12 proton of equal magnitude, and the C-10 protons as a pair of doublets of doublets at δ 1.98 and

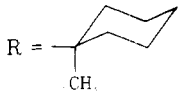
2.75 with J_{gem} = 18 Hz and $J_{10,11}$ = 8 Hz. No evidence for the C-8 epimer of **16** was found.

At this point completion of this prostaglandin E_1 synthesis required only the incorporation of the C-15 allylic hydroxyl function into the scheme. The preparation of an appropriate lithium *trans*-1-alkenylalanate reagent via hydroalumination of a blocked 1-octyn-3-ol for the fulfillment of this step was found to be critically dependent upon the choice of the hydroxy-protecting group, but even in the best of circumstances this could not be accomplished in satisfactory yield. Ultimately, however, a useful preparation of the essential alanate reagent was achieved by an indirect route (see below).

When 1-octyn-3-ol (**20**) was blocked as the *tert*-butyl ether **21**, hydroalumination of the acetylenic function occurred, but not in the expected manner. Reduction of **21** resulted in a net

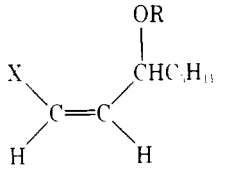


20, R = H
21, R = $C(CH_3)_3$

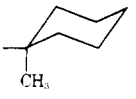


22, R =

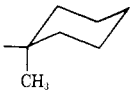
23, R = CH_3
24, R = $Si(CH_3)_2(t\text{-}Bu)$
25, R = $C(C_6H_5)_3$



26, X = $Al(i\text{-}Bu)_2$; R = $C(CH_3)_3$
27, X = D; R = $C(CH_3)_3$
28, X = Br; R = $C(CH_3)_3$

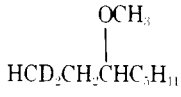


29, X = $Al(i\text{-}Bu)_2$; R =



30, X = D; R =

31, X = $Al(i\text{-}Bu)_2$; R = CH_3
32, X = D; R = CH_3



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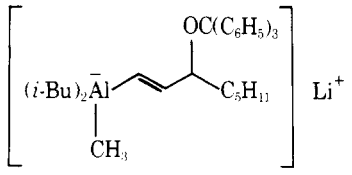
trans addition of DAH to the acetylenic bond to yield the *cis*-octenylalane **26**. The cis configuration for **26** was deduced from its ^1H NMR spectrum, which exhibits the vinylic proton signals as a doublet at δ 6.30 and a doublet of doublets at δ 6.64, with a vinylic coupling of 14.5 Hz.[20] Deuterolysis of **26** gave the *cis*-1-deuteriooctene **27**, ν 806 cm^{-1},[21] and bromination[22] produced the *cis*-vinyl bromide **28**. Similarly, hydroalumination of the methylcyclohexyl ether **22** also gave the *cis*-vinylalane **29** as shown by deuterolysis to produce **30**. The methyl ether **23** was also reduced by DAH to yield the *cis*-vinylalane **31** since deuterolysis gave *cis*-octene **32**. In this instance, however, the reaction was complicated (1) by further DAH reduction of **31** to yield, upon deuterolysis, 1,1-dideuterio-3-methoxyoctane **33**, (2) by partial metalation of **23** to yield 1-deuterio-3-methoxyoctyne, (3) by condensation reactions of the organoaluminum species to produce unidentified higher molecular weight products, and (4) possibly by propargylic ether cleavage reactions. The *tert*-butyldimethylsilyl ether **24** was incompatible with DAH, as no reduction of the acetylenic bond occurred.[23,24] Finally, treatment of cyclopentenone **8** with the "ate complex" derived from *cis*-alane **26** and methyllithium failed to yield a conjugate addition product.

The problem was resolved, although not in satisfactory yield, by use of the more sterically demanding triphenylmethyl group, which allowed the desired cis addition of DAH to the acetylenic bond. Hydroalumination of 3-(trityloxy)-1-octyne (**25**) followed by addition of methyllithium gave the alanate reagent **34**, which upon reaction with cyclopentenone **13**, subsequent protonolysis, and deblocking afforded (±)-



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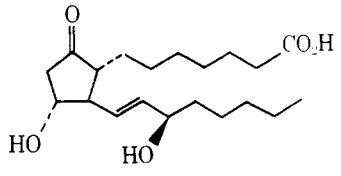
prostaglandin E_1 (**4**) and (±)-15-*epi*-prostaglandin E_1 (**35**) in 12% total yield. The trityl and THP groups were cleaved employing a 4:2:1 acetic acid–tetrahydrofuran–water solution at 45 °C. The C-15 epimers were isolated in nearly equal amounts. Similarly, reaction of alanate reagent **34** with cyclopentenone **8** furnished, after detritylation, an epimeric mixture of (±)-11-deoxyprostaglandin E_1 ethyl esters (**36**) in 20% yield.



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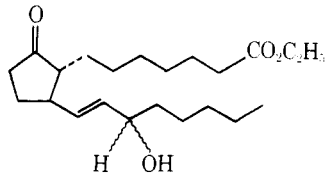

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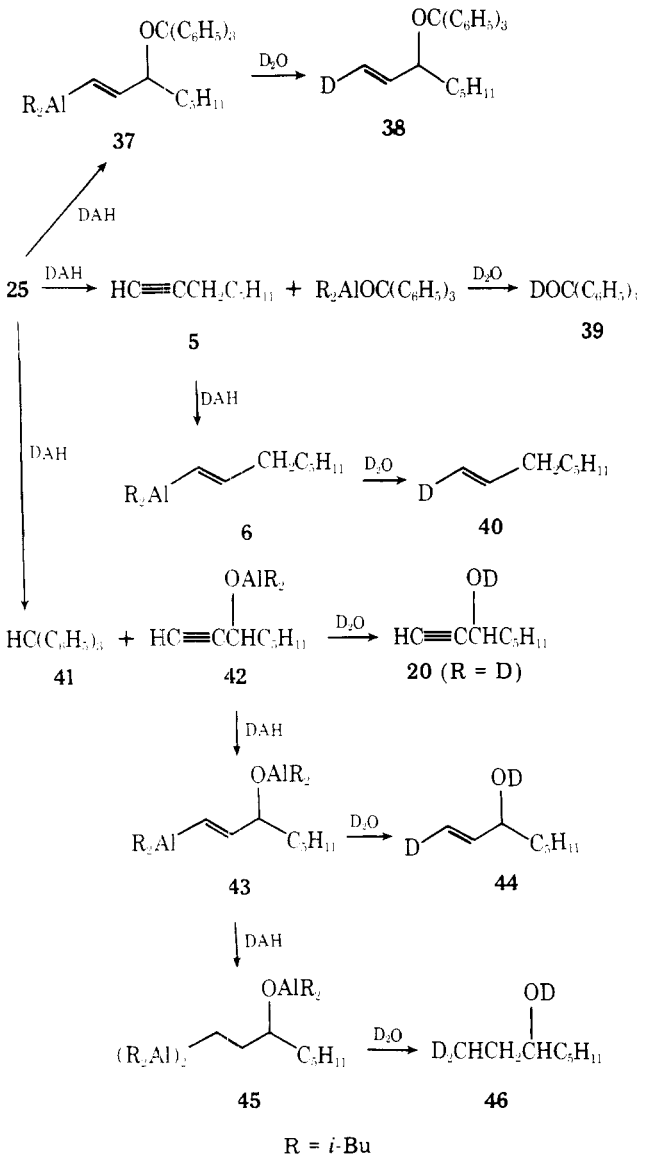
The poor conjugate addition yields obtained with the [(triphenylmethoxy)octenyl]alanate reagent **34** prompted an investigation into its preparation. Treatment of equimolar quantities of 3-(trityloxy)-1-octyne (**25**) and DAH in hexane in the standard fashion followed by the addition of 1 equiv of methyllithium and then deuterolysis gave products which indicated that cleavage at both of the ether bonds competed with acetylenic reduction. Analysis of the product mixture showed the presence of starting 3-(trityloxy)-1-octyne (**25**), *trans*-1-deuterio-3-(trityloxy)-1-octene (**38**), triphenylcarbinol-*O*-*d* (**39**), deuterated octene (**40**), 1-octyn-3-ol-*O*-*d* (**20**, R = D), *trans*-1-deuterio-1-octen-3-ol-*O*-*d* (**44**), and 1,1-dideuteriooctan-3-ol-*O*-*d* (**46**). These products are interpreted as arising from the following: (1) simple cis addition of DAH to the acetylenic bond to yield upon deuterolysis *trans*-1-deuterio-3-(trityloxy)-1-octene (**38**); (2) propargylic ether reductive cleavage to yield triphenylcarbinol-*O*-*d* (**39**) (13%) and 1-octyne (**5**), which suffers further reduction; and (3) triphenylmethyl ether reductive cleavage to yield triphenylmethane (**41**) (25%) and the 3-(diisobutylaluminooxy)-1-octyne (**42**), which undergoes further hydroalumination. This last reaction was more clearly illustrated by treatment of 1-octyn-3-ol (**20**) with 2 equiv of DAH, which yielded upon deuterolysis a mixture of **20** (R = D) (42%), **44** (38% cis-wise monoaddition), and **46** (7%, bisaddition).[25,26]

