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A general approach to carbocyclic sugar analogs: preparation of a carbocyclic analog of β-D-fructofuranose*†

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ABSTRACT

The development and execution of the first examples of a new and general approach to carbocyclic analogs of carbohydrates ("pseudo-sugars") is presented. Complete experimental details for the preparation of the carbocyclic analog of β-D-fructofuranose 6-phosphate are described for the first time. In the conclusion, the success of the synthetic strategy is analyzed and an approach to retrosynthetic analysis based on "unitive synthons" is offered for consideration.

INTRODUCTION

There is a long history of interest in the preparation and study of "pseudo-sugars", or carbocyclic analogs of carbohydrates. Many analogs of furanosides, pyranosides, and nucleosides had been prepared by the early part of the last decade. The impressive work of Ogawa and assoc.[2–6] had demonstrated the use of a furan-cycloaddition approach to pyranose analogs, Vince and assoc.[7,8] had established an important approach to nucleic acid analogs based on another cycloaddition, the reaction of cyclopentadiene with 4-toluenesulfonyl cyanide[7,8]. In work more closely related to our own, several groups had developed methods for generating carbocycles from carbohydratederived precursors. For example, Kiely and Fletcher[9] had demonstrated the nonenzymic biomimetic synthesis of inositols from D-*xylo*-hexos-5-ulose. An elegant rearrangement was developed by Ferrier[10] and affords a very efficient approach to carbocyclic carbohydrates. This valuable reaction continues to be used by Ferrier and others[11–17].

In our own quest for an efficient and general approach to carbocyclic carbohydrate analogs, we were impressed by the practicality of methods which involved the direct cyclization of a carbohydrate-derived precursor. This strategy leads directly to optically pure product and, in the best cases, affords the desired polyhydroxylated product with each stereocenter already incorporated with the correct absolute configuration. The increased interest in carbocyclic carbohydrates that was developing in the

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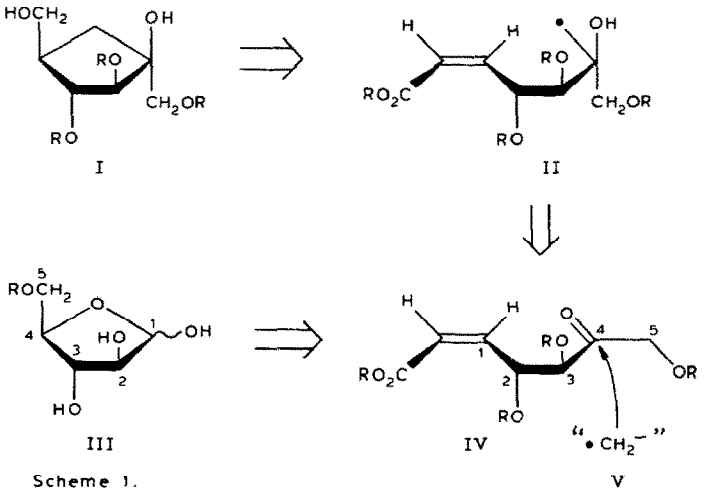
early 1980s was accompanied by another movement, the rebirth of interest in the synthetic utility of radical reactions for carbon–carbon bond formation[18,19]. It was therefore inevitable that a chemist would apply radical reactions to the preparation of carbocyclic analogs of carbohydrates. It happened that we were the first to report success in this area.

Preliminary studies. — The first experiments were carried out on a D-ribose-derived substrate[20]. Protected 5-bromo-5-deoxy-D-ribofuranose (**1**) was converted into the unsaturated ester **6** through the action of a stabilized phosphorus ylide. The preponderant geometrical isomer is the *Z* isomer, which contradicts the expected outcome for the reaction of a stabilized ylide[21]. Recent experiments have demonstrated that this result is due to an effect of the γ-hydroxyl group in **3** during the formation or decomposition of an intermediate oxaphosphetane[22]. The reaction of **4** (assumed to be a required intermediate that must arise from **2**) provides a 95% yield of a 91:9 (*Z*:*E*) mixture of isomers. In startling contrast, **5**, in which the γ-hydroxyl group is protected as a methyl ether, provided an 87% yield of a 1:19 (*Z*:*E*) mixture of isomers.

In the critical first experiment, both geometrical isomers of **9** (prepared by benzoylation of **6**) were treated with tributyltin hydride and gave good yields of cyclopentanoid products. In addition to the successful bond formation, it was observed that only the *Z* isomer gave good stereocontrol. Cyclization of the *E* isomer afforded a 1:1 mixture of stereoisomeric products **10** and **11**. In 1985, we had proposed that this result is due to a steric interaction in the competing transition states leading to the two products. Formation of the minor product requires an unfavorable interaction between the carboalkoxy group of the α,β-unsaturated ester and the γ-alkoxy substituent. In contrast, the major product can arise through a transition state that easily avoids such an interaction[20].

Rationale and synthetic plan for a 5-carba-D-fructofuranose compound. — With these results in hand, the synthesis of a potentially enzyme-regulatory carbohydrate analog, the carbocyclic analog of β-D-fructofuranose 6-phosphate, was undertaken. No carbocyclic analog of a D-fructofuranose compound had been synthesized previously, and the potent allosteric regulatory properties of β-D-fructofuranose 2,6-diphosphate heightened our interest in such an analog[23].

Our interest in D-fructose analogs was stimulated by the discovery that the rate of conversion of D-fructose 6-phosphate to D-fructose 1,6-diphosphate by the enzyme PFK-1 was regulated by β-D-fructose 2,6-diphosphate[24]. It was demonstrated that PFK-1 was able to catalyze the conversion of D-fructose 6-phosphate to D-fructose 1,6-diphosphate at a higher rate in the presence of D-fructose 2,6-diphosphate than in its absence. Approximately a year later, Van Schaftingen and Hers[25], and Pilkis *et. al.*[26], independently found that the reverse reaction, FBPase-1 catalyzed conversion of D-fructose 1,6-diphosphate to D-fructose 6-phosphate, was also regulated by β-D-fructose 2,6-diphosphate and proceeds at a slower rate in its presence than in its absence. These and other observations led us to propose the preparation of carbocyclic analogs of all of these D-fructose derivatives as an important goal to be pursued in our laboratory.



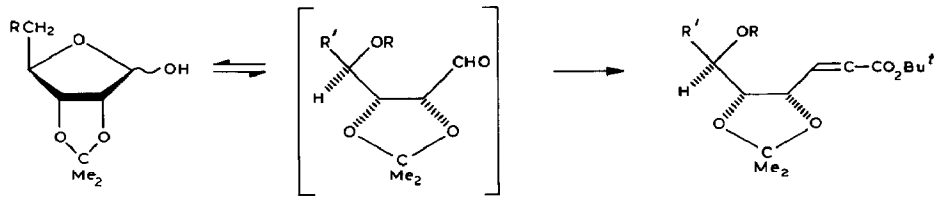
Scheme 1.

A logical retrosynthetic Scheme 1 for the production of carbocyclic D-fructose derivatives was based on our preliminary study[20]. A suitably protected carbocyclic D-fructose derivative (**I**) could be obtained *via* radical cyclization of the radical **II**. The radical could be prepared from the addition of the one carbon synthon (**V**) to the ketose (**IV**). The acyclic ketose could easily be prepared through classic synthetic manipulations of the commercially available D-arabinofuranose derivative **III**. According to this scheme, use of the unitive synthon **V** in conjunction with our radical cyclization strategy would allow for efficient transformation of a carbohydrate into a carbocyclic carbohydrate.

RESULTS AND DISCUSSION

Preparation of the target carbocyclic sugar was carried out starting with commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**12**). Reaction of the arabinose derivative with the stabilized phosphorous ylide, *tert*-butyl-2-(triphenylphosphoranylidene) acetate[27] provided, a 3:2(*Z*:*E*) mixture of α,β-unsaturated esters **13** and **14**. A preponderance of the *Z* isomer of the α,β-unsaturated ester product from the Wittig reaction was expected based on our previous work and was a desirable result since the *Z* geometry was expected to be essential for achieving good stereocontrol in the cyclization step later in the synthesis[20,22]. Oxidation[28] of the mixture resulted in conversion of the 6-hydroxyl (numbering as usual for a heptenoate) to the ketone group. The mixture of ketoses (88% overall yield from **12**) was then easily separated by flash chromatography to provide the desired (*Z*)-α,β-unsaturated ester (**15**) in pure form, along with the *E* isomer **16**.

