Construction of Long-Chain Carbohydrates. Synthesis and Chemistry of a Galactose 6-Phosphorane

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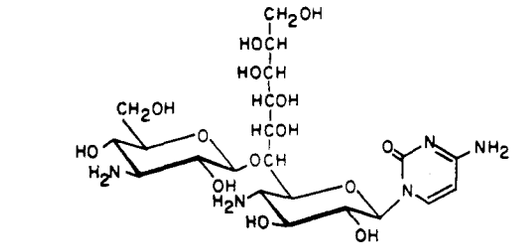
The protected galactose 6-phosphorane **7** has been generated from the phosphonium salt **6d** with *n*-BuLi in 2:1 THF–HMPA at −60 °C. Condensation of **7** with both aliphatic and aromatic aldehydes proceeded in good yield to produce chain-extended compounds. It was also possible to condense **7** with two protected five-carbon carbohydrate aldehydes (**10b** and **12b**) to produce two undecoses (**11a** and **13a**) of *Z* configuration. Isomerization of **11a** and **13a** to the more stable *E* isomers **11b** and **13b** was possible by irradiation in the presence of diphenyl disulfide. In all cases the α-D-*galacto* configuration was maintained during the condensation. The tetra-*O*-methyl-substituted galactose phosphorane derived from **15e** was also prepared and demonstrated to condense with benzaldehyde while maintaining the α-D-*galacto* configuration.

The construction of complex carbohydrates containing more than six or seven carbon atoms has presented a challenge since the time of Fischer.[1] A wide variety of naturally occurring carbohydrates and nucleosides have branched-chain or chain-elongated structures involving simple one- or two-carbon additions, some examples being cladinose in erythromycin,[2] L-olivomycose in olivomycin,[2] D-aldgarose in aldgamycin E,[3] the polyoxins,[4] and septacidin.[4] These structures are approachable by a variety of very useful methods.[5] In the past several years, however, the structures of several complex nucleoside antibiotics with an undecose as the basic carbohydrate unit have been elucidated, namely, anthelmycin (or hikizimycin, **1**),[6] the tunicamycin complex (**2**),[7] sinefungin (**3**),[8] and the related factor C.[8] The ten consecutive chiral



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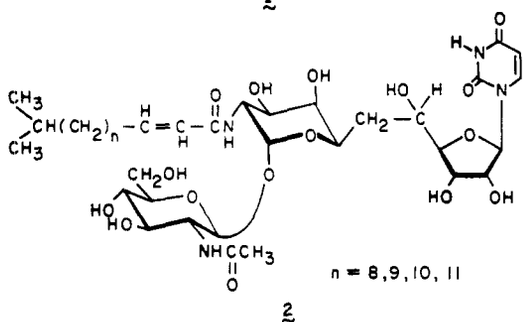

n = 8,9,10, 11

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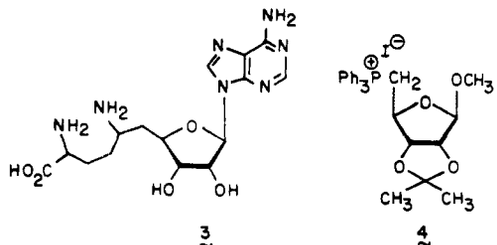

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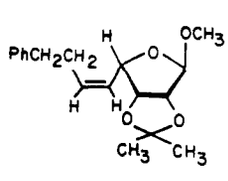
centers in the undecose portion of anthelmycin, for example, make it largely unapproachable by methods presently in the carbohydrate literature. One recent approach to a complex carbohydrate involved the condensation of the dianion of a monounprotected erythrose-derived dithiane with 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose to form a new carbon–carbon bond in unspecified yield.[9] Other isolated cases of complex carbohydrate formation are also known.[10-12]

We have recently developed a method of chain extension by the generation of an unstabilized carbohydrate phosphorane, specifically that derived from phosphonium salt **4**.[13] Condensation of the ylide from **4** with various aldehydes afforded structures such as **5** utilizing 3-phenylpropanal as an



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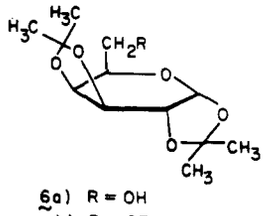
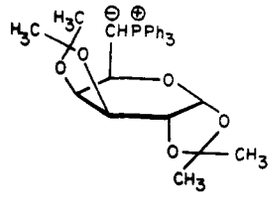


6 a) R = OH
b) R = OTs
c) R = I
d) R = $PPh_3^{\oplus}\ I^{\ominus}$



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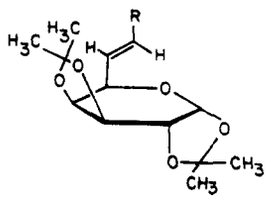
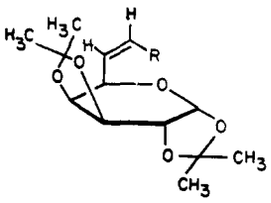
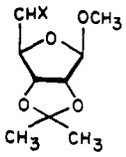


8 a) R = Ph
b) R = pClPh



9 a) R = Ph
b) R = pClPh
c) R = $(CH_2)_3CH_3$
d) R = $(CH_2)_2Ph$



10 a) X = H, OH
b) X = O

example. The yields in the sequence were quite good for all aldehydes examined, and in every case complete inversion of the β-D-*ribo* to the α-L-*lyxo* configuration took place, via ring opening and reclosure of the phosphorane to the apparently more stable α-L-*lyxo* configuration.[14] The conclusion drawn from this initial work was that an unstabilized carbohydrate phosphorane was a viable synthetic intermediate under the proper conditions if the oxygen β to the phosphorus was

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maintained in the molecule through another set of bonds, so that the opening–reclosure of the phosphorane, if it occurred, would be possible in an intramolecular sense.

