Pergamon

Tetrahedron 58 (2002) 7663–7679

TETRAHEDRON

# An inexpensive carbohydrate derivative used as a chiral auxiliary in the synthesis of α-hydroxy carboxylic acids

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Received 4 April 2002; accepted 16 July 2002

**Abstract**—Protected α-hydroxy carboxylic acids were synthesized in moderate yield and high diastereoselectivity by alkylation of glycolate (α-hydroxy acetate) enolates using a D-fructose-derived chiral auxiliary. The new chiral center was assigned the *R* configuration based on comparisons of optical rotations and on one crystal structure analysis. This alkylation methodology is compatible with several hydroxyl protecting groups. The free hydroxy acids were obtained upon removal of the protecting group from the hydroxyl functionality followed by saponification. 

## 1. Introduction

α-Hydroxy carboxylic acids are important building blocks for the synthesis of depsides and depsipeptides, natural products that often exhibit significant biological activity.[1–16] Depsipeptides such as the potent antibiotic vancomycin have been developed into therapeutic agents. One way to make progress in this area is to make analogs of these natural products containing unnatural hydroxy acids. Development of synthetic routes to hydroxy acids will be key to these efforts.

Reported enantioselective routes to α-hydroxy acids[17,18] include hydroxylation of enolates,[19,20] reduction of α-keto-acid derivatives or their precursors,[21–26] Horner–Wittig reaction of aldehydes with a dialkoxymethyl phosphine oxide followed by Sharpless dihydroxylation,[27] carbonyl-ene reactions of glyoxylates,[28,29] addition of cyanide to aldehydes and ketones,[30,31] nucleophilic alkylation of aldehydes[32] or α-oxo acid derivatives,[33–35] Friedel–Crafts reactions of aromatic compounds with glyoxylates,[36] O–H insertions of diazoacetates,[37] condensation of *trans*-1,3-dithiane-1,3-dioxide with aldehydes,[38] reduction of chiral hemiacetals,[39,40] osmium-catalyzed dihydroxylation followed by a second oxidation,[41] nucleophilic alkylation of oxazin-4-ones,[42] [2,3] Wittig rearrangement of propargyloxy acetates,[43] dynamic kinetic resolution,[44] and enzymatic resolution.[45,46] Another straightforward method is the stereoselective alkylation of glycolates (α-hydroxy acetates).[47–54] The most notable of these reports used a *trans*-2,5-disubstituted pyrrolidine,[55] menthone[56] or camphorsulfonamide,[57] or Evans's oxazolidinone[58] as chiral auxiliaries. The first three strategies provided excellent yield and good to excellent diastereomeric excess (de) for the alkylation even with less reactive electrophiles (e.g. butyl iodide), but they suffer the limitation of being cleaved under harshly acidic conditions. The oxazolidinone auxiliary gave excellent yields and diastereoselectivities, but it was only studied with reactive electrophiles, mainly allylic or propargylic iodides. However, no auxiliary that can be removed by basic hydrolysis has been reported to efficiently alkylate glycolates with a wide variety of electrophiles.

One readily available source of inexpensive chiral auxiliaries is carbohydrates. Enolate alkylations using carbohydrate auxiliaries have met with mixed results.[59,60] Costa,[61,62] Mulzer,[63] and Koll[64] achieved moderate yields and selectivities with their systems. We investigated 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (D-fructose diacetonide)[65] because it has proven valuable in asymmetric synthesis. It has been used as an auxiliary in Diels–Alder cycloadditions,[66] and it is the precursor to an epoxidation catalyst developed by Shi and co-workers.[65] Earlier we outlined our preliminary results using D-fructose diacetonide as an auxiliary in glycolate alkylation.[67] Herein we report our complete studies of asymmetric glycolate alkylation.

## 2. Results and discussion

The auxiliary **1** was obtained from D-fructose in one step.[65] Its free 3-hydroxyl group was esterified with benzyloxyacetic acid **2a** using 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to give glycolate

*Keywords*: chiral auxiliary; carbohydrate; asymmetric synthesis; hydroxy carboxylic acid; enolate alkylation; glycolate alkylation.