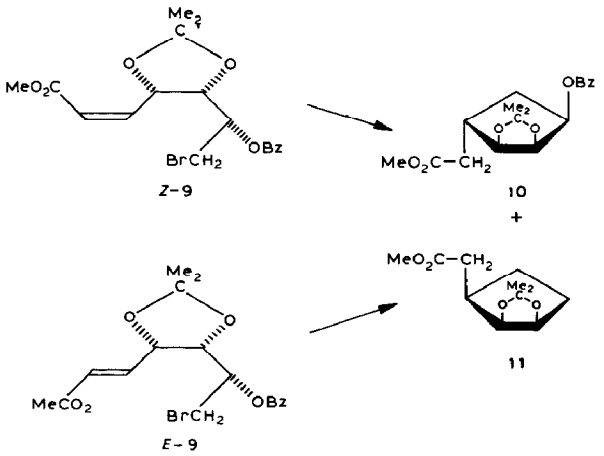
Nucleophilic addition of a synthetic equivalent of the one carbon synthon **V** to ketose **15** (see Scheme 1) was carried out with dibromomethyllithium, which had been used by Taguchi *et al.*[29] for additions to ketones; the geminal dibromide offers a good source for the radical required for cyclization and, thus, combines nucleophilic reac-



1 R = Br
2 R = OCH_2OMe

3 R = H, R′ = Br
4 R = H, R′ = OCH_2OMe
5 R = Me, R′ = OCH_2OMe

6 R = H, R′ = Br
7 R = H, R′ = OCH_2OMe
8 R = Me, R′ = OCH_2OMe



Z-9

10
+
11

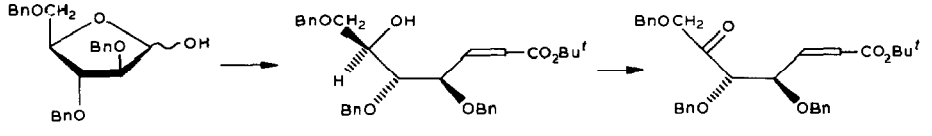
E-9

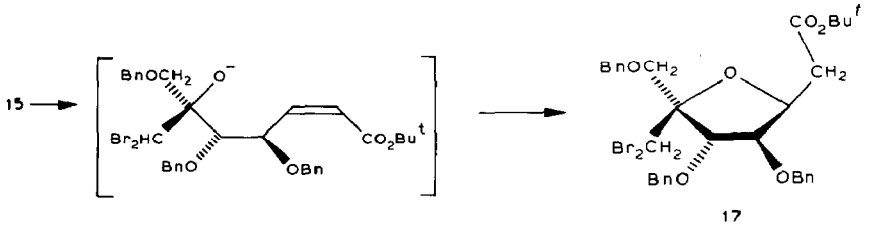
tivity and the potential for radical reactivity. Initial attempts at adding dibromomethyllithium to ketose **15** according to the method of Taguchi *et. al.*[29] provided an anionic intermediate which underwent 1,4-addition and afforded the *C*-glycosyl compound[30] **17**. Performing the addition reaction at $-100°$ and quenching the resulting reaction mixture at low temperature with acetic acid prevented *C*-glycosyl formation but provided (in only 37% yield) a mixture of (*Z* and *E*) α,β,-saturated esters.

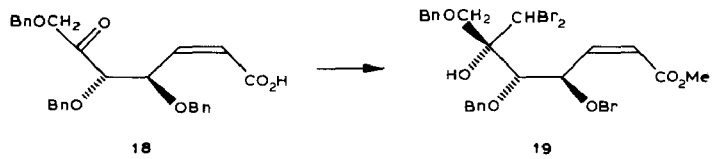
To circumvent the 1,4-addition problem, the α,β-unsaturated ester **15** was converted into its corresponding acid **18** by treatment with trifluoroacetic acid in dichloromethane and used as the lithium carboxylate salt during the nucleophilic addition reaction of dibromomethyllithium. Conversion of the addition product obtained to the methyl ester with diazomethane, followed by flash chromatography, provided a 78% yield of compound **19** along with 22% of the starting material (obtained as the methyl ester). Compound **19** was obtained as a single diastereomer, homogeneous by t.l.c., and ^{1}H-n.m.r. and ^{13}C-n.m.r. spectroscopy. Although no direct proof of stereochemistry was provided at this stage of the synthesis, the Felkin–Ahn type addition was expected since a precedent for this addition of alkyl lithiums to α,β-dibenzyloxyketones exists[31].

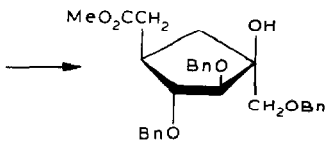
The next step of the synthesis, radical cyclization, was probably the most important since the success of dibromomethane as a synthetic equivalent of the unitive synthon and formation of the carbocyclic framework of the carbohydrate analog

depended on it. When compound **19** was submitted to typical radical cyclization conditions[32], the desired product **20** was isolated in only moderate (50–60%) yield. Attempts to optimize the radical cyclization revealed that this particular reaction was unusual in that it would proceed at room temperature and that the yield of product was highest when the reaction was performed at high concentration and with excess tributyltin hydride. Finally, an 80% yield of product was obtained. Once again the product was as a single diastereomer. Based on the work of Wilcox and Thomasco[20], this high degree of stereocontrol was postulated to have arisen in the transition state from steric interaction of the (*Z*)-α,β-unsaturated ester with the γ-alkoxy substituent. This interaction would result in restricted rotation around the C-3–C-4 bond and lead to rate differences in the addition of the carbon-based radical to one face of the α,β-unsaturated ester over the other. In the radical cyclization of **19**, addition of tributyltin hydride-generated radical to the *re* face of the α,β-unsaturated ester was expected to be favored









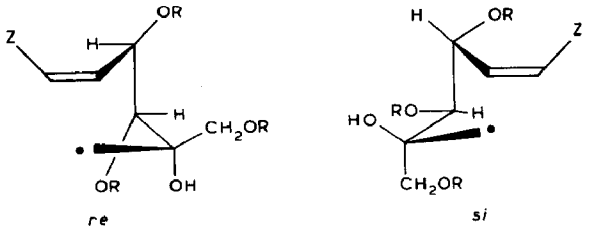


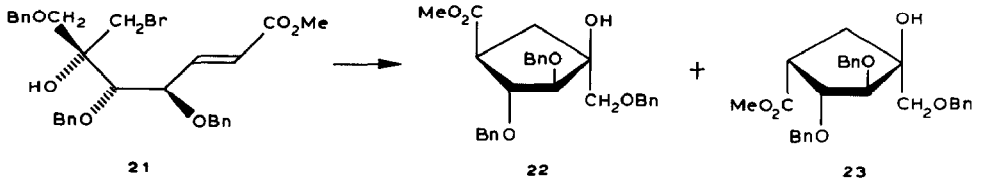
Chart 1.

over addition to the *si* face (Chart 1). The product of radical cyclization **20** was expected to possess all the correct stereochemistry for conversion into a carbocyclic D-fructose derivative. Our model for stereocontrol in the radical cyclization was tested by performing the identical reaction on the (*E*)-α,β-unsaturated ester **21** (prepared from **16** in a manner analogous to the preparation of **19** from **15**). In this reaction, no stereocontrol was observed and a 1:1 ratio of **22** and its diastereomer **23** was obtained. This result is consistent with the model since replacment of the (*Z*)-α,β-unsaturated ester with the (*E*)-α,β-unsaturated ester would eliminate steric interaction between the ester and the γ-benzyloxy group. Because it is this interaction that leads to the selectivity of the process, the result is a loss of stereocontrol in the reaction. Although models rationalizing the stereocontrol seen in the preceeding two reactions seem convincing, definitive proof of the stereochemical relationships depicted in Chart 1 was sought. To establish the relative steric relationship of the two stereocenters generated in the dibromomethyllithium addition and radical cyclization, compound **22** was heated in benzene in the presence of diazabicyclo[5.4.0]undec-7-ene and molecular sieves to provide lactone **24**.

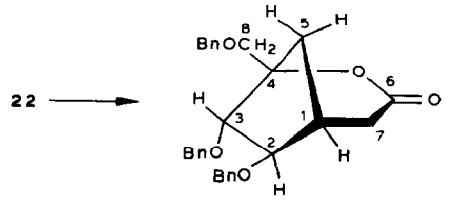
Lactone formation established the relative stereoschemistry of the two centers of interest but the possibility of both stereocenters being inverted would also allow for lactone formation. To rule out this unlikely possibility, n.O.e. experiments[33] were performed. Careful analysis of the n.O.e. enhancements (Table I) led to the conclusion that structure **24** was the only lactone of the two possible whose geometry was consistent with the pattern obtained.

The steric structure of **24** (and thus **22**) being established, only the one carbon degradation of the ester side chain of **22** to give a primary alcohol remained. The Barbier–Wieland degradation of esters[34] was performed and provided the carbocyclic D-fructose derivative **26** in 45% overall yield of isolated product. Complete deprotection to provide the carbocyclic β-D-fructofuranose derivative **27** was accomplished in quantitative yield by hydrogenolysis of **26** in the presence of Pearlman's catalyst[35] and catalytic hydrochloric acid.