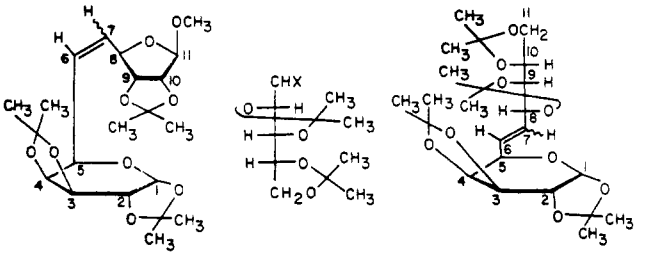
In considering structures of the complexity of anthelmycin and tunicamycin, it is apparent that they might be approached quite efficiently via a carbohydrate phosphorane. For example, condensation of a six-carbon carbohydrate phosphorane with a five-carbon carbohydrate aldehyde would produce an undecose directly. In this manner all asymmetric centers except any to be derived from the carbons of the newly formed double bond could be incorporated with configurations specified exactly. The double bond could then be appropriately oxidized to generate either one or two more chiral centers, as needed. This approach, if successful, would make readily available a multitude of long chain complex carbohydrates stereospecifically. With this goal in mind we set out to investigate the generality of carbohydrate phosphorane preparation and condensation reactions. Anthelmycin, or, more specifically, hikosamine, the undecose portion of the molecule, was selected as a long-range goal to guide us in exploring further chemistry on carbohydrate phosphoranes. A cursory retrosynthetic analysis of hikosamine suggests forming the C_6–C_7 bond during the Wittig reaction. Assuming initially that the nitrogen at C_4 is incorporated by nucleophilic displacement, then C_1–C_6 is derived from D-galactose and C_7–C_{11} from D-arabinose (C_7 is C_1 of arabinose). It should also be mentioned that the skeleton of the undecose portion of tunicamycin might be approached via the formation of the C_5–C_6 bond from D-galactose and D-ribose precursors. In this paper we wish to describe the synthesis and reactions of a galactose phosphorane, including its reaction with several carbohydrate aldehydes to generate the corresponding undecoses relating to hikizimycin and tunicamycin.

As our starting material we chose the readily available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6a**).[15] This was converted via the *p*-toluenesulfonate **6b**[16,17] to the 6-iodo compound **6c**.[17] Sulfolane was found to be the solvent of choice for preparation of the phosphonium salt **6d**, just as was the case with the ribose phosphonium salt.

The red-colored ylide **7** derived from **6d** was generated by the addition of 1 equiv of *n*-BuLi to the salt dissolved in 2:1 THF–HMPA at −60 °C under nitrogen. The ylide was well behaved at low temperatures, and it proved possible to condense **7** with a variety of aldehydes in good yield. The aromatic aldehydes benzaldehyde and *p*-chlorobenzaldehyde provided a mixture of **8a/9a** and **8b/9b** in 86 and 77% yield, respectively, after chromatography. Aliphatic aldehydes pentanal and 3-phenylpropanal condensed with **7** to afford 68 and 75% yields of single isomers **9c** and **9d**, respectively. As with the ylide derived from **4**, attempted condensation with ketones resulted in a complex mixture of products which was not further examined.

Confirmation that the α-D-*galacto* configuration was retained during the Wittig reaction in all cases was obtained by chemical means in a fashion similar to that used in the previous study.[13] Ozonolysis of the **8a** and **9a** mixture, for example, followed by $LiAlH_4$ reduction produced only one carbohydrate product, the alcohol **6a**, identical in all respects with known material. An examination of previous work on the diisopropylidene-blocked galactose derivatives indicated that the six-membered ring is in a twist-boat conformation, and C_6 would much rather stay in its configuration than epimerize via ring opening to the much less stable alternative configuration.[18] Thus in this series there is no evidence as to whether or not the galactose ring is opening and reclosing once the ylide is generated. Proof of the cis geometry in the sole product formed in the aliphatic cases will be presented shortly.