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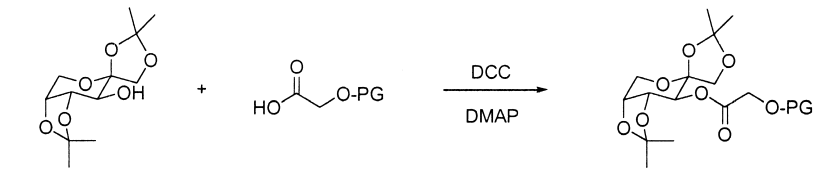
PII: S0040-4020(02)00871-2




**1**

**2a** PG = Bn
**2b** PG = $CH_2C_6H_4NO_2(p)$
**2c** PG = $CH_2C_6H_4OMe(p)$
**2d** PG = $CH_2C_6H_4F(p)$
**2e** PG = Me
**2f** PG = MOM
**2g** PG = BOM
**2h** PG = TBS
**2i** PG = TBDPS
**2k** PG = TIPS

**3a** PG = Bn
**3b** PG = $CH_2C_6H_4NO_2(p)$
**3c** PG = $CH_2C_6H_4OMe(p)$
**3d** PG = $CH_2C_6H_4F(p)$
**3e** PG = Me
**3f** PG = MOM
**3g** PG = BOM
**3h** PG = TBS
**3i** PG = TBDPS
**3j** PG = TES
**3k** PG = TIPS


**4a** PG = Bn, R = Me
**4b** PG = Bn, R= allyl
**4c** PG = Bn, R = Bn
**4d** PG = Bn, R = Et
**4e** PG = Bn, R = $PhCH_2CH_2$

**5a** PG = $CH_2C_6H_4NO_2(p)$, R = Me

**6a** PG = $CH_2C_6H_4OMe(p)$, R = Me

**7a** PG = $CH_2C_6H_4F(p)$, R =Me
**8a** PG = Me, R = Me

**9a** PG = MOM, R = Me

**10a** PG = BOM, R = Me

**11a** PG = TBS, R = Me
**11b** PG = TBS, R = allyl
**11c** PG = TBS, R =Bn

**12a** PG = TBDPS, R = Me
**12b** PG = TBDPS, R = allyl
**12c** PG = TBDPS, R = Bn

**13a** PG = TES, R = Me
**13b** PG = TES, R = allyl
**13c** PG = TES, R = Bn
**13d** PG = TES, R = Et
**13e** PG = TES, R = $PhCH_2CH_2$
**13f** PG = TES, R = $CH_3(CH_2)_4$
**13g** PG = TES, R = 2-naphthylmethyl

**14a** PG = TIPS, R = Me

**Scheme 1.** General route for the synthesis and alkylation of glycolates **3**.

**3a** (Scheme 1). Initial alkylations were conducted with two reactive halides (allyl bromide and allyl iodide) to determine the feasibility of using D-fructose diacetonide as a chiral auxiliary (Scheme 1). Tetrahydrofuran (THF) was used as the solvent for these reactions. Table 1 summarizes the findings of these experiments. Comparison of entry 4 with entries 1–3 shows that lithium bis(trimethylsilyl)amide (LiHMDS) (2 equiv.) was the optimal base in combination with the more reactive allyl iodide. In an effort to maximize the de by performing the alkylation at lower temperature, entry 5 shows that a higher yield was obtained, but that the diastereoselectivity was slightly lower.

**Table 1**. Influences of base and temperature on the alkylation of **3a** to **4b** in THF

| Entry | RX | Base | Temp. (°C) | Yield (%) | de (%) |
|---|---|---|---|---|---|
| 1 | Allyl bromide | LDA (1.5 equiv.) | −78 | 59 | 66 |
| 2 | Allyl iodide | LiHMDS (1.5 equiv.) | −78 | 51 | 92 |
| 3 | Allyl iodide | NaHMDS (1.5 equiv.) | −78 | 41 | 81 |
| 4 | Allyl iodide | LiHMDS (2 equiv.) | −78 | 54 | 92 |
| 5 | Allyl iodide | LiHMDS (2 equiv.) | −92 | 78 | 86 |

Since these initial results were encouraging, we tried to optimize the reaction with respect to a variety of factors, including solvent, additives, base, cation, and hydroxyl protecting group. The next studies examined the reaction as a function of solvent polarity and coordination power. The more Lewis basic solvents were expected to coordinate the cation of the enolate more strongly, giving a more reactive intermediate.[68] The coordination of the enolate with solvent and additives greatly affects the degree of aggregation of the enolate in solution, which can significantly influence its reactivity and selectivity.[69] Some reports have shown that aprotic polar additives such as hexamethylphosphoric

**Table 2**. Reaction conditions, yields, and de's for the optimization of the methylation of **3a** to **4a** (PG=Bn, R=Me)

| Entry | Solvent | Additive | Base | Reaction temp. (°C) | Yield (%) | de (%) |
|---|---|---|---|---|---|---|
| 1 | THF | None | LiHMDS | −78 | 61 | 83 |
| 2 | THF | HMPA | LiHMDS | −78 | 64 | 79 |
| 3 | THF | HMPA | LiHMDS | −95 | 73 | 86 |
| 4 | THF | DMPU | LiHMDS | −95 | 72 | 73 |
| 5 | THF | TMEDA | LiHMDS | −95 | 51 | 86 |
| 6 | THF | HMPA | KHMDS | −95 | 73 | 78 |
| 7 | THF | HMPA | LiHMDS (1 equiv.)+*n*-BuLi (1 equiv.) | −95 | 43 | 69 |
| 8 | THF | HMPA | LiTMP | −95 | 36 | 91 |
| 9 | PhMe | HMPA | LiHMDS | −95 | 21 | 87 |
| 10 | DME | HMPA | LiHMDS | −78 | 52 | 83 |
| 11 | THF | HMPA+$MgBr_2$ (2.4 equiv.) | LiHMDS | −95 | 51 | 92 |
| 12 | THF | HMPA+LiBr (2.0 equiv.) | LiHMDS | −95 | 40 | 91 |
| 13 | THF | HMPA+LiCl (2.2 equiv.) | LiHMDS | −95 | 40 | 93 |