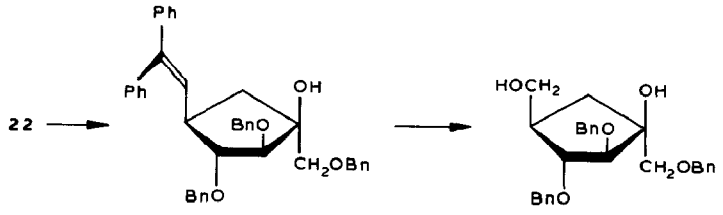
For the synthesis of the carbocyclic β-D-fructofuranose 6-phosphate analog **2**, the choice of the tri-*O*-benzyl protected D-arabinofuranose derivative **13** as starting material was of great advantage because it led directly to a carbocyclic D-fructose derivative **26** that was selectively protected at O-1,3,and 4, leaving OH-2 and -6 D-(fructose carbohydrate numbering) unprotected and available for immediate phosphorylation. The procedure of Chouinard and Bartlett[36] for phosphorylation proved to be particularly



21 22 23



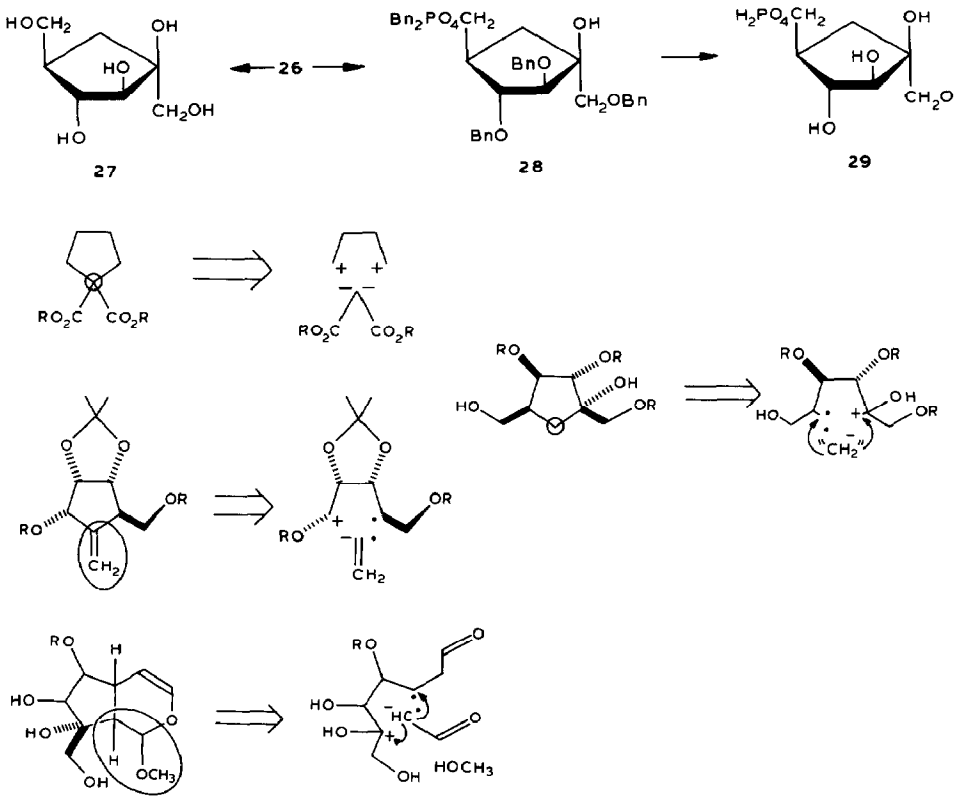
24



25 26

effective. Treatment of an oxolane solution of **26** with butyllithium followed by tetrabenzyl pyrophosphate led to the protected phosphate derivative **28** in 85% yield. Deprotection by the same method used for the deprotection of **26** led to a quantitative yield of the final target, carbocyclic 5-carba-β-D-fructofuranose 6-phosphate (**29**).

In conclusion, the general target **I** of the retrosynthetic Scheme 1 was reduced through two retrosynthetic stages (the disconnection of two carbon–carbon bonds) to the intermediate **IV**. In the forward (synthetic) direction, these two steps were carried out consecutively, and **12** was converted into **22** in two consecutive stereoselective carbon–carbon bond-forming reactions (see Scheme 2). Lithiodibromomethane was shown to be a potent nucleophile and can therefore be incorporated into a substrate by an ionic reaction. In addition, the geminal dibromide can serve as a successive source of two carbon-centered radicals. The use of a geminal dibromide for formation of a cyclopentane ring through radical cyclization may appear to be wasteful, but there is an advantage to this step. A typical side-reaction in such cyclizations is simple reduction of the halide. By use of a geminal dihalide, two opportunities for cyclization were provided. If the first radical that is formed leads to the production of a reduction product, this product still has one bromide group left and, therefore, a second radical may be formed and another chance for cyclization can arise. Ongoing work in our laboratory is directed



Scheme 2.

toward the use of both halide groups for two consecutive carbon–carbon bond formations.

In the creation of **V** from **I**, a single carbon atom was excised and an unbranched, acyclic, polyoxygenated precursor was created. The single carbon atom removed in this instance is unique among all the carbon atoms of the target. It is the only one that, on excision, leaves behind an unbranched acyclic precursor. In the synthetic direction, this carbon atom serves to unite two remote regions of an acyclic chain and, therefore, we have referred to the carbon atom as a "unitive synthon". Lithiodibromomethane is a reagent which is the synthetic equivalent of this unitive synthon.

Unbranched, acyclic, polyoxygenated precursors are readily accessible from carbohydrates and unbranched acyclic molecules are in general rather easily prepared. Retrosynthetic strategies that lead to such intermediates may prove to be economically attractive. We therefore conclude this paper by drawing the reader's attention to a modest heuristic tool that may be useful in the design of synthetic strategies: During the analysis of the carbon skeleton of a synthetic target, be it monocyclic, bicyclic, or polycyclic, it is useful to search for a single carbon or group of carbon atoms which, on excision, will lead to an unbranched and acyclic precursor. We find that, in some cases, further development of the synthetic strategy suggested by this exercise can lead to an

interesting original approach to the chosen target. A few examples of such excisions are illustrated in Scheme 2.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured in a 1-dm cells of 1-mL capacity with Perkin–Elmer model 141 or 241 polarimeters. Infrared spectra were recorded with a Perkin–Elmer 141, a Beckman IR-4, or Matteson Cygnus 100 spectrophotometers. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Nicolet NT-360 MHz, Bruker QM-300 MHz, or Bruker QM-500 MHz spectrometers. High-resolution mass spectra were obtained with either a Dupont (CEC) 21-110B, Varian MAT CH-5, or VG 7070 mass spectrometers.

Gas chromatography was performed with a Varian 3700 gas chromatograph. T.l.c. was performed on Merck Silica Gel 60F-254 (0.25 mm) analytical glass plates. Development of the t.l.c. plates was effected by spraying the plate with either a solution of phosphomolybdic acid (10 g) in ethanol (90 mL); a solution of anisaldehyde (5 mL), of conc. H_2SO_4 (5 mL), and acetic acid (0.5 mL) in ethanol (90 mL); or a solution of $KMnO_4$ (1.5 g), K_2CO_3 (10 g), and 5% NaOH (2.5 mL) in water (150 mL); followed by heating on a hot-plate. Merck Silica Gel 60 (230–400 mesh) was used for flash chromatography which was performed according to the method of Still *et al.*[37].

Yields are reported based on the amount of isolated material obtained following the indicated procedure. The procedures provided homogeneous material as determined by ^{1}H- and ^{13}C-n.m.r. spectrometry, and the purity of these products is therefore estimated to be greater than 95%. Ozonolsis was performed with a Welsbach ozone generator.

Solvents were dried by distillation from the appropriate drying agent under a dry N_2 atmosphere. Oxolan and diethyl ether were distilled from sodium benzophenone. Dichloromethane, toluene, benzene, pentane, triethylamine, and di(isopropyl)amine were distilled from CaH_2. Pyridine was distilled from CaH_2 and stored over KOH pellets. Methanol was distilled from Mg shavings and stored under N_2. Dimethyl sulfoxide was dried over, distilled from, and stored over 4A molecular sieves. Tributyltin hydride and chloromethyl methyl ether were distilled before use. α,α'-Azobis(isobutyronitrile) was recrystallized from dichloromethane. Acetylene gas was purified during use by passage through conc. H_2SO_4, over a 3 × 30 cm column of KOH pellets, and through a dry-ice–acetone cooled trap[2,3,5]. Tri-*O*-benzyl-β-D-arabinofuranose was purchased from Pfanstiehl Laboratories, Inc., Waukegan, Illinois 60085. Lithium diisopropylamide was prepared in powdered form just prior to use according to the method of Ireland[38] and Mueller. *tert*-Butyl 2-(triphenylphosphoranylidene)acetate was prepared according to the method of Griffiths *et al.*,[39]. All other commercially available reagents and solvents were reagent grade and used without further purification. "Removal of solvents under reduced pressure" refers to concentration on a rotary evaporator equipped with a heating bath (< 50°), sometimes followed by further concentration using a high vacuum (< 0,2 kPa) pump.