With the scope of the carbohydrate phosphoranes expanded thusly, the crucial question of the behavior of **7** with a carbohydrate aldehyde was examined. When ylide **7** was condensed with methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**10b**),[19] decolorization occurred rapidly and appropriate processing afforded a single product, **11a**, in 64%

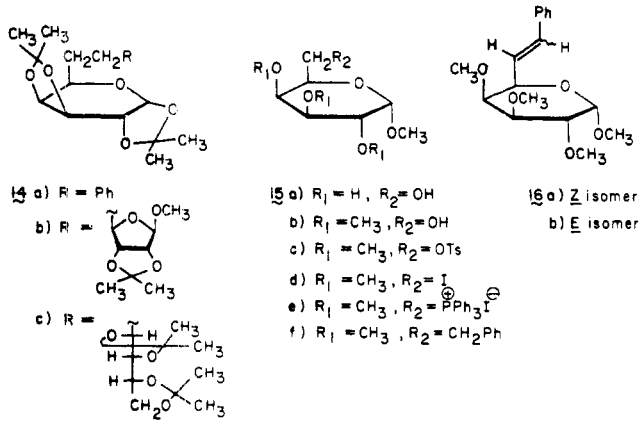


11 a) Z isomer b) E isomer **12** a) X = H,OH b) X = O **13** a) Z isomer b) E isomer

yield. In this case the configurations of both halves needed confirmation. Ozonolysis–reduction produced only two carbohydrate alcohols, readily identifiable as **6a** and **10a** by TLC, ^1H NMR, and ^{13}C NMR, thus indicating no configurational changes in either half. Similarly, condensation of **7** with 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**12b**)[20] also produced a single isomer, **13a**, in 84% yield. The configurational integrity of both halves was again confirmed as described above.

The remaining task was to establish the geometry about the newly formed double bond in **11a**, **13a**, and the aliphatic cases **9c** and **9d**. Examination of the ^1H NMR spectra in $CDCl_3$ proved fruitless, since the chemical shifts of the two vinyl hydrogens were virtually identical and coupling constants could not be determined. However, if the ^1H NMR spectrum of **11a**, for example, was recorded in benzene-d_6 instead, the olefinic protons were pulled apart, and a coupling constant of 11 Hz was measured, clearly indicating a cis double bond. Determination of the ^1H NMR spectra of the other three compounds also revealed similar coupling constants, and hence cis geometries. Since it was absolutely essential to know the geometry of the complex carbohydrates for the purpose of continuing on toward a target molecule, we also sought to confirm the geometry chemically by isomerization studies.[21] Since **11a** and **13a** are disubstituted alkenes, it is quite likely that the trans (*E*) geometry is more stable than the *Z* geometry. When a solution of **11a** and 1 equiv of diphenyl disulfide in cyclohexane was irradiated with a medium-pressure mercury lamp for 25 min, a colorless solid gradually came out of solution. Characterization of this material demonstrated it to be the *E* isomer **11b**, obtained in 83% total yield. In addition, 12% of the starting *Z* isomer was isolated. The ^1H NMR spectrum of **11b** in benzene-d_6 gave a coupling constant of 15.5 Hz, confirming the *E* geometry. Since further irradiation resulted in loss of yield, and the use of only a catalytic amount of diphenyl disulfide was ineffective, we do not know the equilibrium percentages of *E* and *Z* isomers for certain, though our values are probably quite close to them. When the *E* isomer was separated and resubjected to the irradiation conditions, a mixture of *E* and *Z* of similar proportions as described above was formed. A similar experiment with **13a** resulted in the formation of 60% of the crystalline *E* isomer **13b**, coupling constant 16 Hz, and 10% recovered *Z* isomer **13a**. Catalytic reduction of both **11a/11b** and **13a/13b** produced one compound in both cases (**14b** and **14c**, respectively), thus indicating that no double bond migration had occurred during the irradiation.

In order to learn how a less constrained galactose ylide might behave in contrast to **7**, the tetra-*O*-methylgalactose phosphonium salt **15e** was prepared by standard means. Methyl α-D-galactopyranoside (**15a**) was tritylated at O_6 and exhaustively methylated,[22] and the trityl group was removed to afford alcohol **15b**.[23] Conversion to the phosphonium salt



14 a) R = Ph
b) R =
c) R =

15 a) $R_1 = H$, $R_2 = OH$
b) $R_1 = CH_3$, $R_2 = OH$
c) $R_1 = CH_3$, $R_2 = OTs$
d) $R_1 = CH_3$, $R_2 = I$
e) $R_1 = CH_3$, $R_2 = \overset{\oplus}{P}Ph_3\,I^{\ominus}$
f) $R_1 = CH_3$, $R_2 = CH_2Ph$

16 a) Z isomer
b) E isomer

15e was accomplished via the 6-*p*-toluenesulfonate **15c**[24] and the 6-iodide **15d**[25] followed by quaternization with triphenylphosphine. Condensation of the ylide derived from **15e** under the standard conditions with benzaldehyde produced a 65% yield of the *Z* and *E* isomers **16a** and **16b**, with the *Z* predominating (59% *Z*, 6% *E*). The configuration at C_5 of the *Z* isomer was confirmed by the standard ozonolysis–reduction procedure. It appears, therefore, that the D-*galacto* configuration may be retained in a variety of appropriately protected compounds.