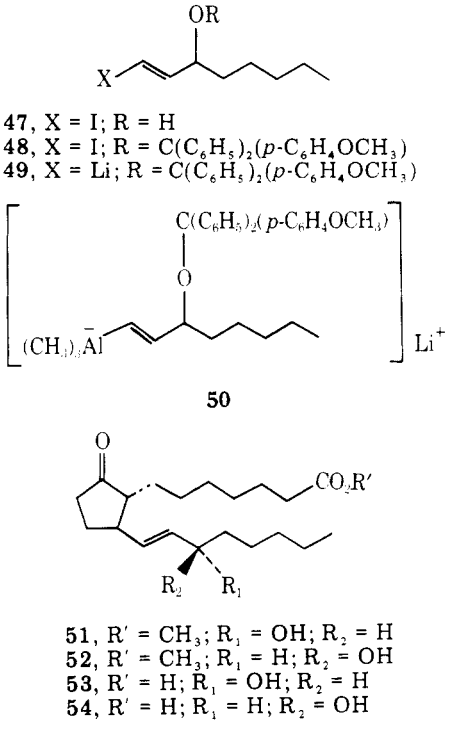
The actual yield of lithium [3-(trityloxy)-*trans*-1-octenyl]-alanate **34**, when prepared in the above manner, is estimated not to exceed 40% of the total product mixture. Attempts to diminish the ether cleavage reactions by variation of temperature, reactant concentration, stoichiometry, and solvent (tetrahydrofuran) were fruitless. Substitution of DAH with dimethylaluminum hydride led almost completely to triphenylmethane (**41**) and 1-octyn-3-ol (**20**), products of triphenylmethyl ether reductive cleavage. It is apparent that the



addition of methyllithium to the DAH–3-(trityloxy)-1-octyne product affords a complex mixture of organometallic species. Consequently, the low yields of conjugate addition products obtained with this reagent are not at all surprising. Since 3-(diisobutylaluminooxy)-1-octyne (**42**) was the only other blocked 1-octyn-3-ol which underwent cis addition of DAH, the "ate complex" formed by reaction of **43** with 1 equiv of methyllithium was treated with cyclopentenone **8**. No discreet identifiable products could be isolated, although the enone system was completely consumed.

These difficulties were circumvented when the lithium alanate reagents were prepared by complexing a trialkylaluminum with a *trans*-1-alkenyllithium. (3-Oxy-*trans*-1-alkenyl)lithium reagents may be obtained almost quantitatively by alkyllithium exchange with the corresponding *trans*-1-alkenyl iodides. The alkenyl iodide **47** required for these studies was prepared by acylation of acetylene with hexanoyl chloride to give *trans*-1-chloro-1-octen-3-one, which was converted to *trans*-1-iodo-1-octen-3-one by treatment with sodium iodide in acetone. Sodium borohydride reduction then produced *trans*-1-iodo-1-octen-3-ol (**47**) from which the monomethoxytrityl ether **48** was prepared.[27]

The monomethoxytrityl ether **48** was metallated with 1 equiv of *n*-butyllithium in toluene at −40 °C to give the alkenyllithium **49**,[28] treatment of which at −78 °C with 1 equiv of trimethylaluminum (heptane solution) afforded the lithium alanate reagent **50**. Submission of alanate **50** to cyclopentenone **9** at ambient temperature for 16 h gave, after protonolysis and deblocking, a 73% yield of (±)-11-deoxyprostaglandin E_1 methyl ester (**51**) and its 15-epimer **52** in a ratio of 45:55.[29,30] Saponification of these esters afforded the corresponding acids **53** and **54**. In subsequent preparations the yield of **51** + **52** was as low as 53%. For a series of six 11-deoxyprostaglandins wherein the α-chain (C_1–C_7) was varied and which were prepared using **50** or the corresponding trityl ether alanate reagent, we have obtained yields in the range of 25 to 51%, and with one exception a similar epimer ratio.[2c]



47, X = I; R = H
48, X = I; R = $C(C_6H_5)_2(p\text{-}C_6H_4OCH_3)$
49, X = Li; R = $C(C_6H_5)_2(p\text{-}C_6H_4OCH_3)$

50

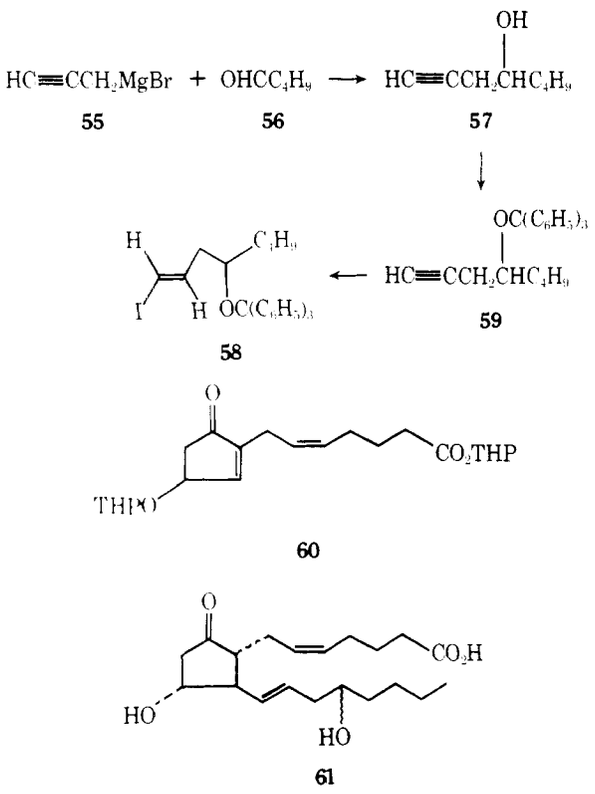
51, R′ = CH_3; R_1 = OH; R_2 = H
52, R′ = CH_3; R_1 = H; R_2 = OH
53, R′ = H; R_1 = OH; R_2 = H
54, R′ = H; R_1 = H; R_2 = OH

To exemplify the application of this process to the synthesis of a fully elaborated prostaglandin, we have chosen to prepare 15-deoxy-16-hydroxyprostaglandin E_2 (**61**), a compound the ready preparation of which by the methods developed by the Harvard group appeared to be problematical. The requisite blocked octenyl iodide **58** was prepared by the sequence shown in Scheme I, the conversion of the acetylene function in **59** to a vinyl iodide being accomplished by the disiamylborane procedure.[3d] Treatment of the lithium trimethylalanate reagent prepared from **58** with the bis(tetrahydropyranyl) derivative **60** of the PGE_2 precursor cyclopentenone[31] gave, after protonolysis and deblocking, a 35% yield of *all-rac*-15-deoxy-16-hydroxy-PGE_2 (**61**). Although **61** could not be separated into its component racemates by the usual chromatographic procedures, the presence of both racemates in about equal amounts was indicated by analysis of the ^{13}C NMR spectrum.

The alanate conjugate addition procedure is a process of some significance since there are only two other organometallic reagents generally capable of effecting this important synthetic step.[32] We should note that in our laboratory the alanate process consistently has provided excellent yields for conjugate additions via hydroalumination of a terminal acetylene which does *not* bear an oxy function. On the other hand, we have found this reaction to be quite capricious, affording a wide range of yields when carried out with oxy-substituted alanates even when prepared via *trans*-1-alkenyllithium intermediates.

In an attempt to isolate at least some of the critical factors of this reaction, we have made some preliminary studies concerning the effects of reaction solvent and of the alkyl ligands upon the course of reaction with these alanate reagents.

Scheme I



These studies have already been reported,[2c] and we do not contemplate any further investigations into the nature of the alanate conjugate addition reaction.

Experimental Section

Diisobutylaluminum hydride, dimethylaluminum hydride, trimethylaluminum, and triisobutylaluminum were obtained in hydrocarbon solutions from Texas Alkyls, Inc. Alternatively, trimethylaluminum was obtained from Ventron and diluted with the indicated solvent. Methyllithium in ether and butyllithium in hexane were obtained either from Foote Mineral Co. or from Alfa Products. All reactions described herein were conducted under an inert atmosphere of argon or nitrogen using the apparatus of Johnson and Schneider.[33] The standard workup employed, i.e., "worked up with", involved extracting the aqueous phase with the indicated solvent, washing the organic phases with water and saturated brine, drying with anhydrous sodium sulfate, and evaporating the solvent at reduced pressure with a Büchi evaporator. All boiling points are uncorrected. Melting points were determined in open capillary tubes with a Mel-Temp apparatus and are uncorrected. VPC data were determined on an F&M Model 720 gas chromatograph using a 6-ft 3% diethylene glycol succinate column isothermally with helium as carrier gas. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. ^{1}H NMR spectra were recorded on either a Varian A-60 or a Varian HA100D instrument, and the chemical shifts are in parts per million downfield relative to internal tetramethylsilane, δ 0.00 ppm. Carbon-13 magnetic resonance spectra were taken in 10% MeOH-d_4–$CDCl_3$ solution on a Varian XL-100 FT NMR spectrometer, 25.2 MHz. Mass spectra were determined on an AEI MS-9 at 70 eV.

Preparation of *trans*-1-Octenyldiisobutylalane (6) and Lithium *trans*-1-Octenyldiisobutylmethylalanate (7). The procedure of Zweifel and Steele was employed as the standard method.[8] To a room temperature solution of 1-octyne (**5**) dissolved in 1–2 volumes of a hydrocarbon (hexane, benzene, toluene) was added 1 equiv of a hydrocarbon solution of diisobutylaluminum hydride at a rate to maintain the exotherm below 40 °C. After the addition was complete and the exotherm had subsided, the solution was heated to 50 °C for 2 h and then cooled to yield a colorless, clear solution of alane **6**. ^{1}H NMR of a sample of **6** from which the solvent had been removed in vacuo exhibited (CCl_4) δ 0.00 and 0.15 (2d, 4 H, J = 7 Hz, $AlCH_2CH$–), 0.83 and 0.88 (2d, 12 H, J = 7 Hz, $AlCH_2CH(CH_3)_2$), 1.67 (m, 2 H, $AlCH_2CH(CH_3)_2$), 2.27 (m, 2 H, $C{=}CCH_2CH_2$–), 5.72 (d, 1 H, $J_{1,2}$ = 20 Hz, $AlCH{=}CHCH_2$–), and 7.35 (d of t, 1 H, $J_{1,2}$ = 20 Hz, $J_{2,3}$ = 6 Hz, $AlCH{=}CHCH_2$–).