Elemental analyses were performed by Atlantic Microlabs of Atlanta Georgia.

tert-*Butyl* (Z *and* E)-*4,5,7,tri*-O-*benzyl*-2,3-*dideoxy*-D-threo-*hept-2-en-6-ulosonate* (**15** *and* **16**). — To a stirred solution of *tert*-butyl 2-(triphenylphosphoranylidene) acetate[27] 5.65 g 15.0 mmol) in dichloromethane (12.5 mL) was added 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**12**; 5.26 g, 12.5 mmol) at room temperature under N_2. After 96 h, the mixture was concentrated to a dark-yellow oil under reduced pressure and loaded neat onto a 16 cm × 30 mm column of silica gel pretreated with 1:4 ethyl acetate–hexane. The oil was then diluted with 1:4 ethyl acetate–hexane (20 mL) and passed through the column with 400 mL of solvent. Concentration of the eluent under reduced pressure provided a yellow-green oil (6.57 g, 92%) which was estimated to be a 3:2 *Z*:*E* ratio of α,β-unsaturated esters (**13** and **14**) by ^{1}H-n.m.r. spectroscopy. The mixture could be partially separated by flash chromatography (16 cm × 60 mm column, SiO_2, 1:4 ethyl acetate–hexane) in 1-g batches. For preparative purposes, the *E* and *Z* isomers were used as a mixture.

Z-*Isomer* (**13**). R_F 0.27 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −43.5° (*c* 1.05, chloroform); $\nu_{max}^{CHCl_3}$ 3570, 3090, 3070, 3040, 2980, 2950, 2930, 2870, 1705, 1495, 1455, 1405, 1390, 1370, 1245, 1235, 1210, 1155, 1090, 1070, and 1030 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.32–7.23 (m, 15 H), 6.27 (dd, 1 H, *J* 11.5, *J* 8.1 Hz), 5.80 (d, 1 H, *J* 11 Hz), 5.36 (dd, 1 H, *J* 8, *J* 2 Hz), 4.60 (d, 1 H, *J* 12 Hz), 4.56 (d, 1 H, *J* 12 Hz), 4.53 (d, 1 H, *J* 12 Hz), 4.52 (d, 1 H, *J* 12 Hz), 4.47 (d, 1 H, *J* 12 Hz), 4.41 (d, 1 H, *J* 12 Hz), 4.06 (m, 1 H), 3.74 (dd, 1 H, *J* 4.1, *J* 2.2 Hz), 3.66 (dd, 1 H, *J* 2.2, *J* 8 Hz), 3.60 (dd, 1 H, *J* 8, *J* 3.1 Hz), 2.82 (d, 1 H, *J* 4 Hz), and 1.44 (s, 9 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 165.2, 146.2, 138.4, 138.3, 138.0, 128.4, 128.3, 128.0, 127.5, 124.3, 81.3, 80.9, 74.8, 74.3, 73.7, 71.8, 71.4, 70.7, and 28.2.

Anal. Calc. for $C_{32}H_{38}O_6$: C, 74.11; H, 7.38. Found: C, 73.96; H, 7.43.

E-*Isomer* (**14**). R_F 0.10 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −13.8° (*c* 1.01, chloroform); $\nu_{max}^{CHCl_3}$ 3550, 3031, 3013, 2983, 2931, 2870, 1708, 1455, 1369, 1310, 1256, 1155, 1094, and 1073 cm^{-1}; ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.37–7.20 (m, 15 H), 6.92 (dd, 1 H, *J* 15.7, *J* 6.1 Hz), 6.03 (d, 1 H, *J* 15.9 Hz), 4.65 (d, 1 H, *J* 11.9 Hz), 4.55 (d, 1 H, *J* 11.4 Hz), 4.50 (s, 2 H), 4.49 (d, 1 H, *J* 11.4 Hz), 4.38 (d, 1 H, *J* 11.8 Hz), 4.28 (dd, 1 H, *J* 7.7, *J* 6.1 Hz), 3.97 (ddd, 1 H, *J* 5.2, *J* 4.0, *J* 3.6 Hz), 3.62 (dd, 1 H, *J* 7.7 Hz, *J* 3.6 Hz), 3.60 (d, 2 H, *J* 4 Hz), 2.64 (d, 1 H, *J* 5.2 Hz), and 1.50 (s, 9 H); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 165.3, 143.9, 138.0, 137.8, 137.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 125.3, 80.7, 80.0, 78.0, 74.3, 73.5, 71.9, 70.8, 70.6, 70.2, and 28.2.

To a stirred solution of oxalyl chloride (1.94 g, 12.7 mmol) in dichloromethane (50 mL) at −60° under N_2 was added dimethyl sulfoxide (1.99 g, 15.4 mmol) in dichloromethane (25 mL) over 30 min by dropping funnel. After stirring for 10 min, the mixture of alcohols **13** and **14** (5.50 g, 10.6 mmol) was added in dichloromethane (25 mL) over 30 min by dropping funnel. After 45 min, triethylamine (6.44 g, 53.0 mmol) was added neat over 10 min by dropping funnel. The cooling bath was then removed and the mixture allowed to warm to room temperature. Water (75 mL) was then added resulting in a two-phase solution. The aqueous phase was isolated and extracted with dichloromethane (1 × 75 mL). The combined organic extracts were washed with water (3 × 200

mL) and with saturated NaCl solution (1 × 200 mL). The combined extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant yellow oil was then pre-flash chromatographed (16 cm × 30 mm column, SiO_2, 1:4 ethyl acetate–hexane) to provide, after concentration under reduced pressure, a pure product ketone (5.00 g, 90%) as a mixture of *E*- (**16**) and *Z*-isomers (**15**). Flash chromatography (16 cm × 60 mm column, SiO_2, 1:4 ethyl acetate–hexane) in 1-g batches gave 2.50 g of chromatographically pure *Z*-isomer (**15**), 1.80 g of pure *E*-isomer (**16**), and 0.70 g of a mixture of *E*- and *Z*-isomers.

Z-Isomer (**15**). R_F 0.37 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −55.5° (*c* 1.15, chloroform); $\nu_{max}^{CHCl_3}$ 3040, 2930, 1733, 1710, 1500, 1455, 1410, 1395, 1370, 1335, 1305, 1240, 1215, 1160, 1110, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.32–7.20 (m, 15 H), 6.20 (dd, 1 H, *J* 11.5, *J* 8.1 Hz), 5.80 (d, 1 H, *J* 11 Hz), 5.37 (dd, 1 H, *J* 8.8, *J* 3.7 Hz), 4.58 (d, 1 H, *J* 12.1 Hz), 4.52 (d, 1 H, *J* 12.1 Hz), 4.49 (d, 1 H, *J* 12.0 Hz), 4.44 (d, 1 H, *J* 12.2 Hz), 4.42 (d, 1 H, *J* 12.2 Hz), 4.31 (d, 1 H, *J* 18.3 Hz), 4.31 (d, 1 H, *J* 12 Hz), 4.19 (d, 1 H, *J* 3.4 Hz), and 1.43 (s, 9 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 205.2, 164.9, 144.5, 137.7, 137.5, 137.0, 128.4, 128.3, 128.0, 127.8, 127.6, 125.0, 85.7, 81.4, 75.9, 74.5, 74.4, 73.3, 71.9, and 28.2. M.s.: Calc. for $C_{17}H_{18}O_3$ ($M^+ - C_{15}H_{18}O_3$): *m/z* 270.1256. Found: *m/z* 270.1248.

E-*Isomer* (**16**). R_F 0.33 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −59° (*c* 1.07, chloroform); $\nu_{max}^{CHCl_3}$ 3627, 3619, 3613, 3029, 3016, 2979, 2932, 2897, 2889, 2876, 1732, 1710, 1497, 1456, 1394, 1370, 1309, 1254, 1242, 1229, 1219, 1211, 1155, 1111, 1103, 1092, 1080, and 1046 cm^{-1}; ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.36–7.21 (m, 15 H), 6.81 (dd, 1 H, *J* 15.9, *J* 6.6 Hz), 5.97 (d, 1 H, *J* 16.7 Hz), 4.60 (d, 1 H, *J* 11.8 Hz), 4.58 (d, 1 H, *J* 11.7 Hz), 4.49 (d, 1 H, *J* 12.0 Hz), 4.44 (d, 1 H, *J* 11.4 Hz), 4.40 (d, 1 H, *J* 11.7 Hz), 4.37 (dd, 1 H, *J* 6.6, *J* 3.1 Hz), 4.33 (d, 1 H, *J* 12.0 Hz), 4.28 (d, 1 H, *J* 12.0 Hz), 4.27 (d, 1 H, *J* 11.7 Hz), 4.00 (d, 1 H, *J* 3.1 Hz), and 1.51 (s, 9 H); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 206.9, 164.9, 142.2, 137.2, 136.9, 136.4, 128.5, 128.4, 128.3, 128.2, 127.9, 126.2, 84.5, 80.8, 78.7, 74.5, 74.2, 73.3, 71.9, and 28.1.