Thus, it is possible to generate the galactose-derived phosphorane **7** and condense it in quite good yields with various aldehydes. Most importantly, the condensation reaction proceeded well with both carbohydrate aldehydes examined to generate the complex carbohydrates **11a** and **13a** as pure *Z* isomers with configurations retained at all centers. It appears that this methodology has utility for the synthesis of a wide variety of complex carbohydrates and nucleoside antibiotics. With careful choice of protecting groups, the undecose portions of anthelmycin and tunicamycin should be constructable in a reasonably short sequence. We are continuing to pursue these and other goals in the area of carbohydrate phosphoranes.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer, and only selected absorptions are given. ^1H NMR spectra were measured with Varian EM-360 or HA-100 instruments and ^{13}C NMR spectra with a Bruker WP-80; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. All ^{13}C assignments are supported by the splittings in off-resonance decoupling experiments. Ozone was generated with a Welsbach Ozonator T-408. Microanalysis was done by Galbraith Laboratories, Inc., and Mr. William Rond, The Ohio State University. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Irradiations were carried out employing a 450-W Hanovia no. 679A36 medium-pressure mercury arc lamp. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in a 1-dm tube.

Tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) were dried by distillation from calcium hydride. Tetramethylene sulfone was dried by distillation from NaOH. In all cases petroleum ether (38–56 °C) was employed.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(triphenylphosphonio)-α-D-galactopyranose Iodide (6d). A solution of 5.8 g (15.6 mmol) of 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6c**) and 5.0 g (19 mmol) of triphenylphosphine in 7.3 mL of tetramethylene sulfone was heated at 110 °C for 39 h. The pale yellow solution was diluted with 25 mL of $CHCl_3$ and then added dropwise to 900 mL of vigorously stirred Et_2O. The product precipitated out as a fine white solid which was filtered off and washed with Et_2O, affording 9.43 g (95%). Recrystallization from methanol–ethyl acetate provided analytically pure material: mp 251–253 °C dec; IR (KBr) 3052, 2986, 1389, 1378, 1219, 1109, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.06, 1.16, 1.36, 1.50 (4 s, 12, $2C(CH_3)_2$), 3.33–5.06 (m, 6, H_2, H_3, H_4, H_5, H_6, $H_{6'}$), 5.25 (d, 1, $J_{1,2}$ = 5 Hz, H_1), 7.46–8.13 (m, 15, ArH); $[\alpha]^{25}_D$ −24.76° (*c* 2.84, $CHCl_3$).

Anal. Calcd for $C_{30}H_{34}IO_5P$: C, 56.97; H, 5.42. Found: C, 56.92; H, 5.39.

General Procedure for Generation of the Ylide and Its Condensation with Aldehydes. A solution of the phosphonium salt **6d** (~0.2 M) in 2:1 THF–HMPA was cooled to ~−60 °C under N_2, and 1 equiv of *n*-BuLi was added via syringe. Within 30 s to 1 min, the aldehyde (1.2–1.5 equiv) was added to the ylide, and the solution warmed up to −10 °C over 45 min. Benzaldehyde, pentanal, and 3-phenylpropanal were added neat, while the others were added as a THF solution. A 1:1 petroleum ether–moist Et_2O mixture was added, and any precipitated triphenylphosphine oxide was filtered off, washing with 1:1 petroleum ether–Et_2O. Volatile solvents were removed from the filtrate under reduced pressure and the residue was taken up in 1:1 petroleum ether–Et_2O, washed with H_2O, saturated $NaHSO_3$, and H_2O, and dried over $MgSO_4$. In some cases the filtration step was omitted. After removal of solvent, purification was accomplished by preparative TLC or HPLC.

(*E*)- and (*Z*)-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-7-phenyl-α-D-*galacto*-hept-6-enopyranose (8a and 9a). Condensation of **6d** (632 mg, 1 mmol) with benzaldehyde afforded 286 mg (86%) in total yield after separation by LC (elution with 97:3 hexane–ethyl acetate), 180 mg (54%) *Z* and 106 mg (32%) *E*.

9a: IR (neat) 3030, 2988, 1646 (weak), 1386, 1377, 1218, 1077 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.03, 1.16, 1.24, 1.52 (4 s, 12, $2C(CH_3)_2$), 3.96 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.17 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.46 (dd, 1, H_3), 4.85 (dd, 1, $J_{5,6}$ = 9 Hz, H_5), 5.56 (d, 1, H_1), 6.26 (dd, 1, $J_{6,7}$ = 12 Hz, H_6, B of ABX), 6.62 (d, 1, H_7, A of ABX), 6.82–7.50 (m, 5, ArH); $[\alpha]^{26}_D$ −110.3° (*c* 0.3, $CHCl_3$).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.69; H, 7.17.

8a: mp 101–103 °C; IR (KBr) 3055, 3014, 2989, 1658 (weak), 1388, 1383, 1219, 1074 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.18, 1.44, 1.48 (4 s, 12, $2C(CH_3)_2$), 4.01 (dd, 1, $J_{3,4}$ = 8 Hz, $J_{4,5}$ = 2 Hz, H_4), 4.21 (dd, 1, $J_{1,2}$ = 5 Hz, $J_{2,3}$ = 2 Hz, H_2), 4.48–4.64 (m, 2, H_3, H_5), 5.61 (d, 1, H_1), 6.47 (dd, 1, $J_{6,7}$ = 16 Hz, $J_{5,6}$ = 6 Hz, H_6, B of ABX), 6.78 (d, 1, H_7, A of ABX), 6.90–7.34 (m, 5, ArH); $[\alpha]^{25}_D$ −171.55° (*c* 0.45, $CHCl_3$).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.71; H, 7.30.