triamide (HMPA) can erode[52,70] or even reverse[62,71] stereoselectivity.

These factors were optimized using glycolate **3a** with MeI as the alkylating agent (Scheme 1 and Table 2). The initial conditions (entry 1) were the same as those used for Table 1, entry 4: 2 equiv. of LiHMDS at −78°C. The moderate yield and de for this reaction indicate that this is an ideal reaction for optimization studies. If one of the reaction conditions makes an important positive or negative impact on the alkylation, the yield and/or selectivity data should be significantly different from the data in this baseline experiment. In addition, this product offers the advantage that its de can be determined by $^1$H NMR.

The data in Table 2 indicate that the baseline conditions were close to optimal, besides the use of HMPA as an additive and lowering the reaction temperature. Comparison of entries 1 and 2 shows that adding HMPA did not significantly affect the reaction. However, with electrophiles besides MeI, a large increase in yield was seen with the addition of HMPA. For example, the addition of HMPA increased the yield of the alkylation from 54% (92% de) to 76% (92% de) when allyl iodide was the electrophile.[67] Comparison of entries 2 and 3 shows that lowering the reaction temperature improved both the yield and de. Comparison of HMPA with the other aprotic polar solvents 1,3-dimethylpropyleneurea (DMPU) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in entries 4 and 5 shows that DMPU gives a comparable yield with slightly lower de while TMEDA gives a much lower yield with comparable stereoselectivity. Comparison of the different bases in entries 6–8 shows that only KHMDS (2 equiv.) gave a comparable yield, but with a slight sacrifice of de. The bulky base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) gave a very low yield but a quite high de for the methylation. Comparison of THF with the other solvents listed in entries 9 and 10, toluene and 1,2-dimethoxyethane (DME), show that THF is superior. These solvents vary widely in their ability to coordinate cations, and various reports have shown each has been tested in certain examples of enolate chemistry.[52] The addition of various metal additives[69,72] in entries 11–13 gave much lower yields but good de's. With the lithium halide salts, about half of the starting material was recovered unreacted.

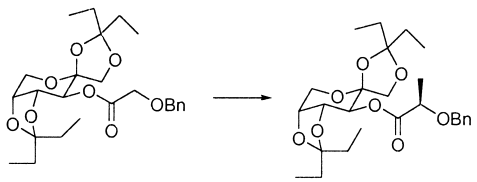
After these optimization studies had been completed, the compatibility of other hydroxyl protecting groups (PG's) besides benzyl with these methylation conditions were studied (Scheme 1 and Table 3). The alkylation conditions used were LiHMDS (2 equiv.) in THF/5% HMPA at −95°C. Substrates in entries 2–11 were prepared by DCC/DMAP coupling of the appropriately protected glycolic acid with the auxiliary **1**, except for glycolate **3j**, which was prepared by hydrogenolysis of **3a** followed by reprotection with the triethylsilyl group. These protecting groups cover a large range of electronic and steric characteristics. The overall impression from this table is that the choice of protecting group had relatively little effect on the stereoselectivity of the alkylation, but that it significantly affected the yield. This was expected because the directing influence of the reaction was assumed to arise almost entirely from the chiral auxiliary. The differences in yield probably arise from differences in stability of the enolates.

**Table 3**. Compatibility of different protecting groups with the optimal methylation conditions

| Entry | Substrate | PG | Product (R=Me) | Reaction temp. (°C) | Yield (%) | de (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | Bn | **4a** | −95 | 73 | 86 |
| 2 | **3b** | $CH_2C_6H_4NO_2$ (*p*) | **5a** | −95 | 19 | 89 |
| 3 | **3c** | $CH_2C_6H_4OMe$ (*p*) | **6a** | −95 | 66 | 91 |
| 4 | **3d** | $CH_2C_6H_4F$ (*p*) | **7a** | −95 | 75 | 93 |
| 5 | **3e** | Me | **8a** | −95 | 66 | 92 |
| 6 | **3f** | MOM | **9a** | −95 | 65 | 91 |
| 7 | **3g** | BOM | **10a** | −95 | 68 | 87 |
| 8 | **3h** | TBS | **11a** | −78 | 76 | 84 |
| 9 | **3i** | TBDPS | **12a** | −78 | 83 | 89 |
| 10 | **3j** | TES | **13a** | −78 | 77 | 88 |
| 11 | **3k** | TIPS | **14a** | −95 | 70 | 84 |