tert-*Butyl 3,6-anhydro-4,5,7-tri*-O-*benzyl-2-deoxy-6*-C-(*dibromomethyl*)-L-xylo-*heptonate* (**17**). — To a stirred solution of ketone **15** (165 mg, 0.32 mmol) in oxolane (2.5 mL) at room temperature under N_2 was added dibromomethane (66 mg, 0.38 mmol). After being cooled to −78°, the mixture was treated with lithium diisopropylamide (37 mg, 0.35 mmol) in oxolane (2.5 mL) by cannulation. After being stirred for 1 h at −78°, the pale-yellow solution was treated with methanol (500 μL) and warmed to 0°. The now bright-yellow solution was diluted with ether (25 mL) and washed with 10% HCl solution (2 × 25 mL), with saturated $NaHCO_3$ solution (2 × 25 mL), and with saturated NaCl solution (1 × 25 mL). The organic extract was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield **17** (205 mg, 93%) of greater than 95% purity as judged by n.m.r. spectroscopy, R_F 0.25 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −8.5° (*c* 1.08, chloroform); $\nu_{max}^{CHCl_3}$ 3075, 3015, 2985, 2935, 2880, 1720, 1498, 1455, 1395, 1370, 1320, 1293, 1258, 1160, 1110, 1075, and 1030 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.34–7.26 (m, 15 H), 6.10 (s, 1 H), 4.84 (d, 1 H, *J* 11.1 Hz), 4.66 (d, 1 H, *J* 11.1 Hz), 4.66 (d, 1 H, *J* 8.5 Hz), 4.59 (d, 1 H, *J* 3.4 Hz), 4.57 (d, 1 H, *J* 3.4 Hz), 4.54

(d, 1 H, *J* 8.5 Hz), 4.49 (m, 1 H), 4.15 (dd, 1 H, *J* 8.2, *J* 8.0 Hz), 3.92 (d, 1 H, *J* 10.4 Hz), 3.73 (d, 1 H, *J* 10.4 Hz), 2.56 (dd, 1 H, *J* 15.5, *J* 4.1 Hz), 2.38 (dd, 1 H, *J* 15.4, *J* 7.3 Hz), and 1.43 (s, 9 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 169.6, 138.2, 138.0, 128.6, 128.5, 128.0, 127.9, 127.7, 87.2, 86.5, 86.1, 80.9, 77.4, 74.0, 73.1, 71.4, 50.4, 40.1, and 28.2. M.s.: Calc. for $C_{22}H_{23}Br_2O_6$ ($M^+ - C_{11}H_{16}$): *m/z* 540.9861. Found: *m/z* 540.9861.

Anal. Calc. for $C_{33}H_{38}Br_2O_6$: C, 57.40; II, 5.55. Found: C, 57.49; H, 5.58.

(Z)-*4,5,7-Tri*-O-*benzyl-2,3-dideoxy*-D-threo-*hept-2-en-6-ulosonic acid* (**18**). — To a stirred solution of the (*Z*)-α,β-unsaturated ester **15** (2.06g, 3.98 mmol) in dichloromethane (5.5 mL) at 0° under N_2 was added trifluoroacetic acid (4.54 g, 72.0 mmol) by pipette. After 3.5 h, the green mixture was diluted to 60 mL with dichloromethane and washed with water (5 × 60 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This was dissolved in ether (15 mL) and extracted with 6% $KHCO_3$ (9 × 15 mL). After each extraction, pentane (3 mL) was added to the ether layer to help force the product into the aqueous phase. The combined aqueous extracts were washed with pentane (2 × 100 mL), and then diluted to 1:1 with dichloromethane, cooled in an ice bath, stirred, and acidified to pH <2.5 with 10% HCl solution. The organic phase was then isolated and the aqueous phase extracted with dichloromethane (1 × 200 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated to provide pure **18** (1.63 g, 89%), $[\alpha]_D^{22}$ −24° (*c* 1.09, chloroform); $\nu_{max}^{CHCl_3}$ 3080, 3030, 2950, 2895, 1740, 1705, 1660, 1505, 1460, 1440, 1230, 1115, 1075, and 1035 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.33–7.13 (m, 15 H), 6.41 (dd, 1 H, *J* 11.9, *J* 8.4 Hz), 5.91 (d, 1 H, *J* 11.7 Hz), 5.42 (dd, 1 H, *J* 7.9, *J* 2.2 Hz), 4.58 (d, 1 H, *J* 11.8 Hz), 4.52 (d, 1 H, *J* 11.8 Hz), 4.49 (d, 1 H, *J* 11.6 Hz), 4.44 (d, 1 H, *J* 11.6 Hz), 4.40 (d, 1 H, *J* 11.8 Hz), 4.34 (d, 1 H, *J* 11.8 Hz), 4.34 (d, 1 H, *J* 14 Hz), 4.28 (d, 1 H, *J* 14 Hz), and 4.24 (d, 1 H, *J* 2.2 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 195.1, 169.8, 148.8, 137.6, 136.9, 128.6, 128.5, 128.4, 128.0, 122.0, 85.4, 76.1, 74.6, 74.4, 73.5, and 72.4. M.s.: Calc. for $C_{28}H_{28}O_6$ (M^+): *m/z* 460.1886. Found: *m/z* 460.1905.

Anal. Calc. for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.81; H, 6.16.

Methyl (Z)-*4,5,7-tri*-O-*benzyl-2,3-dideoxy-6*-C-*(dibromomethyl)*-L-xylo-*hept-2-enonate* (**19**). – To a stirred solution of the (*Z*)-α,β unsaturated acid **18** (2.18g, 4.72 mmol) in oxolane (9.4 mL) at −78° under N_2 was added a solution of lithium diisopropylamide (0.505 g, 4.72 mmol) in oxolane (9.4 mL) by cannulation. To the resultant bright yellow-green solution was added dibromomethane (2.46 g, 14.2 mmol). To the resultant solution was then added lithium diisopropylamide (1.51 g, 14.2 mmol) in oxolane (28 mL) by slow cannulation over 30 min. After 2 h, the brown mixture was treated with 4:1 oxolane–acetic acid (2.8 mL). Without warming, the mixture was poured into 1:1 ether–10% HCl (400 mL) and shaken. The organic extract was separated and the aqueous solution extracted with ether (1 × 50 mL). The organic extract was then washed with 10% HCl (1 × 250 mL), with water (2 × 250 mL), and with saturated NaCl solution (1 × 250 mL), dried ($MgSO_4$), and filtered. The ether solution was then cooled on an ice bath and stirred. Freshly distilled ethereal diazomethane (2.70 g, 50.0 mmol) was then added dropwise. The solution was then concentrated under reduced pressure to an orange oil, pre-flash chromatographed (16 cm × 30

mm column, SiO_2, 1:4 ethyl acetate–hexane), and then flash-chromatographed (16 cm × 60 mm column, SiO_2, 1:4 ethyl acetate–hexane) in 1-g batches to give **19** (2.49 g, 78%). R_F 0.43 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −38.5° (*c* 1.00, chloroform); $\nu_{max}^{CHCl_3}$ 3460, 3100, 3080, 3040, 3020, 2960, 2940, 2870, 1740, 1650, 1500, 1455, 1440, 1400, 1345, 1200, 1100, and 1005 cm^{-1}; ^1H-n.m.r. (360 MHz, $CDCl_3$): δ 7.33–7.22 (m, 15 H), 6.43 (dd, 1 H, *J* 11.8, *J* 8.7 Hz), 5.94 (s, 1 H), 5.92 (d, 1 H, *J* 11.8 Hz), 5.65 (dd, 1 H, *J* 8.7, *J* 3.2 Hz), 4.67 (s, 2 H), 4.57 (d, 1 H, *J* 11.7 Hz), 4.53 (d, 1 H, *J* 11.8 Hz), 4.48 (d, 1 H, *J* 11.8 Hz), 4.42 (d, 1 H, *J* 10.9 Hz), 4.36 (s, 1 H), 4.28 (d, 1 H, *J* 3.2 Hz), 3.92 (d, 1 H, *J* 12 Hz), 3.88 (d, 1 H, *J* 12 Hz), and 3.68 (s, 3 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 166.3, 147.4, 138.1, 137.4, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 122.1, 81.9, 78.6, 75.2, 73.7, 71.7, 71.0, 53.1, 51.7, and 29.8. M.s.: Calc. for $C_{23}H_{25}O_6Br_2$ ($M^+ - C_7H_7$): *m/z* 555.0018. Found: *m/z* 555.0041; In addition, the methyl ester (0.510 g, 22%) of the starting material **18** was recovered.