(*E*)- and (*Z*)-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-7-(*p*-chlorophenyl)-α-D-*galacto*-hept-6-enopyranose (8b and 9b). Condensation of **6d** (632 mg, 1 mmol) with *p*-chlorobenzaldehyde afforded a total of 282 mg (77%) after separation of isomers by preparative TLC (elution four times with 85:15 petroleum ether–ether), 151 mg (41%) of the *Z* isomer and 131 mg (36%) of the *E* isomer.

9b: IR (neat) 3035, 2992, 1645, 1388, 1378, 1220, 1076 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.00, 1.16, 1.49 (3 s, 12, $2C(CH_3)_2$), 3.89 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.13 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.43 (dd, 1, H_3), 4.66 (dd, 1, $J_{5,6}$ = 8 Hz, H_5), 5.50 (d, 1, H_1), 6.20 (dd, 1, $J_{6,7}$ = 12 Hz, H_6, B of ABX), 6.44 (d, 1, H_7, A of ABX), 7.14 (s, 4, ArH); $[\alpha]^{26}_D$ −84.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{19}H_{23}O_5Cl$: C, 62.21; H, 6.32. Found: C, 62.39; H, 6.12.

8b: mp 123.5–125 °C; IR (KBr) 3078, 3001, 1386, 1377, 1221, 1093, 1078 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.17, 1.44, 1.47 (4 s, 12, $2C(CH_3)_2$), 3.99 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.20 (dd, 1, $J_{1,2}$ = 5 Hz, $J_{2,3}$ = 2 Hz, H_2), 4.46–4.60 (m, 2, H_3, H_5), 5.54 (d, 1, H_1), 6.31 (dd, 1, $J_{6,7}$ = 16 Hz, $J_{5,6}$ = 6 Hz, H_6, B of ABX), 6.60 (d, 1, H_7, A of ABX), 6.84–7.20 (m, 4, ArH); $[\alpha]^{25}_D$ −177.2° (*c* 0.25, $CHCl_3$).

Anal. Calcd for $C_{19}H_{23}O_5Cl$: C, 62.21; H, 6.32. Found: C, 62.32; H, 6.25.

(*Z*)-6,7,8,9,10,11-Hexadeoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-undec-6-enopyranose (9c). Condensation of **6d** (632 mg, 1 mmol) with pentanal afforded 213 mg (68%) of the pure, oily *Z* isomer after preparative TLC (elution with 4:1 petroleum ether–ether): IR (neat) 3034, 2933, 1658 (weak), 1386, 1375, 1219, 1078 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.19, 1.48 (3 s, 12, $2C(CH_3)_2$), 0.60–1.70 (m, partially hidden, 7, $CH_2CH_2CH_3$), 1.96–2.30 (m, 2, $CH_2C{=}C$), 4.03 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.19 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.53 (dd, 1, H_3), 4.75 (dd, 1, $J_{5,6}$ = 8 Hz, H_5), 5.53 (d, 1, H_1), 5.40–5.72 (m, partially hidden, 1, H_7), 5.97 (dd, 1, $J_{6,7}$ = 10 Hz, H_6); $[\alpha]^{26}_D$ −106.2° (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.19; H, 9.03.

(*Z*)-6,7,8,9-Tetradeoxy-1,2:3,4-di-*O*-isopropylidene-9-phenyl-α-D-*galacto*-non-6-enopyranose (9d). Condensation of **6d** (632 mg, 1 mmol) with 3-phenylpropanal afforded 270 mg (75%) of the pure, oily *Z* isomer after preparative TLC (elution with 4:1 petroleum ether–ether): IR (neat) 3032, 2991, 1660 (weak), 1387, 1376, 1219, 1079 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.08, 1.18, 1.44, 1.47 (4 s, 12,

2C($\mathbf{CH_3}$)$_2$), 2.24–2.72 (m, 4, –$\mathbf{CH_2CH_2}$–), 3.72 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.17 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.47 (dd, 1, H_3), 4.66 (dd, 1, $J_{5,6}$ = 8 Hz, H_5), 5.52 (d, 1, H_1), 5.40–5.70 (m, partially hidden, 1, H_7), 5.97 (dd, 1, $J_{6,7}$ = 10 Hz, H_6), 7.00–7.22 (m, 5, ArH); $[\alpha]^{25}_D$ −79.2° (*c* 1.15, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.90; H, 7.84.