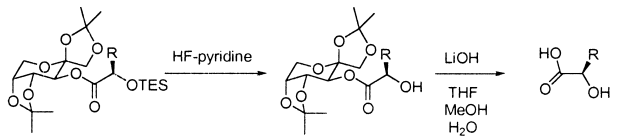
**Table 4**. Yields and de's for the conversion of esters **3a**, **h–j** to **4**, **11–13** in the presence of HMPA at −78°C

| Entry | Substrate | Electrophile (RX) | Product | Yield (%) | de (%) |
|---|---|---|---|---|---|
| 1 | **3a** | BnBr | **4c** | 58 | 98 |
| 2 | **3a** | $CH_3CH_2I$ | **4d** | 74 | 76 |
| 3 | **3a** | $PhCH_2CH_2I$ | **4e** | 52 | 79 |
| 4 | **3h** | $CH_2{=}CHCH_2I$ | **11b** | 88 | 85 |
| 5 | **3h** | BnBr | **11c** | 88 | 86 |
| 6 | **3i** | $CH_2{=}CHCH_2I$ | **12b** | 78 | 89 |
| 7 | **3i** | BnBr | **12c** | 89 | 94 |
| 8 | **3j** | $CH_2{=}CHCH_2I$ | **13b** | 71 | 91 |
| 9 | **3j** | BnBr | **13c** | 75 | 96 |
| 10 | **3j** | $CH_3CH_2I$ | **13d** | 83 | 88 |
| 11 | **3j** | $PhCH_2CH_2I$ | **13e** | 61 | 60 |
| 12 | **3j** | $CH_3(CH_2)_4I$ | **13f** | 58 | 83 |
| 13 | **3j** | 2-(Bromomethyl)naphthalene | **13g** | 71 | 91 |




15 16

**Scheme 2.** Methylation of the glycolate **15** bearing larger protecting groups on the auxiliary.




13 17 18

**Scheme 3.** Deprotection and hydrolysis of the esters **13** to give the free acids **18**.

Entry 1 of Table 3 is the same as entry 3 of Table 2 and served as a baseline for this study. Entries 2–4 include substituted benzyl groups and were included for comparison with entry 1. The literature indicates that the protons of an α-oxy carbonyl compound is more acidic than those of an α-unsubstituted carbonyl compound.[73,74] We hypothesized that altering the electronics of the protecting group would affect the yield of the reaction.

To test if this hypothesis were true for the subtly different cases of unsubstituted and *p*-substituted benzyl groups, we prepared substrates **3b–d**. The reaction in entry 2 seems to represent an odd case because during the addition of base, the solution of substrate **3b** turned dark red in color, unlike those of the other substrates, which were pale yellow. Based on the low p$K_a$ of *p*-nitrotoluene (20.4),[75] competitive deprotonation at the benzylic position may be occurring. Comparison of entries 3 and 4 with entry 1 indicates that the *p*-substituent had only a small effect on the yield of the alkylation. The compound with the electron-withdrawing fluorine (entry 4) gave a slightly greater yield than that for the electron-donating methoxy (entry 3). A possible explanation is that the electron-donating group destabilizes the enolate, so that it undergoes more side reactions.

Entries 5–7 include more alkyl hydroxyl protecting groups: methyl, methoxymethyl (MOM), and benxyloxymethyl (BOM). The yields for these alkylations were slightly lower.

The most successful reactions were carried out with silyl protecting groups (entries 8–11). The groups tested included the *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS), triethylsilyl (TES), and triisopropylsilyl (TIPS) groups. The less bulky groups (TBS, TBDPS, and TES) provided the best yields and selectivities of any protecting group, allowing for the different reaction temperatures. The TIPS group gave a slightly lower yield, with slightly lower selectivity. TIPS must be too large to allow for efficient approach of the electrophile to the enolate.

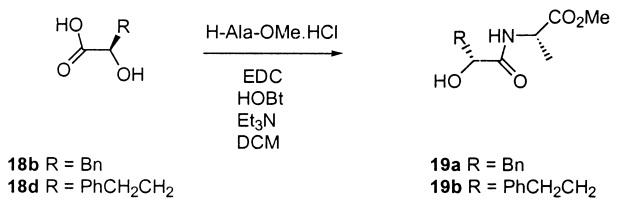
To confirm the conclusions from these studies, additional electrophiles were tested with substrates **3a**, **h–j** (PG=Bn, TBS, TBDPS, and TES, respectively, Scheme 1 and Table 4). Generally substrate **3a** showed lower yield than the other substrates. The TBDPS- and TES-protected substrates (**3i** and **3j**, respectively) gave comparably high yields and selectivity. The TES glycolate **3j** was chosen for further studies with a wide range of electrophiles, including many less reactive iodides (entries 10–12). Moderate yields and good de values were also obtained with these substrates.