The lithium alanate reagent (**7**) was formed by addition of 1 equiv of methyllithium in ether to the hydrocarbon solution of **6** cooled to 0 °C to yield either a colorless solution or a milky suspension depending upon the absence or presence of lithium halide in the methyllithium, respectively. The lithium alanate reagent (**7**) was stirred at 0 °C for 20 min and then used in subsequent reactions.

(±)-11,15-Dideoxyprostaglandin E_1 Ethyl Ester (10). To an ice-cooled solution of lithium diisobutylmethyl-*trans*-1-octenylalanate (**7**), prepared from 27.6 g (0.250 mol) of 1-octyne (**5**), 30 mL of heptane, 203 mL of 25% (0.250 mol) diisobutylaluminum hydride in hexane, and 152 mL of 5.10% (0.250 mol) methyllithium in ether, was added a solution of 54.33 g (0.228 mol) of 2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (**8**)[9] in 30 mL of ether. The resulting mixture was stirred at ambient temperature for 16 h, poured cautiously onto 700 g of ice and 100 mL of concentrated hydrochloric acid, stirred for 1 h, and worked up with ether to yield an oil. Fractional distillation gave 60.9 g (76%) of **10** as a colorless oil: bp 170–176 °C (0.20 torr); IR 1745 (C=O), 967 (*trans*-CH=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3 H, C-20), 1.26 (t, J = 7 Hz, OCH_2CH_3), 2.27 (t, J = 6 Hz, C-2), 4.11 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.39 (dd, 1 H, $J_{13,14}$ = 17.5 Hz, $J_{12,13}$ = 5.5 Hz, C-13), 5.56 (dt, 1 H, $J_{13,14}$ = 17.5 Hz, $J_{14,15}$ = 6.5 Hz, C-14). Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.33; H, 10.89.

11,15-Dideoxyprostaglandin E_1 (11). A mixture of 13.14 g (0.0375 mol) of ester **10**, 10.0 g (0.179 mol) of potassium hydroxide, and 200 mL of 1:1 aqueous methanol was stirred for 16 h at ambient temperature. The solvent was evaporated in vacuo to half its volume, and the residue was partitioned between water and ether. The aqueous phase was acidified with hydrochloric acid and worked up with ether to yield an oil. Evaporative distillation at 165 °C (0.035 torr) produced 11.24 g (93.2%) of **11** as a colorless oil: IR (film) 1745 (C=O), 1715 (C=O, acid), 968 (*trans*-CH=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 3 H, C-20), 2.05 (m, C-15), 2.22 (m, C-12), 2.33 (t, 2 H, $J_{2,3}$ = 7 Hz, C-2), 5.35 (dd, 1 H, $J_{13,14}$ = 15 Hz, $J_{12,13}$ = 7 Hz, C-13), 5.50 (dt, 1 H, $J_{13,14}$ = 15 Hz, $J_{14,15}$ = 5.5 Hz, C-14). Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.62; H, 10.53.

4-Bromo-2-(6-carbethoxyhexyl)cyclopent-2-en-1-one. A stirred mixture consisting of 40.8 g (0.171 mol) of 2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (**8**),[9] 33.5 g (0.188 mol) of *N*-bromosuccinimide, and 600 mL of carbon tetrachloride was irradiated with a 300-W photolamp while refluxing for 35 min. The mixture was cooled to 5 °C and filtered. The filtrate was washed with cold water, dried, and taken to dryness to give an oil (51.6 g). This crude product was used as such without further purification.

4-Acetoxy-2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (14). A mixture consisting of the above crude 4-bromo-2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (51.6 g), 27 g (0.162 mol) of silver acetate, and 200 mL of glacial acetic acid was stirred at reflux for 4.5 h. The mixture was cooled, and solids were removed by filtration. The filtrate was concentrated and extracted with hot hexane. The extract was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried, and concentrated to a crude oil, which was distilled at reduced pressure to give 21.2 g (52% overall) of **14** as an oil: bp 152–163 °C (0.01 mm); UV (MeOH) 223 nm (ϵ 10 700); IR (film) 1745 (ester carbonyl groups), 1725 (ketone carbonyl groups), 1235 (acetoxy group) cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.10; H, 8.26.

4-Hydroxy-2-(6-carboxyhexyl)cyclopent-2-en-1-one (12). A stirred mixture of 35.9 g (0.171 mol) of 2-(6-carboxyhexyl)cyclopent-2-en-1-one, 35.0 g (0.197 mol) of *N*-bromosuccinimide, and 600 mL of carbon tetrachloride was refluxed for 30 min. The resulting mixture was cooled and filtered. The filtrate was evaporated at room temperature to give 53.0 g of light orange oil.

A 10.6-g portion of this crude product was dissolved in 100 mL of acetone and 65 mL of water. To the stirred solution was added 8.80 g (45.2 mmol) of silver fluoroborate during 2 min. The reaction was maintained at a temperature of 25–30 °C for 90 min. The mixture was filtered, and the filtrate was saturated with sodium chloride and extracted with ether. The extract was washed with water and brine, dried over magnesium sulfate, and concentrated. The crude product was purified by partition chromatography on Celite using the solvent system heptane–dichloromethane–methanol–water (45:55:15:6) to give 3.34 g (43% overall) of the known[14] 4-hydroxycyclopentenone acid **12**.

2-[6-(Carbotetrahydropyranyloxy)hexyl]-4-(tetrahydropyranyloxy)cyclopent-2-en-1-one (13). To a stirred solution of 17.1 g (0.0756 mol) of 2-(6-carboxyhexyl)-4-hydroxycyclopent-2-en-1-one (**12**) and 31.8 g (0.378 mol) of dihydropyran in 300 mL of methylene chloride at 20 °C was added 0.144 g (0.76 mmol) of *p*-toluenesulfonic acid monohydrate, and the mixture was maintained at 20 °C with

cooling for 1.5 h. The solution then was diluted with 400 mL of ether and washed with a solution made up of 120 mL of saturated sodium bicarbonate, 120 mL of saturated brine, and 240 mL of water. The aqueous phase was worked up with ether to yield 30.3 g (103%) of **13** as a faintly yellow, mobile oil. The product was used without further purification: IR (film) 1730 (C=O, ester), 1705 (C=O, ketone), 1117, 1033, 1023, 984, 869 cm^{-1}; UV (MeOH) 223 nm (ϵ 7500).[4c]

(±)-15-Deoxyprostaglandin E_1 (15). To a solution of the alanate reagent **7** prepared from 7.16 g (0.065 mol) of 1-octyne (**5**), 12 mL of benzene, 52 mL of 1.2 M (0.063 mol) diisobutylaluminum hydride in hexane, and 28.5 mL of 2.1 M (0.060 mol) methyllithium in ether was added at 0 °C a solution of 20.1 g (0.0509 mol) of 2-[6-(carbotetrahydropyranyloxy)hexyl]-4-(tetrahydropyranyloxy)cyclopent-2-en-1-one (**13**) in 30 mL of ether during 10 min. The mixture was then stirred at ambient temperature for 20 h and then poured cautiously onto 90 mL of 4 N hydrochloric acid and 400 g of ice. The mixture was stirred for 0.45 h, and the phases were separated. The aqueous phase was washed with ether, and the combined organic phases were washed with water and saturated brine, dried ($MgSO_4$), and evaporated in vacuo (<35 °C) to an oil. The latter was stirred at 45 °C for 3.5 h with 1000 mL of 4:2:1 acetic acid–tetrahydrofuran–water and then evaporated in vacuo (<35 °C) with the aid of 250 mL of xylene. The oily residue was chromatographed upon 475 g of SilicAR-CC4 packed in benzene, and the column was eluted with a benzene–ethyl acetate gradient. Elution with 3:2 to 2:3 benzene–ethyl acetate (v/v) produced 6.895 g (40.0%) of (±) 15-deoxyprostaglandin E_1 (**15**) as an oil: IR (film) 3410 (OH), 1740 (CO, ketone), 1717 (C=O, acid), 1075, 967 (*trans*-CH=CH) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.89 (m, 3 H, C-20), 2.61 (dd, 1 H, J_{gem} = 18 Hz, $J_{9,10}$ = 8 Hz, C-10), 4.08 (q, 1 H, $J_{9,10}$ = $J_{10,11}$ = 8 Hz, C-11), 5.43 (dd, 1 H, $J_{13,14}$ = 15 Hz, $J_{12,13}$ = 6 Hz, C-13), 5.65 (dt, 1 H, $J_{13,14}$ = 15 Hz, $J_{14,15}$ = 6 Hz, C-14). Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.79; H, 10.07.