(*Z*)-1-(Methyl 2,3-*O*-Isopropylidene-β-D-*ribo*-tetrafuranosid-4-yl)-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)ethylene (11a). Condensation of **6d** (948 mg, 1.5 mmol) with methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**10b**) afforded 410 mg (64%) of the oily *Z* isomer after preparative TLC (elution with 6:5 petroleum ether–ether): IR (neat) 2992, 1386, 1377, 1218, 1076 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.15, 1.46, 1.53 (4 s, 18, 3C(CH_3)$_2$), 3.10 (s, 3, OCH_3), 4.07 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.17 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.48 (dd, partially hidden, 1, H_3), 4.46–4.65 (m, 2, H_9, H_{10},), 4.82 (dd, 1, $J_{5,6}$ = 8 Hz, H_5), 5.03 (s, 1, H_{11}), 5.22 (d, 1, $J_{7,8}$ = 8 Hz, H_8), 5.51 (d, 1, H_1), 5.70 (dd, 1, $J_{6,7}$ = 10.5 Hz, H_7), 5.95 (dd, 1, H_6); ^{13}C NMR ($CDCl_3$) δ 24.32, 24.95, 25.14, 26.02, 26.11, 26.55 (6C($\mathbf{CH_3}$)$_2$), 54.47 (OCH_3), 64.03, 70.34, 70.93, 73.30 (C_2–C_5), 83.01, 85.25, 85.68 (C_8–C_{10}), 96.46 (C_1), 109.38 (C_{11}), 108.60, 109.23, 112.34 (3C($\mathbf{CH_3}$)$_2$), 128.75, 132.63 (C_6, C_7); $[\alpha]^{28}_D$ −94.7° (*c* 0.72, $CHCl_3$).

Anal. Calcd for $C_{21}H_{32}O_9$: C, 58.86; H, 7.53. Found: C, 59.14; H, 7.58.

(*Z*)-6,7-Dideoxy-1,2:3,4:8,9:10,11-tetra-*O*-isopropylidene-D-*arabino*-α-D-*galacto*-undec-6-enopyranose (13a). Condensation of **6d** (1.264 g, 2 mmol) with 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**12b**) afforded 770 mg (84%) of the syrupy *Z* isomer after preparative TLC (elution with 7:5 petroleum ether–ether): IR (neat) 2987, 1387, 1379, 1221, 1076 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.08, 1.15, 1.28, 1.32, 1.42, 1.46, 1.51 (7 s, 24, 4C(CH_3)$_2$), 3.76–5.00 (m, 9, H_{2-5}, H_{8-10}, H_{11}, $H_{11'}$), 5.45 (d, 1, $J_{1,2}$ = 5.2 Hz, H_1), 5.62 (dd, 1, $J_{6,7}$ = 11 Hz, $J_{7,8}$ = 7.8 Hz, H_7), 6.07 (dd, 1, $J_{5,6}$ = 7.8 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 24.42, 25.00, 25.39, 26.02, 26.11, 26.60, 26.99, 27.28 (8CH_3), 64.27, 70.29, 70.97, 73.69 (C_2–C_5), 66.17 (C_{11}), 75.88, 76.03, 81.31 (C_8–C_{10}), 96.66 (C_1), 108.45, 109.23, 109.52, 109.67 (4C($\mathbf{CH_3}$)$_2$), 129.96, 130.69 (C_6, C_7); $[\alpha]^{27}_D$ −66.3° (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.61; H, 8.04.

(*E*)-1-(Methyl 2,3-*O*-Isopropylidene-β-D-*ribo*-tetrafuranosid-4-yl)-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)ethylene (11b). A solution of **11a** (300 mg, 0.7 mmol) and diphenyl disulfide (150 mg, 0.68 mmol) in 3 mL of cyclohexane was irradiated for 25 min (the solution warmed gradually from room temperature over this period). As the solution cooled a crystalline solid formed which was filtered off, affording 220 mg of pure **11b**. The filtrate was concentrated and separation of the two isomers was accomplished by preparative TLC (elution two times with 3:1 petroleum ether–ether), affording another 30 mg of **11b** (83% in total) and 36 mg of **11a** (12%). Recrystallization of **11b** from cyclohexane provided analytically pure material: mp 141.5–142 °C (needles); IR (KBr) 2995, 1683 (weak), 1388, 1380, 1222, 1094 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.07, 1.12, 1.16, 1.40, 1.44 (5 s, 18, 3C(CH_3)$_2$), 3.16 (s, 3, OCH_3), 3.91 (dd, 1, $J_{4,5}$ = 2 Hz, $J_{3,4}$ = 8 Hz, H_4), 4.17 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{1,2}$ = 5 Hz, H_2), 4.30–4.66 (m, 4, H_3, H_8, H_9, H_{10}), 4.81 (d, 1, $J_{5,6}$ = 7.2 Hz, H_5), 5.06 (s, 1, H_{11}), 5.52 (d, 1, H_1), 5.78 (dd, 1, $J_{6,7}$ = 15.4 Hz, $J_{7,8}$ = 4.4 Hz, H_7), 6.02 (dd, 1, H_6); ^{13}C NMR ($CDCl_3$) δ 24.51, 24.95, 25.14, 26.02, 26.11, 26.55 (6C$\mathbf{C}H_3$), 54.42 (OCH_3), 68.21, 70.54, 70.97, 73.40 (C_2–C_5), 84.81, 85.68, 87.53 (C_8–C_{10}), 96.51 (C_1), 109.28 (C_{11}), 108.45, 109.38, 112.39 (3C(CH_3)$_2$), 129.18, 132.39 (C_6, C_7); $[\alpha]^{25}_D$ −105.7° (*c* 0.58, $CHCl_3$).

Anal. Calcd for $C_{21}H_{32}O_9$: C, 58.86; H, 7.53. Found: C, 59.04; H, 7.63.