To test the importance of the bulkiness of the fructose diol protecting groups, substrate **15** was prepared (Scheme 2). Methylation of **15** proceeded in comparable yield and selectivity at −95°C (71% yield, 85% de) compared with **3a** (73% yield, 86% de). The similarity of the results indicates that the alkyl substituents of the ketals have little effect on the selectivity. A possible explanation is that the dioxolane rings of the ketals favor a particular conformation of the auxiliary that leads to high asymmetric induction. Therefore, the steric hindrance provided by the alkyl groups on the ketal is less important than the conformational bias provided by the ketals.

**Table 5**. Specific optical rotations of the α-hydroxy carboxylic acids **16**

| α-Hydroxy carboxylic acid | $[\alpha]_D$ (°) | Absolute configuration |
|---|---|---|
| 2-Hydroxypropionic acid (**18a**) | −12.7 (*c* 0.33, EtOH) | |
| 2-Hydroxy-3-phenylpropionic acid (**18b**) | +12.7 (*c* 0.43, EtOH) | *R*[a] |
| 2-Hydroxybutanoic acid (**18c**) | −10.4 (*c* 0.12, EtOH) | |
| 2-Hydroxy-4-phenylbutanoic acid (**18d**) | −13.3 (*c* 0.45, EtOH) | *R*[a] |
| 2-Hydroxyheptanoic acid (**18e**) | −12.3 (*c* 0.41, $CHCl_3$) | *R*[79] |
| 2-Hydroxy-3-naphthalen-2-yl-propionic acid (**18f**) | −18.0 (*c* 0.74, EtOH) | |

[a] Comparison with data from the Aldrich Chemical catalog.




**Scheme 4.** The modified Cavelier's method for determining if racemization had occurred during the deprotection or hydrolysis of **13**.

The configuration of the newly generated stereocenter was determined by the optical rotation of the free acids. Compounds **4a**,**c** were hydrolyzed in LiOH/THF/$H_2O$ to give the hydroxyl-protected acid. Upon comparing their specific rotations with the literature,[76,77] they were concluded to have the *R* configuration. In addition, the absolute configurations of the enolate alkylation products **13** were assigned by comparisons of the specific rotations of the α-hydroxy carboxylic acids **18** obtained upon cleavage of the protecting group with HF/pyridine followed by saponification (Scheme 3) to those in the literature. The results are listed in Table 5. These results indicated that the newly formed chiral center had the *R* configuration.

To determine if racemization had occurred during the deprotection or the saponification, Cavelier's method (Scheme 4) was followed.[78] Alkylated products **13c**,**e** were deprotected with hydrogen fluoride-pyridine. $^1$H NMR of the crude compounds **17** indicated that they had the same de (within experimental error, 5%) as compounds **13**. These crude compounds **17** were saponified as above to give the free acids **18b**,**d**, respectively. These acids were coupled to H-Ala-OMe to give the amides **19** (Scheme 4). $^1$H NMR of the crude amides indicated they had the same de (within experimental error, 5%) as compounds **13** and **17**, respectively. The deprotection, saponification, and amidation steps were all high yielding (>86%), minimizing any effects of kinetic resolution.

To probe the factors responsible for the high stereoselectivity of these alkylations and to confirm the assignment of the *R* configuration at the α-center, two of the compounds were submitted for X-ray crystallography. Glycolate **3a** and product **4c** were selected for analysis. The stereoview of **3a** (Fig. 1) shows the pyranose ring in a boat conformation. The acyl group lies in a chain. The stereoview of **4c** (Fig. 2) shows that the alkylated acyl chain lies roughly perpendicular to the acetonide protecting groups on the carbohydrate. The pyranose ring is still in a

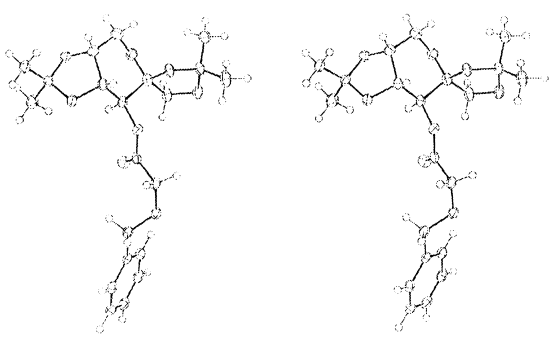


**Figure 1.** Stereoview of glycolate **3a**.

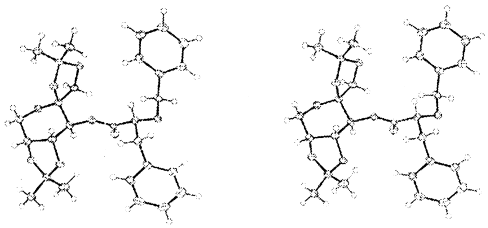


**Figure 2.** Stereoview of alkylated ester **4c**.

boat-like conformation. More importantly, it is seen that the new stereocenter has the *R* configuration.