Methyl (1R,2R,3S,4S)-2,3-bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanylacetate (**20**). – To a stirred solution of **19** (2.35 g, 3.80 mmol) in benzene (5.1 mL) at room temperature under N_2 was added tributyltin hydride (5.50 g, 19.0 mmol), followed by α,α′-azobis(isobutyronitrile) (6.2 mg, 0.04 mmol). After 4 h, the mixture was concentrated under reduced pressure, diluted with 1:1 acetonitrile–hexane (120 mL), shaken, and the acetonitrile solution isolated. It was then washed with hexane (2 × 60 mL) and concentrated under reduced pressure to give **20** (1.42 g, 80%), R_F 0.53 (SiO_2, 2:3 ethyl acetate–hexane), $[\alpha]_D^{22}$ +19.6° (*c* 1.01, chloroform); $\nu_{max}^{CHCl_3}$ 3550, 3100, 3080, 3020, 2970, 2940, 2880, 1735, 1610, 1500, 1455, 1440, 1360, 1230, 1180, 1100, 1065, 1030, and 1000 cm^{-1}; ^1H-n.m.r. (360 MHz, $CDCl_3$): δ 7.32–7.23 (m, 15 H), 4.66 (s, 2 H), 4.65 (d, 1 H, *J* 8.4 Hz), 4.56 (d, 1 H, *J* 8.4 Hz), 4.53 (s, 2 H), 3.89 (d, 1 H, *J* 6.9 Hz), 3.76 (dd, 1 H, *J* 7.2, *J* 7.2 Hz), 3.61 (s, 3 H), 3.35 (dd, 2 H, *J* 13.3, *J* 8.9 Hz), 2.97 (s, 1 H), 2.60 (dd, 1 H, *J* 4.2, *J* 15 Hz), 2.36 (dd, 1 H, *J* 15, *J* 8.3 Hz), 2.24 (m, 2 H), and 1.46 (m, 1 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 172.9, 138.6, 138.1, 128.4, 128.1, 127.9, 127.7, 88.1, 86.2, 76.6, 74.8, 73.6, 73.5, 72.7, 51.5, 38.8, and 36.0. M.s.: Calc. for $C_{23}H_{27}O_6$ ($M^+ - C_7H_7$): *m/z* 399.1808. Found: *m/z* 399.1816.

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.56; H, 7.01.

Methyl (E)-*4,5,7-tri*-O-*benzyl-2,3-dideoxy-6*-C-*(dibromomethyl)*-L-xylo-*hept-2-enonate* (**21**). — Ester **16** was first deprotected to provide (*E*)-4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-*threo*-hept-2-enoic acid as follows. To a stirred solution of **16** (485 mg, 0.94 mmol) in dichloromethane (1.3 mL) at 0° under N_2 was added trifluoroacetic acid (1.93 g, 16.9 mmol) by pipette. After 3.5 h, the green mixture was diluted to 30 mL with dichloromethane and washed with water (5 × 30 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This was dissolved in ether (10 mL) and extracted with 6% $KHCO_3$ solution (9 × 10 mL). After each extraction, pentane (1 mL) was added to force the product into the aqueous phase. The combined aqueous extracts were washed with pentane (2 × 50 mL), then diluted to 1:1 with dichloromethane, cooled in an ice bath, stirred, and acidified to pH < 2.5 with 10% HCl. The organic phase was separated and the aqueous phase extracted with dichloromethane (1 × 100 mL). The combined organic extracts were dried

($MgSO_4$), filtered, and concentrated to provide the (*E*)-α,β-unsaturated acid (379 mg, 88%), $[\alpha]_D^{22}$ −70° (*c* 1.02, chloroform); $\nu_{max}^{CHCl_3}$ 3027, 3014, 2977, 2933, 2895, 1733, 1730, 1721, 1702, 1687, 1656, 1455, 1420, 1395, 1391, 1230, 1225, 1211, 1205, 1107, 1079, 1045, and 1029 cm^{-1}; ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.37–7.22 (m, 15 H), 6.99 (dd, 1 H, *J* 15.8, *J* 6.0 Hz), 6.08 (d, 1 H, *J* 15.9 Hz), 4.60 (d, 1 H, *J* 11.8 Hz), 4.58 (d, 1 H, *J* 11.5 Hz), 4.50 (d, 1 H, *J* 11.9 Hz), 4.44 (d, 1 H, *J* 11.8 Hz), 4.43 (m, 1 H), 4.41 (d, 1 H, *J* 11.9 Hz), 4.33 (d, 1 H, *J* 11.5 Hz), 4.30 (s, 2 H), and 4.04 (d, 1 H, *J* 3.2 Hz); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 206.8, 170.5, 146.2, 137.0, 136.6, 136.2, 128.5, 128.4, 128.1, 127.9, 123.3, 83.9, 78.5, 74.4, 74.2, 73.2, and 72.2.

To a stirred solution of the just described (*E*)-α,β-unsaturated acid (340 mg, 0.74 mmol) in oxolane (1.5 mL) at −78° under N_2 was added a solution of lithium diisopropylamide (79.0 mg, 0.74 mmol) in oxolane (1.5 mL) by cannulation. To the resultant bright yellow-green solution were added dibromomethane (257 mg, 1.5 mol), and then lithium diisopropylamide (160 mg, 1.5 mmol) in oxolane (3 mL) by slow cannulation. After 2 h, the mixture was treated with oxolane–4:1 acetic acid (300 μL). Without warming, the mixture was poured into 1:1 ether–10% HCl (60 mL) and shaken. The organic extract was separated and the aqueous solution extracted with ether (1 × 30 mL). The combined organic extracts were washed with 10% HCl (1 × 30 mL), water (2 × 30 mL), and saturated NaCl solution (1 × 30 mL), dried ($MgSO_4$), and filtered. The filtrate was cooled in an ice bath, stirred, and fresly distilled ethereal diazomethane (210 mg, 5 mmol) added dropwise. The solution was concentrated under reduced pressure to give an orange oil which was flash-chromatographed (16 cm × 60 mm column, SiO_2, 1:4 ethyl acetate–hexane) to yield **21** (257 mg, 55%), R_F 0.21 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ −23.5° (*c* 1.02, chloroform); $\nu_{max}^{CHCl_3}$ 3476, 3458, 3449, 3067, 3030, 3013, 2953, 2870, 1721, 1455, 1438, 1282, 1253, 1228, 1219, 1205, 1173, 1101, and 1028 cm^{-1}; ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 15 H), 7.10 (dd, 1 H, *J* 15.8, *J* 6.4 Hz), 6.09 (d, 1 H, *J* 15.8 Hz), 5.80 (s, 3 H), 4.68 (s, 2 H), 4.64 (d, 1 H, *J* 11.7 Hz), 4.53 (d, 1 H, *J* 11.8 Hz), 4.51 (m, 1 H), 4.48 (d, 1 H, *J* 11.7 Hz), 4.41 (d, 1 H, *J* 11.6 Hz), 4.22 (d, 1 H, *J* 3.9 Hz), 3.95 (s, 1 H), 3.91 (d, 1 H, *J* 10.2 Hz), 3.84 (d, 1 H, *J* 10.1 Hz), and 3.76 (s, 3 H); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 166.3, 145.3, 137.6, 136.9, 128.7, 128.5, 128.4, 128.1, 127.9, 123.0, 80.9, 78.5, 78.2, 75.2, 73.6, 71.8, 70.4, 52.8, and 51.8. M.s.: Calc. for $C_{23}H_{25}O_6Br_2$ ($M^+ - C_7H_7$): *m/z* 556.9997. Found: *m/z* 556.9998.

Radical cyclization of (E)*-olefin* **21** *to give methyl (1*S*,2*R*,3*S*,4*S*)-2,3-bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanyl-acetate* (**23**) *and methyl (1*R*,2*R*,3*S*,4*S*)-2,3-bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanylacetate* (**22**). — To a stirred solution of **21** (212 mg, 0.34 mmol) in benzene (0.45 mL) at room temperature under N_2 was added tributyltin hydride (495 mg, 1.7 mmol), followed by α,α′-azobis(isobutyronitrile) (1 mg, 6 μmol). After 4 h, the mixture was concentrated under reduced pressure and then diluted with 1:1 acetonitrile–hexane (60 mL), and shaken. The acetonitrile solution was separated, washed with hexane (2 × 30 mL) and concentrated under reduced pressure to give a mixture of carbocyclic products (153 mg, 90%). H.p.l.c. (SiO_2, 3:17 ethyl acetate–hexane) provided a pure sample of ester **23**, ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.30–7.19 (m, 15 H), 4.66 (d, 1 H, *J* 11.5 Hz), 4.60 (d, 1

H, *J* 11.7 Hz), 4.52 (s, 2 H), 4.42 (d, 1 H, *J* 11.8 Hz), 4.35 (d, 1 H, *J* 11.8 Hz), 3.99 (dd, 1 H, *J* 4.0, *J* 2.2 Hz), 3.88 (d, 1 H, *J* 4.0 Hz), 3.60 (s, 3 H), 3.40 (d, 1 H, *J* 9.4 Hz), 3.32 (d, 1 H, *J* 9.4 Hz), 3.17 (s, 1 H), 2.81 (m, 1 H), 2.58 (dd, 1 H, *J* 7.6, *J* 16.0 Hz), 2.30 (dd, 1 H, *J* 7.4, *J* 16.0 Hz), 1.90 (dd, 1 H, *J* 7.5, *J* 13.4 Hz), and 1.68 (dd, 1 H, *J* 9.5, *J* 13.7 Hz).