(*E*)-6,7-Dideoxy-1,2:3,4:8,9:10,11-tetra-*O*-isopropylidene-D-*arabino*-α-D-*galacto*-undec-6-enopyranose (13b). A solution of **13a** (410 mg, 0.9 mmol) and diphenyl disulfide (400 mg, 1.83 mmol) in 3 mL of cyclohexane was irradiated for 40 min at room temperature (the solution warmed during the process). Solvent was removed and separation of isomers was accomplished by preparative TLC (elution three times with 3:1 petroleum ether–ether) to afford 248 mg (60%) of **13b** and 43 mg (10%) of **13a**. Recrystallization of **13b** from hexane provided analytically pure material: mp 100–101 °C; IR (KBr) 2996, 1681 (weak), 1385, 1377, 1220, 1074 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 1.06, 1.14, 1.22, 1.29, 1.36, 1.40 (6 s, 24, 4C(CH_3)$_2$), 3.60–4.56 (m, 9, H_2–H_5, H_8–H_{10}, H_{11}, $H_{11'}$), 5.51 (d, 1, $J_{1,2}$ = 5.2 Hz, H_1), 6.02 (dd, 1, $J_{6,7}$ = 16 Hz, $J_{7,8}$ = 4 Hz, H_7), 6.22 (dd, 1, $J_{5,6}$ = 5 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 24.46, 24.95, 25.34, 26.11, 26.65, 26.99 (8CH_3, two overlapping), 67.14 (C_{11}), 68.45, 70.63, 70.97, 73.55 (C_2–C_5), 76.90, 79.52, 81.31 (C_8–C_{10}), 96.51 (C_1), 108.45, 109.33, 109.52, 109.62 (4C(CH_3)$_2$), 128.46, 130.74 (C_6, C_7); $[\alpha]^{25}_D$ −86.8° (*c* 0.38, $CHCl_3$).

Anal. Calcd for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.65; H, 8.18.

Hydrogenation of 8a/9a, 11a/11b, 13a/13b, and 16a/16b. A mixture of the alkene (0.1–0.25 mmol) and 10% Pd/C (10% by weight) in 5 mL of ethanol was hydrogenated (Parr shaker) at 3 atm for several hours. The catalyst was filtered off and washed with ether. Removal of solvent was followed by purification by preparative TLC (elution with petroleum ether–ether in all cases, in ratios of 1:3 for **14a**, 2:1 for **14b**, 7:5 for **14c**, 1:3 for **15f**). In all cases a single product was isolated for each *E*/*Z* pair of isomers. For **8a/9a** and **16a/16b**, an *E*/*Z* mixture was hydrogenated, while for **11a/11b** and **13a/13b** each isomer was hydrogenated separately.

14a (90%): ^1H NMR (60 MHz, $CDCl_3$) δ 1.31 and 1.45 (2 s, 12, 2C(CH_3)$_2$), 1.67–2.30 (m, 2, $\mathbf{CH_2}CH_2Ph$), 2.75 (br t, 2, *J* = 7 Hz, $\mathbf{CH_2}Ph$), 3.50–3.83 (m, 1, H_5), 4.06 (dd, 1, $J_{3,4}$ = 8 Hz, $J_{4,5}$ = 2 Hz, H_4), 4.26 (dd, 1, $J_{1,2}$ = 5.2 Hz, $J_{2,3}$ = 2 Hz, H_2), 4.55 (dd, 1, H_3), 5.55 (d, 1, H_1), 7.20 (s, 5, ArH); mass spectrum calcd *m*/*e* 334.1780, found *m*/*e* 334.1789; $[\alpha]^{25}_D$ −57.5° (*c* 1.05, $CHCl_3$).

14b (91% from **11a**, 82% from **11b**): mp 94–95 °C; ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.18, 1.20, 1.46 (4 s, 18, 3C(CH_3)$_2$), 1.54–2.20 (m, 4, –CH_2CH_2–), 3.16 (s, 3, OCH_3), 3.78–4.66 (m, 7, H_2–H_5, H_8–H_{10}), 5.02 (s, 1, H_{11}), 5.49 (d, 1, $J_{1,2}$ = 5 Hz, H_1); ^{13}C NMR ($CDCl_3$) δ 24.61, 25.00, 25.19, 26.07, 26.65, 30.68 (6C($\mathbf{CH_3}$)$_2$, C_6, C_7, some signals overlap), 55.00 (OCH_3), 66.51, 70.73, 71.22, 73.01 (C_2–C_5), 84.42, 85.73, 86.61 (C_8–C_{10}), 96.75 (C_1), 108.31, 109.18, 112.29 (3C($\mathbf{CH_3}$)$_2$), 109.72 (C_{11}); mass spectrum calcd *m*/*e* 415.1968 (M − 15), found *m*/*e* 415.1975; $[\alpha]^{26}_D$ −70.4° (*c* 0.5, $CHCl_3$).