In both structures the side closer to the 4,5-acetonide appears to be more open. This is confirmed by analysis of the crystal structures. In the starting material **3a** the distance of closest approach of a hydrogen atom on the α-carbon to the 1,2-acetonide is 3.37 Å, while its distance of closest approach to the 4,5-acetonide is greater than 5.0 Å. In the product **4c** the distance of closest approach of a hydrogen atom on the α-carbon to the carbons of the 1,2-acetonide is 3.49 Å, while its distance of closest approach to the 4,5-acetonide is greater than 5.0 Å.

It is understood that these structures of the starting material and the product do not provide information about the conformation of the reactive intermediate, the enolate. The factors responsible for the high de of the alkylations are stereoselective formation of the enolate and selective approach of the electrophile to one face of the enolate. Literature precedent indicates that the enolate should have the *Z* geometry.[80,81] If the general conformation of the enolate is similar to that of the starting material and the product, the *Z* enolate is consistent with the *R* configuration of the new chiral center.

## 3. Conclusion

The synthesis of α-hydroxy carboxylic acids using auxiliary **1** has been successfully executed. The following features were notable: (1) the crystalline auxiliary 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose **1** was easily obtained on a large scale from an inexpensive starting material, D-fructose; (2) the enolate alkylation proceeded in high de; (3) the addition of HMPA increased the yield without sacrificing diastereoselectivity; (4) the alkylation was compatible with several hydroxyl protecting groups; and (5) the other enantiomer of the auxiliary is readily available.[65,82] It is difficult to compare this auxiliary with the others that have been reported in the literature, partly because different electrophiles were used in each study. However, on the whole, it seems that D-fructose diacetonide is comparable with or better than most other auxiliaries that have been used for glycolate alkylation. The fructose auxiliary gave slightly lower yields and stereoselectivity than Katsuki's pyrrolidine[55] and Uang's[57] and Pearson's[56] dioxolanone auxiliaries. It is not quite as selective as the Evans auxiliary,[58] but it gave good yields with a variety of electrophiles. However, none of these other systems were tested with the range of alkylating agents that were used in this study. With the Evans auxiliary only especially reactive electrophiles were examined. D-fructose diacetonide offers

competitive selectivity and reactivity compared to these proven auxiliaries. Furthermore, the D-fructose auxiliary offers the advantage of low cost. Further development of chiral auxiliaries available from inexpensive carbohydrates will broaden the arsenal of tools available for the preparation of α-hydroxy acids in a variety of situations.

## 4. Experimental

### 4.1. General

All reactions were performed in flame-dried or oven-dried glassware (>120°C, >4 h) that was cooled under vacuum. Some reagents were purified according to standard procedures[83] as noted below. Dichloromethane (DCM) was distilled from $CaH_2$. THF was distilled from sodium and benzophenone. HMPA and DMPU were distilled under vacuum from $CaH_2$ before use. TMEDA was used as received (redistilled, Aldrich Sure-Seal™ bottle). LiHMDS was purchased as a solution in THF (Aldrich Sure-Seal™ bottle) and was titrated.[84] NaHMDS was used as a 1.0 M solution in THF (Aldrich Sure-Seal™ bottle). KHMDS was used as a 0.5 M solution in toluene (Aldrich Sure-Seal™ bottle). Reaction temperatures are the temperatures of heating or cooling baths. Analytical thin-layer chromatography (TLC) was performed with Scientific Adsorbents plastic-backed TLC silica gel 60F hard layer plates. TLC plates were visualized with a 5% (w/v) solution of phosphomolybdic acid in ethanol. Flash chromatography was performed with Scientific Adsorbents silica gel (flash, 32–63 μm). Column chromatography was followed by combining appropriate fractions, rotovapping, and drying under oil pump vacuum. Mass spectrometry (MS) analyses were performed by the Mass Spectrometry Laboratories of North Carolina State University and the University of Kansas. $^1H$ and $^{13}C$ NMR spectra were recorded with a Varian Gemini 300, GE Omega 300, Varian Mercury 300, or Varian Mercury 400 NMR spectrometer. Chemical shifts ($\delta$) were given in ppm relative to TMS for $^1H$ spectra and relative to residual solvent for $^{13}C$ spectra. IR spectra were recorded of thin films of each compound cast from DCM or chloroform on NaCl plates. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, Georgia. All melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Specific rotations were determined on an AUTOPOL III automatic polarimeter.