(±)-11-*O*-Acetyl-15-deoxyprostaglandin E_1 Ethyl Ester (16). To a solution of the alanate reagent **19** prepared from 2.20 g (0.020 mol) of 1-octyne (**5**), 4 mL of benzene, 15.0 mL of 1.2 M (0.018 mol) diisobutylaluminum hydride in hexane, and 10.0 mL of 1.6 M (0.016 mol) *n*-butyllithium in hexane was added at 0 °C a solution of 4.45 g (0.015 mol) of 4-acetoxy-2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (**14**)[19] in 15 mL of ether. The resulting mixture was stirred at ambient temperature for 24 h, poured cautiously onto 50 mL of 2 N hydrochloric acid and 50 g of ice, and then stirred for 0.5 h. The mixture was extracted with ether, and the organic phase was washed with cold water and saturated brine, dried ($MgSO_4$), and evaporated in vacuo (<35 °C) to yield a mobile oil. The latter was chromatographed upon 250 g of silica gel packed in benzene. Elution with a benzene–ether gradient, 15:1 to 8:1 (v/v), produced 3.27 g (53%) of **16** as a colorless oil: IR (film) 1745 (C=O), 1240 (acetate), 1053, 967, (*trans*-CH=CH) cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (m, 3 H, C-20), 1.25 (t, 3 H, OCH_3CH_3), 2.00 (s, 3 H, $-O_2CCH_3$), 2.82 (dd, 1 H, J_{gem} = 18 Hz, $J_{10,11}$ = 8 Hz, C-10), 4.10 (q, 2 H, CCH_2CH_3), 5.00 (q, 1 H, $J_{10,11}$ = $J_{11,12}$ = 8 Hz, C-11), 5.45 (m, 2 H, C-13, C-14). Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.85; H, 9.70.

3-*tert*-Butoxy-1-octyne (21). Through a solution of 20.0 g (0.158 mol) of 1-octyn-3-ol (**20**) in 300 mL of methylene chloride was passed a stream of isobutylene for 0.5 h. Concentrated sulfuric acid (2 mL) was cautiously added, and the reaction mixture was sealed and allowed to stand at ambient temperature for 6 days. The mixture was then poured into 300 mL of 5% sodium carbonate solution, and the organic phase was worked up to yield an oil. Distillation gave 22.0 g (76.3%) of **21** as a colorless oil: bp 70–71 °C (10 torr); IR (film) 3289 (HC≡CH), 1393 (CH_3), 1368 (CH_3), 1193, 1060 (C–O–C), 882 cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (m, 3 H, CH_2CH_3), 1.24 (s, 9 H, $OC(CH_3)_3$), 2.33 (d, 1 H, J = 2 Hz, HC≡CH), 4.08 (dt, 1 H, J = 2 Hz, J = 7 Hz, CHO–). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.73; H, 12.18.

Hydroalumination of 3-*tert*-Butoxy-1-octyne (21). A solution of 18.23 g (0.100 mol) of 3-*tert*-butoxy-1-octyne (**21**) in 25 mL of benzene was hydroaluminated with 115 mL of a 15% toluene solution of diisobutylaluminum hydride and then evaporated in vacuo to yield alane **26** as a colorless oil. The ^1H NMR spectrum of an aliquot exhibited ($CDCl_3$) δ −0.03 and 0.07 (2d, 4 H, J = 6 Hz, $AlCH_2CH$–), 0.90 and 0.94 (2d, 12 H, J = 6 Hz, $AlCH_2CH(CH_3)_2$), 1.47 (s, 9 H, $OC(CH_3)_3$), 4.60 (m, 1 H, AlCH=CHCHO), 6.30 (d, 1 H, $J_{1,2}$ = 14.5 Hz, AlCH=CHCHO–), and 6.64 (dd, 1 H, $J_{1,2}$ = 14.5 Hz, $J_{2,3}$ = 2 Hz, AlCH=CHCHO–).

Deuteration. A 2-mL aliquot was withdrawn and treated with 2 mL of deuterium oxide for 1 h and then worked up with ether to yield 3-*tert*-butoxy-*cis*-1-deuterio-1-octene (**27**): IR (film) 1363, 1195, 972, 917, 806 (*cis*-CHD=CH–) cm^{-1};[21] ^1H NMR ($CDCl_3$) δ 1.18 (s, 9 H, $C(CH_3)_3$), 3.88 (m, 1 H, –CHO), 4.98 (d, 1 H, $J_{1,2}$ = 12 Hz, *cis*-DHC=CH–), 5.80 (m, 1 H, DHC=CH–).

Bromination. The vinylalane **26** was diluted with 40 mL of tetrahydrofuran and treated with a solution of 39.5 g (0.11 mol) of bromine according to the procedure of Zweifel and Witney[22] to produce a yellowish oil. Distillation yielded 12.94 g (50%) of *cis*-1-bromo-3-*tert*-butoxy-1-octene (**28**) as a colorless oil: bp 103–105 °C (10 torr); IR (film) 1616, 1364, 1190, 887, 712, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (m, 3 H, $-CH_3$), 1.18 (s, 9 H, $C(CH_3)_3$), 4.34 (q, 1 H, J = 6 Hz, –CHO–), 6.05 (d, 1 H, $J_{1,2}$ = 7 Hz, CHBr=CH–), 6.15 (dd, 1 H, $J_{1,2}$ = 7 Hz, $J_{2,3}$ = 6 Hz). Anal. Calcd for $C_{12}H_{23}OBr$: C, 54.76; H, 8.81; Br, 30.36. Found: C, 54.17; H, 8.65; Br, 31.22.

3-(1-Methylcyclohexoxy)-1-octyne (22). A mixture of 12.6 g (0.10 mol) of 1-octyn-3-ol (**20**), 28.8 g (0.30 mol) of 1-methyl-1-cyclohexene, and 1 drop of concentrated sulfuric acid was stoppered and allowed to stand at ambient temperature for 2 months. The mixture was poured into dilute sodium bicarbonate solution and worked up with ether to yield an oil. The latter was chromatographed upon 500 g of Florisil. Elution with hexane yielded 10.3 g of a colorless oil. Distillation gave 7.99 g (35.5%) of **22** as a colorless oil: bp 64–65 °C (0.07 torr); IR (film) 3305 (HC≡C), 1373 (CH_3), 1059 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (m, 3 H, CH_2CH_3), 1.23 (s, 3 H, $-CCH_3$), 2.34 (d, 1 H, J = 2 Hz, HC≡C), 4.14 (dt, 1 H, J = 2 Hz, –OCH–). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.75; H, 12.16.

Hydroalumination of 3-(1-Methylcyclohexoxy)-1-octyne (22). A solution of 2.10 g (0.010 mol) of 3-(1-methylcyclohexoxy)-1-octyne (**22**) in 5 mL of heptane was hydroaluminated with 6.74 mL (0.010 mol) of 1.49 M diisobutylaluminum hydride in heptane, cooled to −10 °C, and treated dropwise with 5 mL of 5 M CH_3CO_3D. The mixture was worked up with ether to yield 1.78 g of a colorless oil, which by IR and ^1H NMR contained 70% of deuterated olefin **30** and 30% starting acetylene **22**: IR **30**, (film) 1373 (CH_3), 1054 (C–O–C), 804 (*cis*-CHD=CH–) cm^{-1};[21] ^1H NMR (CCl_4) δ 0.92 (m, 3 H, CH_2CH_3), 1.10 (s, 3 H, CCH_3), 3.89 (m, 1 H, O–CH), 4.94 (dd, 1 H, $J_{1,2}$ = 10 Hz, $J_{H,D\ gem}$ = 1 Hz, CHD=CH), 5.76 (m, 1 H, $J_{1,2}$ = 10 Hz, $J_{2,3}$ = 8.5 Hz, $J_{H,D\ trans}$ = 1 Hz, CHD=CH–).

3-(Triphenylmethoxy)-1-octyne (25). A mixture of 39.6 g (0.314 mol) of 1-octyn-3-ol (**20**) and 113 g (0.350 mol) of triphenylmethyl bromide in 200 mL of anhydrous pyridine was stirred at 100 °C for 1.5 h, cooled, and filtered. The filtrate was partitioned between ice water and ether. The organic phase was washed with water, cold dilute hydrochloric acid, and saturated sodium bicarbonate and worked up to yield an oil. The latter was dissolved in hexane and passed through a column of 2.5 kg of Florisil, completing the elution with 9:1 (v/v) hexane–benzene to yield a colorless oil which crystallized from hexane: 68 g (59%); mp 67.5–69.5 °C; IR (KBr) 3290 (HC≡C), 1605, 1034 (C–O–C) cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (m, 3 H, CH_2CH_3), 2.02 (d, 1 H, J = 2 Hz, HC≡C–), 4.01 (m, 1 H, –CHO–). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66. Found: C, 88.09; H, 7.64.