14c (77% from **13a**, 70% from **13b**): ^1H NMR (100 MHz, benzene-d_6) δ 1.09, 1.18, 1.24, 1.28, 1.31, 1.37, 1.43, 1.45 (8 s, 24, 4C(CH_3)$_2$), 1.70–2.34 (m, 4, –CH_2CH_2–), 3.52–4.60 (m, 9, H_2–H_5, H_8–H_{11}, $H_{11'}$), 5.49 (d, 1, $J_{1,2}$ = 5 Hz, H_1); ^{13}C NMR ($CDCl_3$) δ 24.56, 25.05, 25.44, 26.12, 26.50, 26.70, 27.09, 27.47, 28.42 (8CH_3, C_6, C_7, one overlapping), 67.28, 67.53, 70.78, 71.17, 72.87, 77.24, 80.05, 81.07 (C_2–C_5, C_8–C_{11}), 96.75 (C_1), 108.26, 108.89, 109.13, 109.57 (4C(CH_3)$_2$); mass spectrum calcd *m*/*e* 458.2516, found *m*/*e* 458.2524; $[\alpha]^{26}_D$ −27.2° (*c* 1.5, $CHCl_3$).

15f (86%): ^1H NMR (60 MHz, $CDCl_3$) δ 1.56–2.30 (m, 2, $\mathbf{CH_2}CH_2Ph$), 2.53–3.00 (m, 2, $\mathbf{CH_2}Ph$), 3.40, 3.53, 3.56 (3 s, 12, 4OCH_3), 3.26–3.86 (m, partially hidden, 4, H_2–H_5), 4.86 (d, 1, $J_{1,2}$ = 3 Hz, H_1), 7.20 (s, 5, ArH); mass spectrum calcd *m*/*e* 279.1596 (M − OCH_3), found *m*/*e* 279.1603; $[\alpha]^{26}_D$ +131.7° (*c* 1.0, $CHCl_3$).

Methyl 6-Deoxy-2,3,4-tri-*O*-methyl-6-(triphenylphosphonio)-α-D-galactopyranoside Iodide (15e). A solution of 1.95 g (5.63 mmol) of methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-D-galactopyranoside (**15d**)[25] and 2.20 g (8.39 mmol) of triphenylphosphine in 2.8 mL of sulfolane was heated for 24 h at 110 °C. The solution was diluted with 11 mL of $CHCl_3$ and added dropwise to 500 mL of rapidly stirred Et_2O. Recrystallization of the collected precipitate from methanol–ethyl acetate afforded 2.94 g (86%) of colorless needles: mp 237–238 °C dec; IR (KBr) 3053, 2923, 1442, 1119, 1053 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.50, 3.44, 3.48, 3.74 (4 s, 12, 4OCH_3), 3.30–5.20 (m, partially hidden, 7, H_1–H_5, H_6, $H_{6'}$), 7.30–8.15 (m, 15, ArH); $[\alpha]^{25}_D$ +94.04° (*c* 2.55, $CHCl_3$).

Anal. Calcd for $C_{28}H_{34}IO_5P$: C, 55.27; H, 5.63. Found: C, 54.98; H, 5.68.

Methyl (*Z*)- and (*E*)-6,7-Dideoxy-2,3,4-tri-*O*-methyl-7-phenyl-α-D-*galacto*-6-heptenopyranoside (16a and 16b). A mixture of the phosphonium salt **15e** (1.824 g, 3.00 mmol) in 30 mL of 2:1 THF–HMPA was cooled to −55 °C under N_2 (the salt does not completely dissolve), and 1 equiv of *n*-BuLi was added via syringe. In less than 1 min, 1.5 equiv of benzaldehyde was added, and processing was continued as in the general procedure, affording after preparative TLC (eight elutions with 3:2 petroleum ether–ether) 548 mg of oily **16a** and 54 mg of oily **16b** (total yield 65%, 10:1 *Z*/*E*).

16a: IR (neat) 3026, 2917, 2827, 1363, 1142, 1057 cm^{-1}; ^1H NMR (100 MHz, benzene-d_6) δ 3.20, 3.22, 3.26 (3 s, 12, 4OCH_3), 3.00–3.96 (m, partially hidden, 3, H_2–H_4), 4.76–4.92 (m, 2, H_1 and H_5), 6.18 (dd, 1, $J_{5,6}$ = 8.6 Hz, $J_{6,7}$ = 12 Hz, H_6), 6.58 (d, 1, H_7), 7.02–7.40 (m, 5, ArH); ^{13}C NMR ($CDCl_3$) δ 55.49, 58.06, 58.64, 61.46 (4CH_3), 66.61, 77.63, 79.37, 79.96 (C_2–C_5), 98.40 (C_1), 127.15, 128.02, 128.12, 128.27 (ortho, meta, and para aromatics and either C_6 or C_7), 132.39 (C_6 or C_7), 136.47 (ipso aromatic carbon); $[\alpha]^{25}_D$ +88.3° (*c* 1.0, $CHCl_3$).

16b: IR (neat) 3024, 2924, 2826, 1138, 1055 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.42, 3.50, 3.54 (3 s, 12, 4OCH_3), 3.40–4.44 (m, partially hidden, 4, H_2–H_5), 4.94 (d, 1, $J_{1,2}$ = 3 Hz, H_1), 6.32 (dd, 1, $J_{5,6}$ = 6.4 Hz, $J_{6,7}$ = 16 Hz, H_6), 6.72 (d, 1, H_7), 7.18–7.66 (m, 5, ArH).

Anal. Calcd for $C_{17}H_{24}O_5$ (**16a**): C, 66.21; H, 7.85. Found: C, 66.02; H, 7.94.

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).

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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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