(1R,2R,3S,4S)-2,3-Bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanylacetic acid-1,4-lactone (**24**). — To a stirred solution of **22** (109 mg, 0.22 mmol) in benzene (4.4 mL) at room temperature under N_2 was added diazabicyclo[5.4.0]undec-7-ene (7.0 mg, 0.04 mmol) and 4A molecular sieves (20 mg). After being heated to reflux, the mixture was stirred for 72 h, and then diluted with benzene (100 mL), treated with Celite (5 g), filtered, and concentrated under reduced pressure. The crude product was flash-chromatographed (16 cm × 15 mm column, SiO_2, 3:7 ethyl acetate–hexane) to yield, after concentration under reduced pressure, **24** (59 mg, 60%), R_F 0.28 (SiO_2, 2:3 ethyl acetate–hexane), $[\alpha]_D^{22}$ −15° (*c* 1.14, chloroform); $\nu_{max}^{CHCl_3}$ 3100, 3080, 3030, 2960, 2930, 2880, 1740, 1500, 1455, 1415, 1395, 1365, 1335, 1280, 1250, 1200, 1095, 1045, 1030, 1000, and 975 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.37–7.25 (m, 15 H), 4.59 (d, 1 H, *J* 11.7 Hz), 4.57 (d, 1 H, *J* 11.9 Hz), 4.50 (d, 1 H, *J* 11.9 Hz), 4.49 (d, 1 H, *J* 11.4 Hz), 4.47 (d, 1 H, *J* 11.7 Hz), 4.41 (d, 1 H, *J* 11.4 Hz), 3.98 (s, 1 H), 3.72 (s, 1 H), 3.69 (d, 1 H, *J* 10.6 Hz), 3.59 (d, 1 H, *J* 10.6 Hz), 2.77 (dd, 1 H, *J* 18.9, *J* 6.2 Hz), 2.55 (d, 1 H, *J* 18.9 Hz), 2.44 (dd, 1 H, *J* 6.1, *J* 4.3 Hz), 2.32 (dd, 1 H, *J* 14.4, *J* 4.3 Hz), and 1.87 (d, 1 H, *J* 14.4 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 168.9, 137.9, 128.6, 128.5, 128.0, 127.8, 88.8, 88.3, 87.1, 73.8, 72.5, 71.4, 71.3, 60.4, 36.6, 35.9, and 34.1. M.s.: Calc. for $C_{29}H_{30}O_5$ (M^+): *m/z* 458.2093. Found: *m/z* 458.2105.

Anal. Calc. for $C_{23}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 77.75; H, 6.56.

(1S,2S,3R,4R)-2,3-Bis(benzyloxy)-1-[(benzyloxy)methyl]-4-(2,2-diphenylvinyl)cyclopentanol (**25**). — To a stirred solution of **22** (1.60 g, 3.26 mmol) in oxolane (52.5 mL) at 0° under $N_2$was added phenylmagnesium bromide (5.19 g, 32.6 mmol) by dropping funnel as a solution in ether (98 mL). After the addition was complete, the mixture was allowed to warm to room temperature for 16 h, and then cooled to ice-bath temperature and treated with saturated NH_4Cl solution (15 mL). The mixture was then diluted to 400 mL with 2:1 dichloromethane–saturated NH_4Cl solution and shaken. The dichloromethane layer was isolated and the aqueous phase extracted with dichloromethane (1 × 100 mL). The combined organic extract was washed with saturated $NaHCO_3$ solution (1 × 150 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow-green oil. This was stirred in 5:1 acetic acid–water (44 mL) and heated at reflux for 6 h. The mixture was then concentrated under reduced pressure and the brown residue dissolved in dichloromethane (10 mL). The acid was neutralized by careful addition of saturated $NaHCO_3$ solution, and the resultant two-phase solution was diluted to 100 mL with 1:1 dichloromethane–saturated $NaHCO_3$ solution and shaken. The organic phase was separated and washed with saturated $NaHCO_3$ solution (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Pre-flash chromatography (16 cm × 30 mm column, SiO_2, 1:4 ethyl acetate–hexane) provided, after concentration under reduced pressure, a yellow-green oil which was flash-chromatographed (16 cm × 60 mm column, SiO_2, 1:4 ethyl acetate–hexane) in 1-g batches to

provide, after concentration under reduced pressure, **25** (1.36 g, 70%), R_f 0.36 (SiO_2, 1:4 ethyl acetate–hexane), $[\alpha]_D^{22}$ +35° (*c* 1.01, chloroform); $\nu_{max}^{CHCl_3}$ 3540, 3080, 3060, 3025, 3005, 2930, 2860, 1495, 1455, 1355, 1090, and 1055 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.36–7.15 (m, 25 H), 6.11 (d, 1 H, *J* 10.3 Hz), 4.73 (d, 1 H, *J* 11.5 Hz), 4.65 (d, 1 H, *J* 11.6 Hz), 4.63 (d, 1 H, *J* 11.5 Hz), 4.55 (d, 1 H, *J* 11.6 Hz), 4.48 (d, 1 H, *J* 12.0 Hz), 4.43 (d, 1 H, *J* 12.0 Hz), 4.05 (dd, 1 H, *J* 7.8, *J* 7.8 Hz), 3.80 (d, 1 H, *J* 7.6 Hz), 3.29 (d, 1 H, *J* 13.4 Hz), 3.26 (d, 1 H, *J* 13.4 Hz), 3.00 (s, 1 H), 2.73 (m, 1 H), 2.16 (dd, 1 H, *J* 14.1, *J* 9.6 Hz), and 1.68 (dd, 1 H, *J* 14.2, *J* 8.2 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 142.6, 141.9, 140.0, 138.4, 138.3, 133.0, 130.0, 129.0, 128.8, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.2, 127.2, 89.4, 85.3, 76.8, 76.2, 74.6, 73.6, 73.5, 72.6, 40.3, and 39.5. M.s.: Calc. for $C_{41}H_{40}O_4$ (M^+): *m/z* 596.2926. Found: *m/z* 596.2951.

Anal. Calc. for $C_{41}H_{40}O_4$: C, 82.52; H, 6.76. Found: C, 82.41; H, 6.76.

(1R,2R,3S,4S)-2,3-Bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanylmethanol (**26**). — To a stirred solution of **25** (191 mg, 0.32 mmol)in 9:1 methanol–dichloromethane (20 mL) at −78° was added a stream of O_3 gas until the solution was just blue. The solution was then purged with N_2 to remove excess O_3 and treated with $NaBH_4$ (60.0 mg, 1.6 mmol) under N_2. The cooling bath was then removed and the reaction allowed to warm to room temperature. After 1 h, the solution was concentrated to a solid under reduced pressure, stirred in dichloromethane (50 mL), and treated with 1% HCl (15 mL). After 15 min, the organic solution was separated, washed with saturated $NaHCO_3$ solution (1 × 50 mL), dried ($MgSO_4$), filtered, concentrated to an oil under reduced pressure, and flash-chromatographed (16 cm × 20 mm column, SiO_2, 3:2 ethyl acetate–hexane) to yield, after concentration under reduced pressure, **26** (102 mg, 72%), R_f 0.34 (SiO_2, 3:2 ethyl acetate–hexane), $[\alpha]_D^{22}$ +16.5° (*c* 1.09, chloroform); $\nu_{max}^{CHCl_3}$ 3530, 3090, 3070, 3030, 3010, 2930, 2870, 1495, 1455, 1360, 1260, 1095, 1075, and 1030 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.38–7.18 (m, 15 H), 4.67 (d, 1 H, *J* 11.4 Hz), 4.63 (d, 1 H, *J* 11.4 Hz), 4.61 (s, 2 H), 4.53 (d, 1 H, *J* 12 Hz), 4.47 (d, 1 H, *J* 12 Hz), 4.06 (dd, 1 H, *J* 6.7, *J* 6.7 Hz), 3.97 (d, 1 H, *J* 6.9 Hz), 3.66 (d, 2 H, *J* 4.7 Hz), 3.36 (d, 1 H, *J* 9.5 Hz), 3.34 (d, 1 H, *J* 9.5 Hz), 2.19 (dd, 1 H, *J* 10.4, *J* 22.8 Hz), 2.16 (m, 1 H), 1.53 (dd, 1 H, *J* 12.8, *J* 4.2 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 138.6, 138.2, 128.4, 128.1, 127.8, 86.4, 86.2, 77.6, 73.6, 73.2, 72.4, 65.4, 42.1, and 34.5. M.s.: Calc. for $C_{21}H_{25}O_5$ ($M^+ - C_7H_7$): *m/z* 357.1702. Found: *m/z* 357.1695.

(1R,2R,3S,4S)-2,3,4-Trihydroxy-4(hydroxymethyl)cyclopentanylmethanol (**27**). — To a solution of **26** (90 mg, 0.2 mmol) in absolute ethanol (4 mL) was added Pearlman's catalyst[35] (14 mg, 0.02 mmol) and 10% HCl (40 μL). The mixture was shaken on a Parr shaker under H_2 gas for 15 h under a pressure of 0.4 MPa. Pearlman's catalyst was removed by filtration through glass wool and the solution was concentrated under reduced pressure to give a pale-yellow oil. Water (10 mL) was added and lyophilized three times to yield **27** (35 mg, 100%), $[\alpha]_D^{22}$ +36° (*c* 0.38, water); ^{1}H-n.m.r. (360 MHz, D_2O): δ 3.82 (dd, 1 H, *J* 8.7, *J* 8.8 Hz), 3.75 (dd, 1 H, *J* 5, *J* 11 Hz), 3.67 (d, 1 H, *J* 8.7 Hz), 3.58 (dd, 1 H, *J* 7.3, *J* 11.0 Hz), 3.51 (s, 2 H), 2.16 (dd, 1 H, *J* 10, *J* 14.6 Hz), 1.89 (m, 1 H), and 1.45 (dd, 1 H, *J* 7.6, *J* 14.6 Hz); ^{13}C-n.m.r. (90 MHz, D_2O): δ 81.3, 80.3, 79.2, 68.8, 66.4, 44.0, and 36.2.