Reaction of Lithium Diisobutylmethyl[3-(triphenylmethoxy)-*trans*-1-octenyl]alanate (34) with 2-[6-(Carbotetrahydropyranyloxy)hexyl]-4-(tetrahydropyranyloxy)cyclopent-2-en-1-one (13). To a solution of the alanate reagent **34**, prepared from 13.6 g (0.307 mol) of 3-(triphenylmethoxy)-1-octyne (**25**), 19 mL of benzene, 31.0 mL of 1.2 M (0.037 mol) diisobutylaluminum hydride in hexane, and 21.0 mL of 1.7 M methyllithium in ether, was added at 0 °C a solution of 10.97 g (0.0246 mol) of 2-[6-(carbotetrahydropyranyloxy)hexyl]-4-(tetrahydropyranyloxy)cyclopent-2-en-1-one (**13**) in 20 mL of ether. The cooling bath was removed, and the mixture was stirred at ambient temperature for 20 h. The mixture was then poured cautiously onto 120 mL of 2 M hydrochloric acid and 200 g of ice and stirred for 15 min. The mixture was extracted into ether, and the organic phase was washed with cold water and saturated brine, dried ($MgSO_4$), and evaporated in vacuo (<35 °C) to yield an oil. The latter was heated at 45 °C with 490 mL of 4:2:1 (v/v/v) acetic acid–tetrahydrofuran–water for 3.5 h, cooled, and poured into 600 mL of water. The mixture was extracted with 4 × 300 mL of ether and 3 × 250 mL of ethyl acetate, and the combined organic phase was washed with 2 × 300 mL of water and 3 × 300 mL of saturated brine, dried ($MgSO_4$), and evaporated in vacuo (<35 °C) with the aid of 400 mL of toluene to yield 22.3 g of an oil. The latter was chromatographed upon 550 g of SilicAR-CC4 packed in 4:1 hexane–ethyl acetate (v/v). Elution with 2:3 hexane–ethyl acetate produced 0.47 g (5.4%) of (±)-15-*epi*-prostaglandin E_1 (**35**) as an oil. Elution with 10:2:1 (v/v/v) ethyl acetate–hexane–acetone produced 0.80 g of an oily (±)-prostaglandin E_1 (**4**) fraction. The latter was further purified by partition chromatography on Celite using heptane–ethyl acetate–methanol–water (55:45:15:6) as the solvent system to yield 0.58 g (6.6%) of crystalline **4**, which upon crystallization from ethyl acetate–petroleum ether afforded colorless crystals, mp 101–106 °C. Both **35** and **4** were homogeneous by TLC, and **4** was identical with (−)-prostaglandin

E_1 in mobility with several TLC systems. **35:** IR (film) 3378 (OH), 1733 (C=O), 1715 (C=O, acid), 968 (*trans*-CH=CH) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.89 (m, 3 H, C-20), 2.28 (t, 2 H, C-2), 2.64 (dd, 1 H, J_{gem} = 18 Hz, $J_{10,11}$ = 7.5 Hz, C-10), 4.10 (m, 2 H, C-11, C-15), 5.68 (m, 2 H, C-13, C-14). **4:** IR (KBr) 3390 (OH), 1724 (C=O), 1704 (C=O, acid), 971 (*trans*-CH=CH) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.89 (m, 3 H, C-20), 2.28 (t, 2 H, C-2), 2.64 (dd, 1 H, J_{gem} = 18 Hz, $J_{10,11}$ = 7.5 Hz, C-10), 4.10 (m, 2 H, C-11, C-15), 5.64 (m, 2 H, C-13, C-14).

Reaction of Lithium Diisobutylmethyl[3-(triphenylmethoxy)-*trans*-1-octenyl]alanate (34) with 2-(6-Carbethoxyhexyl)cyclopent-2-en-1-one (8). To a solution of the alanate reagent **34,** prepared from 59.6 g (0.162 mol) of 3-(triphenylmethoxy)-1-octyne (**25**), 80 mL of benzene, 135 mL of 1.2 M (0.162 mol) diisobutylaluminum hydride in hexane, and 69 mL of 2.1 M (0.145 mol) methyllithium in ether, was added 32.4 g (0.136 mol) of 2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (**8**) in 41 mL of ether at 0 °C. The cooling bath was removed, and the mixture was stirred at ambient temperature for 18 h. The mixture was cautiously poured onto 70 mL of concentrated hydrochloric acid and 400 g of ice and stirred for 20 min. The mixture was worked up with ether to yield a viscous oil. The latter was heated at 45 °C for 3.5 h with 1.5 L of 4:2:1 (v/v/v) acetic acid–tetrahydrofuran–water, cooled, diluted with 3 L of saturated brine, and worked up with ether to a viscous oil. The oil was dissolved in petroleum ether and refrigerated, whereupon 25 g of triphenylcarbinol was collected. The filtrate was chromatographed upon silica gel using a benzene–ether gradient. Elution with 4:1 to 3:1 benzene–ether produced 10.1 g (20.3%) of a nearly colorless oil, identified as a mixture of the C-15 epimers of (±)-11-deoxyprostaglandin E_1 ethyl ester (**36**): IR (film) 3420 (OH), 1725 (C=O), 970 (*trans*-CH=CH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (m, 3 H, $CH_2CH_2CH_3$), 1.24 (t, 3 H, OCH_2CH_3), 2.27 (t, 2 H, $CH_2CO_2C_2H_5$), 4.10 (m, 1 H, -CHOH), 4.12 (q, 2 H, OCH_2CH_3), 5.60 (m, 2 H, -CH=CH-). Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.65; H, 10.14.

Diisobutylaluminum Hydride Reduction of 3-(Triphenylmethoxy)-1-octyne (25). A solution of 3.68 g (0.0100 mol) of 3-(triphenylmethoxy)-1-octyne (**25**) in 15 mL of benzene was hydroaluminated with 6.90 mL of 1.45 M diisobutylaluminum hydride in the standard fashion, cooled, and treated with 4.77 mL of 2.1 M methyllithium in ether. The resulting mixture was stirred at ambient temperature for 18 h and was then treated with 3 mL of 10 M acetic-*O*-*d* acid in D_2O. The mixture was stirred for 1 h, and the insolubles were filtered and extracted with boiling benzene. This extract was combined with the filtrate, the solution was washed with water and saturated brine and dried ($MgSO_4$), and the solvent was distilled at atmospheric pressure. The residue was distilled at 0.5 torr, bath 110 °C, and the distillate was collected in a dry ice–acetone cooled receiver to yield 0.54 g of a distillate A and 3.06 g of a pot residue B. VPC analysis (6-ft 3% DEGS) of distillate A indicated the presence of 3-octanol **46,** 1-octen-3-ol **44,** and 1-octyn-3-ol **20** (R = D) in a ratio of 12:71:18. Distillate A was passed through a short column of Florisil, eluting with benzene, and the solvent was fractionated at atmospheric pressure to yield a pot residue C which contained deuterated octene **40** (*m/e* 113). Pot residue B was chromatographed upon silica gel in benzene. Elution with benzene produced 2.64 g of a mobile fraction D, and elution with 4:1 benzene–ethyl acetate produced 0.334 g of a more polar fraction E. Fraction E was identical with triphenylcarbinol-*O*-*d* (**39**) by IR and TLC (12.8%). Fraction D consisted mainly of *trans*-1-deuterio-3-(trityloxy)-1-octene (**38**) and in lesser amounts triphenylmethane (**41**) and 3-(trityloxy)-1-octyne (**25**): IR (film) 3290 (HC≡C), 2265 (DC≡C), 978 and 896 (*trans*-HDC=CH) cm^{-1}; ^1H NMR (CCl_4) δ 1.97 (d, J = 2 Hz, HC≡C-), 3.90 (m, -OCH-), 4.78 (d, J = 18 Hz, *trans*-HDC=CH-), 5.46 (s, $HC(C_6H_5)_3$), 5.60 (dd, J = 18 Hz, J = 7 Hz, *trans*-HDC=CH-). Fraction D was refluxed with 35 mL of 4:2:1 acetic acid–tetrahydrofuran–water, cooled, and partitioned between water and benzene. The organic phase was worked up, the solvent was distilled off at atmospheric pressure, and the mixture was distilled at 0.5 torr, bath 110 °C, collecting the distillate in a dry ice cooled receiver to yield 0.481 g of distillate F and 2.14 g of pot residue G. Distillate F by VPC analysis consisted of *trans*-1-deuterio-1-octen-3-ol-*O*-*d* (**44**), 1-octyn-3-ol-*O*-*d* (**20,** R = D) and 3-octanol **46** in a ratio of 70:29.5:0.5. Pot residue G was chromatographed upon silica gel to yield with benzene 0.610 g fraction H and with 4:1 benzene–ethyl acetate 1.50 g of fraction I. Fraction H was identical by IR and TLC with triphenylmethane (**41**), 24.9%. Fraction I was identical by IR and TLC with triphenylcarbinol-*O*-*d* (**39**), 57.6%.

Hydroalumination of 1-Octyn-3-ol (20). To 2.677 g (0.0212 mol) of 1-octyn-3-ol (**20**) cooled to 0 °C was added dropwise 29.0 mL of 1.485 M (0.0431 mol) diisobutylaluminum hydride in heptane over 0.25 h. The mixture was then heated to 50 °C for 3 h, cooled, and treated with 20 mL of 10 M acetic-*O*-*d* acid in deuterium oxide. The mixture was stirred for 1 h and partitioned between water and ether. The organic phase was washed with saturated sodium bicarbonate and saturated brine, dried (Na_2SO_4), and distilled at atmospheric pressure to remove solvent. The residue was distilled to yield 2.37 g of a colorless oil, bp 80–84 °C (14 torr). VPC analysis indicated the presence of *trans*-1-deuterio-1-octen-3-ol-*O*-*d* (**44**), 1-octyn-3-ol-*O*-*d* (**20,** R = D), and 1,1-dideuterio-3-octanol-*O*-*d* (**46**) in a ratio of 44:48:8, respectively: IR (film) 3390 (HC≡C-), 2383 (*trans*-DHC=CH-), 2128 (-C≡C-), 1621 (DHC=CH-), 981 and 849 (*trans*-DHC=CH-) cm^{-1};[21] ^1H NMR (CCl_4) δ 0.90 (m, >3 H, CH_2CH_3 and CH_2CHD_2), 2.33 (d, J = 2 Hz, HC≡C-), 4.00 (m, C=CHCHO-), 4.24 (dt, J = 2 Hz, J = 7 Hz, C≡CCHO-), 5.12 (dd, J = 17.5 Hz, J = 1 Hz, *trans*-HDC=CH-), 5.80 (dd, J = 17.5 Hz, J = 7 Hz, *trans*-HDC=CH-).