**4.1.1. Benzyloxyacetic acid (2a).**[85] In a 2-neck 250 mL round bottom flask sodium hydride (7.08 g, 177 mmol, 60% dispersion in mineral oil) was washed with hexanes (3×20 mL) and the remaining solvent was removed under oil pump vacuum for 15 min. Into a rapidly stirred suspension of this solid in dry THF (60 mL) at rt was cannulated a solution of benzyl alcohol (15 mL, 145 mmol, freshly distilled) in 50 mL dry THF (5 mL rinse) over 25 min. Additional benzyl alcohol (2 mL, 19 mmol, freshly distilled) was added neat. After the mixture had stirred at rt for 5 min, 15-crown-5 (0.10 mL, 0.50 mmol) and sodium iodide (600 mg, 4 mmol, oven-dried) were added. Into this white suspension, a solution of chloroacetic acid (7.30 g, 77.2 mmol, freshly recrystallized from $CHCl_3$) in dry THF (30 mL, 5 mL rinse) was cannulated over 10 min. The reaction flask was insulated with aluminum foil and heated to reflux. After 12 h, heating was discontinued. After the mixture had cooled at rt for 3 h, it was poured onto crushed ice and washed with EtOAc (4×40 mL). The aqueous layer was cooled with crushed ice and acidified with concentrated HCl until white material oiled out. The aqueous layer was extracted with EtOAc (5×40 mL). (The aqueous layer was reacidified after each extraction.) These combined organic layers were washed with saturated NaCl (10 mL), dried ($MgSO_4$), filtered, rotovapped, and dried on the oil pump to give an orange liquid (12.7 g). It was purified on a flash silica column (2–10% MeOH/DCM). Fractions were combined, rotovapped, and dried on the oil pump to give **2a** as a pale yellow liquid (11.4 g, 89% yield). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.37 (m, 5H), 4.66 (s, 2H), 4.14 (s, 2H).

**4.1.2. Representative esterification procedure for the preparation of the chiral glycolates. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl benzyloxyacetate (3a).** To a solution of benzyloxyacetic acid (**2a**, 2.7 g, 14.5 mmol) in dry DCM (25 mL) were added DCC (3.18 g, 14.5 mmol), 1,2:4,5-*O*-diisopropylidene-β-D-fructopyranose **1** (2.0 g, 7.68 mmol) and DMAP (0.4 g, 3.08 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h and at rt for 45 h. DCM was removed on the rotovap. The residue was resuspended in EtOAc and kept in the freezer for 30 min before the solid was filtered off. The organic solution was washed with saturated $NaHCO_3$, 10% citric acid, and saturated NaCl and dried ($MgSO_4$). Upon filtration and rotovapping, the residue was purified by flash chromatography on silica gel (hexanes/EtOAc 5:1 to 4:1) to afford **3a** as a white solid (4.9 g, 78%). Mp 103–104°C. $[\alpha]_D=-128.7°$ (*c* 0.46, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.30–7.37 (m, 5H), 5.22 (d, *J*=8.1 Hz, 1H), 4.31–4.10 (m, 6H), 4.65 (d, *J*=1.5 Hz, 2H), 3.98 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=9.2 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 170.3, 137.2, 128.7, 128.3, 128.2, 112.3, 109.9, 103.7, 74.9, 73.9, 73.5, 72.1, 71.1, 67.2, 60.8, 28.0, 26.5, 26.4, 26.3. IR: $\nu$ 2990, 2931, 2884, 1760, 1737, 1454, 1384, 1372, 1221, 1195, 1127, 1085, 1028, 976, 914, 886, 851, 824, 809, 744, 698 $cm^{-1}$. EIMS: 408 ($M^+$). Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.48; H, 6.80.

### 4.2. General procedure for the alkylation

To a solution of LiHMDS (2 mmol) in dry THF (6 mL) (Method A) or in dry THF (6 mL) and HMPA (5 or 10% v/v) (Method B) was added dropwise a solution of substrate (1 mmol) in dry THF (4 mL) in 5 min at −78°C. The resulting mixture was stirred at −78°C for 30 min, neat alkyl iodide (5 mmol) was added. The reaction mixture was stirred at −78°C until starting material had disappeared by TLC (hexanes/EtOAc 3:2 or hexanes/$Et_2O$ 4:1). The reaction was quenched at −78°C with saturated $NH_4Cl$. After the temperature of the mixture had reached about 0°C, the mixture was transferred to a separatory funnel and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with saturated NaCl and dried ($MgSO_4$). Upon removing solvent on the rotovap, the residue was purified by flash chromatography on silica

gel (hexanes/$Et_2O$) to afford the product. Method C was the same as Method B except that the reaction was stirred at −95°C.