Dibenzyl (1R,2R,3S,4S)-2,3-bis(benzyloxy)-4-[(benzyloxy)methyl]-4-hydroxycyclopentanylmethyl phosphate (**28**). — To a stirred solution of the diol **26** (150 mg, 0.33 mmol) in oxolane (1 mL) at −78° under N_2 was added butyllithium (24 mg, 0.36 mmol) by syringe as a solution in hexane (0.2 mL). After 15 min, tetrabenzyl pyrophosphate (234 mg, 0.432 mmol) was added by cannulation as a solution in oxolane (0.2 mL). The cooling bath was removed and replaced by an ice bath, and the mixture was stirred at 0° for 2 h. The resulting white slurry was treated with saturated $NaHCO_3$ solution (0.1 mL) for 15 min, and then diluted to 30 mL with ether and washed with water (3 × 30 mL), with saturated NaCl (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Flash chromatography (16 cm × 20 mm column, SiO_2, 3:2 ethyl acetate–hexane) yielded **28** (209 mg, 88%), homogeneous by h.p.l.c., ^{1}H-, ^{13}C-, and ^{31}P-n.m.r. spectroscopy, R_f 0.41 (SiO_2, 3:2 ethyl acetate–hexane); $[\alpha]_D^{22}$ +10.8° (*c* 1.08, chloroform); $\nu_{max}^{CHCl_3}$ 3560, 3105, 3080, 3040, 3020, 2960, 2910, 2880, 1500, 1460, 1385, 1365, 1275, 1215, 1100, and 1025 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 7.37–7.17 (m, 25 H), 5.04 (d, 4 H, *J* 8.3 Hz), 4.65 (d, 1 H, *J* 11.5 Hz), 4.60 (d, 1 H, *J* 11.5 Hz), 4.56 (d, 1 H, *J* 11.7 Hz), 4.51 (d, 1 H, *J* 12.0 Hz), 4.50 (d, 1 H, *J* 11.7 Hz), 4.46 (d, 1 H, 12 Hz), 4.10 (ddd, 1 H, *J* 6.4, *J* 6.4, *J* 12.5 Hz), 4.01 (ddd, 1 H, *J* 6.2, *J* 6.3, *J* 9.9 Hz), 3.92 (d, 1 H, *J* 6.6 Hz), 3.86 (dd, 1 H, *J* 6.3, *J* 6.3 Hz), 3.31 (s, 2 H), 2.78 (s, 1 H), 2.17 (m, 1 H), 2.08 (dd, 1 H, *J* 9.7, *J* 13.8 Hz), and 1.52 (dd, 1 H, *J* 5.3, *J* 13.8 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 138.4, 138.1, 136.0, 135.9, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 86.1, 85.8, 77.3, 73.8, 73.5, 73.1, 72.3, 69.6, 69.2, 40.9, and 34.1. M.s.: Calc. for $C_{35}H_{38}O_8P$ ($M^+ - C_7H_7$): *m/z* 617.2304. Found: *m/z* 617.2304.

(1R,2R,3S,4S)-2,3,4-Trihydroxy-4-hydroxymethylcyclopentanylmethyl dihydrogen phosphate (**29**). — To a solution of monophosphate **28** (78 mg, 0.11 mmol) in absolute ethanol (2.2 mL) was added Pearlman's catalyst[35] (7.7 mg, 0.01 mmol) and 10% HCl solution (20 μL). The mixture was then shaken on a Parr shaker under H_2 (0.4 MPa) for 15 h. Pearlman's catalyst was removed by filtration through glass wool, and the solution was then concentrated under reduced pressure to give a pale-yellow oil, and water (10 mL) was added and lyophillized three times to yield **29** (28 mg, 100%), $[\alpha]_D^{22}$ +20.5° (*c* 1.03, water); ^{1}H-n.m.r. (300 MHz, D_2O): δ 4.00 (m, 2 H), 3.92 (dd, 1 H, *J* 8.8, *J* 8.8 Hz), 3.68 (d, 1 H, *J* 8.8 Hz), 3.50 (s, 2 H), 2.16 (dd, 1 H, *J* 10.1, *J* 14.3 Hz), 2.03 (m, 1 H), and 1.43 (dd, 1 H, *J* 7.4, *J* 14.4 Hz); ^{13}C-n.m.r. (125 MHz, D_2O): δ 80.7, 79.3, 78.9, 69.6, 68.3, 42.4, and 35.2.

REFERENCES

1 John J. Gaudino, Ph.D. thesis, University of Texas at Austin, Austin, Texas 1989.
2 T. Suami, S. Ogawa, K. Nakamoto, and I. Kasahara, *Carbohydr., Res.* 58 (1977) 240–244.
3 S. Ogawa, T. Toyokuni, T. Kondoh, Y. Hattori, S. Iwasaki, M. Suetsugu, and T. Suami, *Bull. Chem. Soc. Jpn.*, 54 (1981) 2739–2746.
4 S. Ogawa, Y. Iwasawa, and T. Suami, *Chem. Lett.*, 1984 (1984) 355–356.
5 S. Ogawa, I. Kasahara, and T. Suami, *Bull. Chem. Soc. Jpn.*, 52 (1979) 118–123.
6 S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, 52 (1979) 1174–1176.
7 S. Daluge and R. Vince, *J. Org. Chem.*, 43 (1978) 2311–2320.
8 R. Vince, R. H. Turakhia, W. M. Shannon, and G. Arnett, *J. Med. Chem.*, 30 (1987) 2026–2030.

9 D. E. Kiely and H. G. Fletcher, Jr., *J. Org. Chem.*, 34 (1969) 1386–1390.
10 R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, (1979) 1455–1458.
11 A. S. Machado, A. Olesker, and G. Lukas, *Carbohydr. Res.*, 135 (1985) 231–239.
12 D. Semeria, M. Philippe, J. Delaumeny, A. Sepulchre, and S. D. Gero, *Synthesis*, (1983) 710–713.
13 P. Belanger and P. Prasit, *Tetrahedron Lett.*, 29 (1988) 5521–5524.
14 R. Blattner, R. J. Ferrier, and P. Prasit, *J. Chem. Soc., Chem. Commun.*, (1980) 944–945.
15 F. Sugawara and H. Kuzuhara, *Agric. Biol. Chem.*, 45 (1981) 301–304.
16 N. Sakairi and H. Kuzuhara, *Tetrahedron Lett.*, 23 (1982) 5327–5330.
17 I. Pelyvas, F. Sztaricskai and R. Bognar, *J. Chem. Soc., Chem. Commun.*, (1984) 104–105.
18 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986.
19 D. Hart, *Science*, 223 (1984) 883.
20 C. S. Wilcox and L. M. Thomasco, *J. Org. Chem.*, 50 (1985) 546–547.
21 A. W. Johnson, *Ylide Chemistry*, Academic Press, New York, 1966.
22 T. H. Webb, L. M. Thomasco, S. T. Schlachter, J. J. Gaudino, and C. S. Wilcox, *Tetrahedron Lett.*, 29 (1988) 6823–6826.
23 H. Hers and E. Van Schaftingen, *Biochem. J.*, 206 (1982) 1–12.
24 E. Van Schaftingen and H. G. Hers, *Biochem. Biophys. Res. Commun.*, 96 (1980) 1524–1531.
25 E. Van Schaftingen and H. G. Hers, *Proc. Natl. Acad. Sci. U.S.A.*, 78 (1981) 2861–2863.
26 S. J. Pilkis, M. R. El-Maghrabi, J. Pilkis, J. T. H. Claus, and D. A. Cumming, *J. Biol. Chem.*, 256 (1981) 3171–3174.
27 G. F. Griffiths, G. W. Kenner, K. M. McCombie, K. M. Smith, and M. J. Sutton, *Tetrahedron*, 32 (1976) 275–283.
28 K. Omura and D. Swern, *Tetrahedron*, 34 (1978) 1651–1660.
29 H. Taguchi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 96 (1974) 3010–3011.
30 C. H. Kuo and N. L. Wendler, *Tetrahedron Lett.*, 25 (1084) 2291–2294.
31 K. Mead and T. L. Macdonald, *J. Org. Chem.*, 50 (1985) 422–423.
32 D. P. Curran, *Synthesis*, (1988) 417–439.
33 R. Benn and H. Gunther, *Angew. Chem., Int. Ed. Eng.*, 22 (1983) 350–380.
34 G. Stork, A. Meisels, and J. E. Davies, *J. Am. Chem. Soc.*, 85 (1963) 3419–3425.
35 P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, 1967, p. 464.
36 P. M. Chouinard and P. A. Bartlett, *J. Org. Chem.*, 51 (1986) 75–78.
37 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43 (1978) 2923–2925.
38 R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 94 (1972) 5897–5898.