In another experiment, the reactants were mixed at 0 °C and allowed to warm to room temperature. The conversion to products at ambient temperatures was followed by VPC analysis of hydrolyzed aliquots (Table I).

Table I

	temp (°C), time (h)	1-octyn-3-ol, %	1-octen-3-ol, %	3-octanol, %
1	0, 2	98	2	
2	25, 2	89	8	2
3	25, 4	80	16	3
4	25, 22	49	42	8
5	25, 46	31	57	12
6	25, 94	25	59	16

Reaction of Dimethylaluminum Hydride with 3-(Triphenylmethoxy)-1-octyne (25). To a solution of 3.68 g (0.010 mol) of 3-(triphenylmethoxy)-1-octyne (**25**) in 5 mL of benzene was added 6.53 mL of 1.535 M (0.010 mol) dimethylaluminum hydride in heptane, whereupon heat was evolved. When the temperature began to decline, the mixture was heated to 50 °C for 2 h, cooled, and poured onto ice and dilute hydrochloric acid. The mixture was worked up with ether to yield an oil. The latter was chromatographed upon 75 g of Florisil in hexane, and the column was eluted with a hexane–benzene gradient. Elution with hexane to 3:2 hexane–benzene (v/v) produced 2.49 g of solid fraction A. Elution with benzene produced 0.181 g (7.0% of propargyl ether cleavage) of triphenylcarbinol **39.** Elution with 1:1 benzene–ether (v/v) produced 0.790 g of alcohol fraction B, which by VPC contained 1-octyne-3-ol, 1-octen-3-ol, and 3-octanol in a ratio of 93:6:1. Fraction A was heated to 80 °C for 1 h with a solution of 32 mL of acetic acid, 8 mL of water, and 10 mL of tetrahydrofuran. The mixture was cooled, poured into 100 mL of water, and extracted into ether. The organic phase was washed with water, saturated sodium bicarbonate, and saturated brine, dried (Na_2SO_4), and evaporated. The resulting mixture was chromatographed upon 75 g of Florisil as above to yield 1.960 g of triphenylmethane (**41**) (trityl ether cleavage), 0.288 g of triphenylcarbinol **39,** and 0.080 g of alcohol fraction C, consisting of 1-octyn-3-ol and 1-octen-3-ol in a ratio of 85:15.

***trans*-1-Iodo-1-octen-3-ol (47).** *trans*-1-Chloro-1-octen-3-one was prepared in 94% yield by acylation of acetylene with hexanoyl chloride by the procedure of Price and Pappalardo:[34] bp 51–52 °C (0.10 torr); IR (film) 1680 (C=O), 1585 (C=C), 941 (*trans*-C=C) cm^{-1}. VPC analysis and the ^1H NMR spectrum indicate the presence of 5% of *cis*-1-chloro-1-octen-3-one: ^1H NMR ($CDCl_3$) δ 2.54 (t, 2 H, $-C(=O)CH_2-$), 6.55 (d, 1 H, $J_{1,2}$ = 13.5 Hz, *trans*-CHCl=CHC(=O)-), 7.29 (d, 1 H, *trans*-CHCl=CHC(=O)-), 6.42 and 6.59 (2d, $J_{1,2}$ = 8.5 Hz, *cis*-CHCl=CHC(=O)-).

The *trans*-1-chloro-1-octen-3-one above was refluxed with 1.5 equiv of sodium iodide in acetone for 24 h. The mixture was cooled and filtered, and the solvent was evaporated. The residue was partitioned between water and benzene, and the organic phase was decolorized with sodium bisulfite solution and worked up to yield a solid. Crystallization from hexane gave *trans*-1-iodo-1-octen-3-one as colorless crystals: mp 35–37 °C; IR (KBr) 1650 (C=O), 1570 (C=C), 961 (*trans*-C=C) cm^{-1}.

The *trans*-1-iodo-1-octen-3-one was dissolved in absolute ethanol and added to a slurry of sodium borohydride in ethanol cooled to 0 °C during a 2-h period. The mixture was then stirred for an additional 0.75 h, poured into water, and extracted with benzene. The organic phase was decolorized with dilute sodium bisulfite and worked up to yield **47** contaminated with traces of 1-iodo-1,3-octadiene and ketone impurities. The contaminants were removed by converting the ketonic material into its *p*-carboxyphenylhydrazone and passing the mixture through a column of Florisil in hexane. Elution with hexane removed

the diene impurity. Elution with benzene gave **47**: bp 74–76 °C (0.005 torr); IR (film) 3344 (OH), 1605 (C=C), 947 (*trans*-CHI=CH–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (m, 3 H, CH_3), 4.24 (m, 1 H, –CHO–), 6.30 (d, 1 H, $J_{1,2}$ = 14 Hz, CHI=CH–), 6.64 (dd, 1 H, $J_{1,2}$ = 14 Hz, $J_{2,3}$ = 5.5 Hz, CHI=CH–). Anal. Calcd for $C_8H_{15}OI$: C, 37.81; H, 5.95; I, 49.94. Found: C, 37.43; H, 5.87; I, 50.67.

1-Iodo-3-(*p*-anisyldiphenylmethoxy)-*trans*-1-octene (48). A mixture of 14.92 g (0.0588 mol) of 1-iodo-*trans*-1-octen-3-ol (**47**) and 18.2 g (0.0590 mol) of *p*-anisyldiphenylmethyl chloride in 165 mL of pyridine was stirred at 60 °C for 18 h.[35] The solvent was evaporated in vacuo, and the residue was partitioned between water and ether. The organic phase was worked up to yield an oil. The latter was chromatographed upon 600 g of Florisil, and the product was eluted with hexane and 9:1 v/v hexane–benzene as an oil: 23.0 g (74%); IR (film) 1610 (*trans*-CHI=CH), 1250 and 1178 (=$COCH_3$), 1036 (C–O–C), 943 (*trans*-CHI=CH–), 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (m, 3 H, CH_2CH_3), 3.10 (s, 3 H, OCH_3), 3.11 (m, 1 H, –OCH–), 5.54 (d, 1 H, $J_{1,2}$ = 15 Hz, CHI=CH–), 6.16 (dd, 1 H, $J_{1,2}$ = 15 Hz, $J_{2,3}$ = 7 Hz, CHI=CH–). Anal. Calcd for $C_{28}H_{31}IO_2$: C, 63.88; H, 5.94; I, 24.11. Found: C, 64.39; H, 6.13; I, 23.46.

Reaction of Lithium Trimethyl[3-(*p*-anisyldiphenylmethoxy)-*trans*-1-octenyl]alanate (50) with 2-(6-Carbomethoxyhexyl)-2-cyclopentenone (9). To a solution of 9.05 g (0.0172 mol) of 1-iodo-3-(*p*-anisyldiphenylmethoxy)-*trans*-1-octene (**48**) in 20 mL of toluene at −78 °C was added 7.4 mL (0.017 mol) of 2.34 M *n*-butyllithium (Ventron) in hexane over 5 min. The resulting solution was allowed to warm to −40 °C, maintained at −40 °C for 1 h, cooled to −78 °C, and then treated with 7.1 mL (0.017 mol) of a 2.4 M solution of trimethylaluminum in heptane. The solution was allowed to warm to −10 °C (0.5 h), cooled to −40 °C, and treated with a solution of 3.86 g (0.0172 mol) of 2-(6-carbomethoxyhexyl)-2-cyclopentenone (**9**)[9] in 15 mL of ether. The nearly colorless, two-phase mixture was stirred at room temperature for 18 h, whereupon a single, clear phase had formed. The reaction mixture was cautiously poured onto ice and 8 mL of hydrochloric acid, stirred for 0.5 h, and worked up with ether to yield a colorless oil: IR (film) 1736 (C=O), 1250, 1037, 973 (*trans*-C=C) cm^{-1}. The oil was heated to 80 °C for 0.5 h with 150 mL of 80% (v/v) aqueous acetic acid, cooled, and evaporated to dryness at 35 °C (1 torr) with 150 mL of xylene. The resulting oil was chromatographed upon 335 g of silica gel (Davison) employing a benzene–ethyl acetate gradient. Elution with 4:1 to 3:2 (v/v) benzene–ethyl acetate afforded 4.39 g (72.5%) of a mixture of 15-*epi*-11-deoxyprostaglandin E_1 methyl ester (**52**) and 11-deoxyprostaglandin E_1 methyl ester (**51**).

Resolution of **52** and **51** was achieved by dry column chromatography upon silica gel (Waters Associates) employing 4:1 (v/v) benzene–ethyl acetate as eluent to afford 1.87 g (30.9%) of **51** and 2.43 g (40.1%) of **52**. **51**: IR (film) 3497 (OH), 1742 (C=O), 971 (*trans*-CH=CH–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 3 H, C-20), 2.30 (t, C-2), 3.67 (s, 3 H, –OCH_3), 4.12 (m, 1 H, C-15), 5.61 (m, 2 H, C-13, C-14). Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 70.61; H, 10.53. **52**: IR (film) 3484 (OH), 1742 (C=O), 971 (*trans*-CH=CH–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 3 H, C-20), 2.31 (t, C-2), 3.67 (s, 3 H, –OCH_3), 4.12 (m, 1 H, C-15), 5.61 (m, 2 H, C-13, C-14). Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.58; H, 10.66.

***dl*-15-*epi*-11-Deoxyprostaglandin E_1 (54).** A 1.359-g (0.00385-mol) sample of 15-*epi*-11-deoxyprostaglandin E_1 methyl ester (**52**) was saponified to yield 1.280 g (98%) of an oil which crystallized from hexane–ethyl acetate: mp 53–56 °C; IR (KBr) 3378 (OH), 1730 (C=O), 978 (*trans*-CH=CH–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 3 H, C-20), 2.33 (t, J = 7 Hz, C-2), 4.12 (m, 1 H, C-15), 5.60 (m, 2 H, C-13, C-14). Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.89; H, 10.08.

***dl*-11-Deoxyprostaglandin E_1 (53).** A 1.523-g (0.00432-mol) sample of 11-deoxyprostaglandin E_1 methyl ester (**51**) was saponified to yield 1.432 g (98%) of crystalline **53**: mp 83.5–85.0 °C (from ethyl acetate); IR (KBr) 3413 (OH), 1727 (C=O), 977 (*trans*-CH=CH–) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 3 H, C-20), 2.34 (t, J = 7 Hz, C-2), 4.12 (m, 1 H, C-15), 5.61 (m, 2 H, C-13, C-14). Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.00; H, 10.30.

1-Octyn-4-ol (57).[36] A stirred suspension of 121.6 g (5.0 mol) of magnesium in 1 L of anhydrous ether was treated with 0.6 g of mercuric chloride and about 100 mg of iodine. After several min, 3 mL of propargyl bromide was added and if no exotherm was noted a small amount of already reacting propargyl bromide and magnesium in ether was added. After reaction initiation, a mixture of 431 g (5.0 mol) of valeraldehyde and 595 g (5.0 mol) of propargyl bromide was added dropwise at a rate that maintained vigorous refluxing of the solution. (The propargyl bromide must always be present in some excess; otherwise the reaction will stop. If this happens, the addition of about 1 mL of propargyl bromide will restart the reaction.) After about half of the propargyl bromide–valeraldehyde mixture had been added, another 500–750 mL of ether was added to dilute the reaction mixture. At the end of the addition, the reaction mixture was refluxed for at least 0.5 h, cooled, and poured into 4 L of saturated ammonium chloride with good stirring. Workup gave 583 g of a dark oil which was distilled to yield 364 g, bp 71–77 °C/11 mm. Fractional distillation using a packed distillation column provided 345 g, bp 72–74 °C/11 mm.[37]

4-(Triphenylmethoxy)-1-octyne (59). A mixture of 10 g of 1-octyn-4-ol (**57**) and 30.75 g of triphenylmethyl bromide in 85 mL of dry pyridine was stirred at 100 °C for 2 h. The cooled solution was poured into 425 mL of ice water and extracted several times with ether. The combined extracts were washed with ice-cold 2% hydrochloric acid and saturated sodium chloride solution, dried, and taken to dryness to give an oil. The oil was dissolved in 50 mL of hexane, and the solution was chilled for several hours. Triphenylmethylcarbinol, which separated, was removed by filtration. Evaporation of the mother liquor gave 29 g of an oil. Column chromatography on 350 g of Florisil using hexane for elution gave 21 g (72%) of product **59** as an oil: IR (film) 3.00, 4.75, 6.28, 12.90, 13.10, 13.40, 14.15 μm; ^1H NMR ($CDCl_3$) δ 3.6 (m, 1, >CHO–), 1.96 (m, 3 H, HC≡CCH_2–). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66. Found: C, 88.19; H, 7.72.

1-Iodo-4-(triphenylmethoxy)-*trans*-1-octene (58). A suspension of 3.25 g (0.074 mol) of sodium borohydride in 200 mL of 1,2-dimethoxyethane was stirred under nitrogen at −5 °C, and 15.8 g (0.22 mol) of 2-methyl-2-butene was added followed by 16.2 g (0.11 mol) of boron trifluoride etherate. After 2 h at −5 to 0 °C, a solution of 37.5 g (0.10 mol) of 4-(triphenylmethoxy)-octyne (**59**) in 50 mL of 1,2-dimethoxyethane was added during 5–10 min and the solution was allowed to warm to 25 °C during about 2 h. The solution was again cooled to 0 °C, and 30 g (0.4 mol) of crystalline anhydrous trimethylamine *N*-oxide was added during 5 min with stirring. The suspension was allowed to warm spontaneously to ~40 °C and was kept between 30 and 40 °C for 1 h and then allowed to cool to room temperature. The reaction mixture was poured into 1 L of stirred ice-cold 15% sodium hydroxide solution, and a solution of 80 g of iodine in 200 mL of tetrahydrofuran was added. After being stirred for 0.5 h, the organic layer was separated and the aqueous layer was washed three times with ether. The combined organic layers were washed with water, 5% sodium thiosulfate, and saturated sodium chloride. After drying, the filtered solution was concentrated to 50 g of oil. A solution of the oil in 200 mL of hexane was chromatographed on a 1500-g alumina column (5.1 cm d.). Elution with hexane and evaporation of solvent from appropriate fractions yielded 33 g of desired product: ^1H NMR ($CDCl_3$) δ 7.1–7.6 (m, 15 H, aryl H), 6.35 (dt, J = 15 and 7 Hz, 1 H, C=CHCH$_2$), 5.82 (d, J = 15 Hz, 1, ICH=C), 3.48 (m, 1 H, OCH), 1.92 (t, J = 7 Hz, 2 H, C=CHCH_2). Anal. Calcd for $C_{27}H_{29}IO$ (496.40): C, 65.32; H, 5.89. Found: C, 64.88; H, 6.21.

2-[6-(Carbotetrahydropyranyloxy)-*cis*-2-hexenyl]-4-(tetrahydropyranyloxy)cyclopent-2-en-1-one (60). To an ice-cooled solution of 4.007 g (0.0178 mol) of 2-(6-carboxy-*cis*-2-hexenyl)-4-hydroxycyclopent-2-en-1-one[31] and 7.5 g (0.089 mol) of freshly distilled dihydropyran in 85 mL of dry methylene chloride was added 0.034 g (0.178 mmol) of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at 0 °C for 10 min, the ice bath was removed, and the solution was stirred at ambient temperature for 1.25 h. The mixture was partitioned between ether and a solution made up of 40 mL of saturated brine, 40 mL of saturated sodium bicarbonate, and 80 mL of water. The organic phase was washed twice with saturated brine, dried ($MgSO_4$–K_2CO_3), and evaporated in vacuo (<35 °C) with the aid of 100 mL of toluene to yield a mobile oil: 7.011 g (100%); IR (film) 1742 (C=O, ester), 1712 (C=O, ketone), 1631 (–C=C–, ring), 1114, 1032, 1019, 983, 870, 813 cm^{-1}. This product was used as such for further transformations.

***dl*-15-Deoxy-16ξ-hydroxyprostaglandin E_2 (61).** To a stirred solution of 26.8 g (51 mmol) of 1-iodo-4-(triphenylmethoxy)-*trans*-1-octene (**58**) in 50 mL of toluene was added 26.3 mL of 1.9 M *n*-butyllithium in hexane at −70 °C. After the addition, the solution was stirred for 60 min at −40 °C. This solution containing [4-(triphenylmethoxy)-*trans*-1-octenyl]lithium was treated with 26.8 mL of 1.45 M trimethylaluminum in hexane at −40 °C, and the resulting solution was stirred at 0 °C for 20 min.

To the above solution containing lithium trimethyl[4-(triphenylmethoxy)-*trans*-1-octenyl]alanate was added a solution of 16.7 g (42.5 mmol) of 4-(tetrahydropyranyloxy)-2-[6-(carbotetrahydropyranyloxy)-2-*cis*-hexenyl]cyclopent-2-en-1-one (**60**) in 60 mL of ether at 0–8 °C. The mixture was stirred at 0 °C for 1 h and at 25 °C for 20 h, diluted with ether, and poured into a stirred mixture of ice and 20 mL of 37% hydrochloric acid. The aqueous phase was worked up to give a crude oil which was dissolved in 425 mL of 4:2:1 acetic acid–tetra-

hydrofuran–water, and the resulting solution was heated at 45 °C for 4 h. The solvents were removed in vacuo at 20 °C to give a mixture of oil and crystals.

The crude product was purified by partition chromatography on acid-washed silica gel using the conjugate phases from benzene–methanol–water (15:5:2). A mobile portion of the mixture was shown to contain 15-deoxy-16-hydroxyprostaglandin A_2 (0.75 g, 5%). The more polar portion containing **61** was further purified by partition chromatography on Celite with the system heptane–ethyl acetate–methanol–water (60:40:15:6) to give a total of 5.23 g (35%) of **61** as a light amber oil: ^{1}H NMR (acetone-d_6) δ 3.61 (m, 16-H) and 4.10 (q, 11-H); ^{13}C NMR (the numbers in parentheses which are denoted by an asterisk are chemical shifts of the corresponding 16-epimer; the two peaks of these carbons are approximately of equal height) 132.72 (C-13), 130.88 (C-5), 130.04 (C-4), 126.87 (C-6), 72.03 (C-11), 71.50 (71.03*) (C-16), 54.90 (C-8), 53.87 (53.31*) (C-12), 46.61 (46.55*) (C-10), 40.80 (40.19*) (C-15), 36.86 (36.42*) (C-17), 33.56 (C-2) ppm; IR (film) 3300 (broad, OH), 1735, 1710, 970 cm^{-1}. High-resolution mass spectrum (M − H_2O): calcd for $C_{20}H_{32}O_5$, 334.2126; found, 334.2144.

Acknowledgments. We would like to thank Mr. R. E. Schaub for the preparation of 3-*tert*-butoxy-1-octyne and the C-15 epimers of 11-deoxyprostaglandin E_1 ethyl ester and Dr. P. J. Kohlbrenner, Mr. J. Nocera, and Dr. K. Sax for the preparation of certain intermediates. We thank Mr. L. Brancone and staff for elemental analyses, Mr. W. Fulmor and Mr. G. Morton for spectral data, Dr. G. Van Lear for mass spectral data, and Dr. S-M. L. Chen for the interpretation of the ^{13}C NMR data. We thank Dr. C. A. Streuli, Mr. J. Baker, and Mr. R. Mills for certain chromatographic separations.

Registry No.–**4,** 20348-58-7; **5,** 629-05-0; **6,** 40098-43-9; **7,** 40964-30-5; **8,** 40098-44-0; **9,** 34546-57-1; **10,** 40098-45-1; **11,** 40098-50-8; **12,** 22099-78-1; **13,** 41264-03-3; **14,** 52419-10-0; **15,** 37730-21-5; **16,** 69140-17-6; **19,** 69140-49-4; **20** (R = H), 818-72-4; **20** (R = D), 69140-30-3; **21,** 69140-18-7; **22,** 69140-19-8; **25,** 52418-74-3; **26,** 69140-20-1; **27,** 69140-21-2; **28,** 69140-22-3; **30,** 69140-23-4; **34,** 42568-76-3; **35,** 20897-96-5; **36** (isomer 1), 57378-32-2; **36** (isomer 2), 61045-36-1; **38,** 69140-24-5; **39,** 2913-56-6; **41,** 519-73-3; **44,** 69140-25-6; **46,** 69140-26-7; **47,** 39178-65-9; **48,** 52487-91-9; **50,** 55836-04-9; **51,** 34603-79-7; **52,** 34603-81-1; **53,** 34603-80-0; **54,** 40098-34-8; **57,** 52517-92-7; **58,** 57113-71-0; **59,** 67693-56-5; **60,** 62407-95-8; **61** (isomer 1), 69177-19-1; **61** (isomer 2), 69177-20-4; 4-bromo-2-(6-carbethoxyhexyl)cyclopent-2-en-1-one, 52419-09-7; 3-octanol, 589-98-0; 1-octen-3-ol, 3391-86-4; *trans*-1-chloro-1-octen-3-one, 39198-04-4; *cis*-1-chloro-1-octen-3-one, 69140-27-8; *trans*-1-iodo-1-octen-3-one, 39178-64-8; [4-(triphenylmethoxy)-*trans*-1-octenyl]lithium, 69140-28-9; lithium trimethyl[4-(triphenylmethoxy)-*trans*-1-octenyl]alanate, 57105-30-3; (±)-15-deoxy-16-hydroxyprostaglandin A_2, 69140-29-0; methyllithium, 917-54-4; dihydropyran, 25512-65-6; *n*-butyllithium, 109-72-8; isobutylene, 115-11-7; 1-methyl-1-cyclohexene, 591-49-1; triphenylmethyl bromide, 596-43-0; *p*-anisyldiphenylmethyl chloride, 14470-28-1; propargyl bromide, 106-96-7; valeraldehyde, 110-62-3; trimethylaluminum, 75-24-1; 2-(6-carboxy-*cis*-2-hexenyl)-4-hydroxycyclopent-2-en-1-one, 52419-12-2; diisobutylaluminum hydride, 1191-15-7.

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(25) The possibility of allylic ether reductive cleavage of alumino species **37** and **43** and propargylic ether cleavage in **42** cannot be excluded.
(26) The existence of **45** is alluded to by Sih and co-workers in the iodination of the alane prepared from 1-octyn-3-ol (**19**) and 2 equiv of DAH.[3e]
(27) Alcohol **47** has since been described by (a) A. F. Kluge et al.,[3d] (b) C. J. Sih et al.,[3b] and (c) E. J. Corey and D. J. Beams, *J. Am. Chem. Soc.*, **94,** 7210 (1972). A shorter and more convenient preparation is available from 3-hydroxy-1-octyne by a hydroboration–oxidation–iodination process.[3d] The *p*-anisyldiphenylmethyl ether was used rather than the more common unsubstituted trityl ether because of the greater facility with which such ethers undergo hydrolysis.[35] Probably the most convenient procedure to alkenyllithium reagents is via hydrostannation.[1]
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(29) It is interesting to note that this ratio of epimers is obtained whether alanate reagents or cuprate reagents are employed.[3d]
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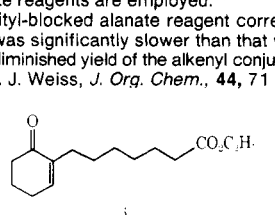

i

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Synthesis and Structure of Benziodazoles

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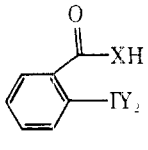
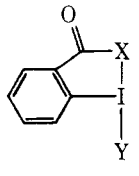
N-Alkylbenziodazoles **5a** and **5b** were prepared by dehydrochlorination of amides **3a** and **3b.** An X-ray structure determination showed **5b** to be a tricoordinate iodinane and not *N*-chloroamide **6b.** The chemical shift of the carbon α to iodine was found to be sensitive to the oxidation state of iodine. Preparation of a six-membered iodinane heterocycle, **12**, was unsuccessful.

Brief reports of iodinanes (tricoordinate iodine) with nitrogen and chlorine ligands have been made by several groups.[1,2] Naae and Gougoutas[2] have reported the preparation and crystal structure of a *N*-chlorobenziodazole. Only one *N*-alkylbenziodazole (**2b**) has been described and the structural assignment was not absolute.[2] This note outlines the synthesis of two *N*-alkylbenziodazoles **5a** and **5b.** An X-ray structure determination confirms that **5b** exists as a tricoordinate iodinane.

Results and Discussion

Aryl dichloroiodinanes are bright yellow highly crystalline compounds. Heating these materials in chloroform induces reductive elimination of chlorine to give the monovalent iodides.[3] Acid **1a** is a notable exception and with or without solvent cyclizes to **2a.**[4] Amide **1b** is reported to undergo a similar cyclization on heating in methanol.[2] No yield was reported. Our interest in *N*-alkylated benziodazoles, of which **5a** and **5b** are examples, led us to this method. Adding **4a** to boiling methanol gives reduced amide **3a** as the major product. Examination of the ^{13}C NMR spectrum of the crude reaction mixture indicates only a small amount (<5%) of **5a** is formed





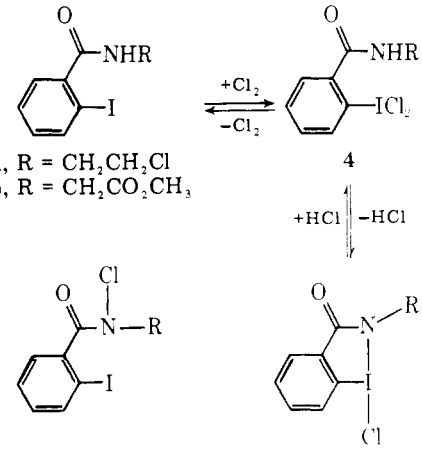
1 2

a, X = O; Y = Cl
b, X = NCH_3; Y = Cl
c, X = O; Y = OH

(see later text for ^{13}C assay technique). Cyclization does not compete favorably with reductive elimination of chlorine.

The 1-chloro-3-oxobenziodazoles **5a** and **5b** can be prepared in good yields if the respective dichloride (**4**) is added in portions to a stirred solution of acetic acid saturated with sodium acetate. The intense yellow color of the dichloride rapidly disappears and a white precipitate forms. Addition of cold water and filtration give **5a** and **5b** in yields of 79 and 84%, respectively.

Iodinanes **5a** and **5b** are stable at ambient temperature in the dark. These compounds are not hydrolyzed when washed with water and are unaffected by recrystallization from methanol. Bubbling HCl into a stirred mixture of **5a** and chloroform gives a homogeneous solution. Boiling this solution followed by removal of the solvent gives the reduction product **3a.**



3a, R = CH_2CH_2Cl
3b, R = $CH_2CO_2CH_3$

4

6 5

Field desorption mass spectra of **5a** and **5b** both exhibit strong molecular ions. Minor peaks are found for $M^{+\cdot} - Cl$. The proton spectra (Me_2SO-d_6) are characterized by low-field multiplets for the protons ortho to iodine. An absorption at δ 8.52 is observed for **5b** as compared with δ 7.89 for the same proton in the reduced species **3b.** This anisotropic effect of the I–Cl hypervalent bond is similar to that observed for the S–Cl bond in chlorosulfuranes.[5]

An X-ray structure determination described in the next section establishes an iodinane structure for **5b,** in the solid state. In solution this substance could exist in equilibrium with the *N*-chloro isomer **6b.** On obtaining a routine ^{13}C spectrum of **5b,** we have noticed a striking downfield shift of the carbon α to iodine, relative to the same carbon in the low valent precursor **3b** (see Table I). It should be noted that the carbon of monovalent aryl iodides is dramatically shielded relative to an unsubstituted carbon (note iodobenzene). NMR data on several compounds of known oxidation state are listed in Table I. Spectra of compounds **7–10** (structures of which are well defined in the literature[6]) clearly reflect the oxidation state of iodine. Chemical shift correlation of **5b** (also **5a**) with these standards is good and suggests a tricoordinate iodinane structure is predominant in solution. A rapid interchange between **5b** and a small amount of **6b** cannot, of course, be ruled out.[7]

Our efforts to prepare six-membered iodinane heterocycle **12** have failed. The procedure described above gives the *N*-chloro isomer **13** (26%) as confirmed by the chemical shift of the α carbon (δ 90.12). We have been unable to convert **13** to **12** either thermally or photochemically.

Molecular Structure of 5b. Pertinent intramolecular

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