**4.2.1. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)propionate (4a).** The product was obtained in 73% yield using alkylation Method C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40–7.29 (m, 5H), 5.19 (d, *J*=8.1 Hz, 1H), 4.73 (d, *J*=11.7 Hz, 1H), 4.44 (d, *J*=11.7 Hz, 1H), 4.31 (dd, *J*=5.1, 7.8 Hz, 1H), 4.23 (dd, *J*=1.5, 5.1 Hz, 1H), 4.18–4.08 (m, 3H), 3.99 (d, *J*=9.6 Hz, 1H), 3.86 (d, *J*=9.6 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.48 (d, *J*=7.5 Hz, 3H), 1.38 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 173.3, 137.7, 128.6, 128.3, 128.0, 112.3, 109.9, 103.8, 74.9, 74.2, 73.9, 72.2, 72.1, 71.1, 60.8, 28.0, 26.6, 26.5, 26.4, 19.0. IR: ν 3031, 2987, 2936, 2885, 1755, 1496, 1454, 1372, 1326, 1296, 1240, 1220, 1194, 1140, 1085, 1066, 1028, 976, 912, 888, 862, 851, 836, 810, 741, 699 cm$^{-1}$. EIMS: 421 (M−H$^+$). Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.69; H, 7.11.

**4.2.2. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)-4-pentenoate (4b).** The product was obtained in 76% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.38–7.29 (m, 5H), 5.92–5.78 (m, 1H), 5.21–5.09 (m, 3H), 4.75 (d, *J*=11.7 Hz, 1H), 4.43 (d, *J*=11.7 Hz, 1H), 4.30 (dd, *J*=5.1, 8.1 Hz, 1H), 4.23 (dd, *J*=1.5, 5.1 Hz, 1H), 4.15 (dd, *J*=2.4, 14.1 Hz, 1H), 4.12 (m, 1H), 4.05 (d, *J*=6.6 Hz, 1H), 3.98 (d, *J*=9.6 Hz, 1H), 3.87 (d, *J*=8.7 Hz, 1H), 2.58 (t, *J*=7.5 Hz, 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 172.2, 137.6, 133.0, 128.5, 128.3, 128.0, 112.3, 109.8, 103.8, 77.9, 74.8, 73.9, 72.3, 72.2, 72.1, 71.2, 60.8, 37.5, 28.0, 26.6, 26.4. IR: ν 2990, 2931, 2884, 1755, 1643, 1454, 1372, 1337, 1220, 1190, 1112, 1085, 1026, 976, 913, 888, 851, 837, 810, 738, 698 cm$^{-1}$. FABMS: 447 (M−H$^+$). Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.16.

**4.2.3. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)-3-phenylpropionate (4c).** The product was obtained in 58% yield using alkylation Method A. $^1$H NMR (300 MHz, $CDCl_3$): δ 5.19 (d, *J*=7.7 Hz, 1H), 4.71 (d, *J*=11.7 Hz, 1H), 4.36 (d, *J*=11.7 Hz, 1H), 4.27–4.15 (m, 3H), 4.14 (dd, *J*=2.4, 13.2 Hz, 1H), 4.07 (d, *J*=13.4 Hz, 1H), 3.94 (d, *J*=9.4 Hz, 1H), 3.77 (d, *J*=9.4 Hz, 1H), 3.11 (m, 2H), 1.55 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 172.1, 137.5, 137.1, 129.8, 128.5, 128.1, 127.9, 126.9, 112.3, 109.9, 103.7, 79.2, 74.8, 73.9, 72.5, 72.2, 71.3, 60.9, 39.5, 28.0, 26.6, 26.4. IR: ν 2990, 2931, 1747, 1649, 1455, 1449, 1384, 1372, 1337, 1237, 1220, 1190, 1161, 1114, 1084, 973, 914, 864, 817 cm$^{-1}$. CIMS: 497 (M−H$^+$). Anal. Calcd for $C_{28}H_{34}O_8$: C, 67.45; H, 6.87. Found: C, 67.38; H, 6.89.

**4.2.4. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)butanoate (4d).** The product was obtained in 74% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): δ 5.20 (d, *J*=7.6 Hz, 1H), 4.74 (d, *J*=11.6 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 4.29 (dd, *J*=5.2, 7.6 Hz, 1H), 4.23 (dd, *J*=1.6, 5.2 Hz, 1H), 4.15 (dd, *J*=2.4, 13.2 Hz, 1H), 4.10 (d, *J*=13.2 Hz, 1H), 4.00 (d, *J*=9.2 Hz, 1H), 3.94 (dd, *J*=5.6, 6.8 Hz, 1H), 3.88 (d, *J*=9.2 Hz, 1H), 1.85 (m. 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.01 (t, *J*=7.6 Hz, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 172.7, 137.6, 128.5, 128.2, 128.1, 127.9, 127.8, 112.2, 109.7, 103.7, 79.2, 74.8, 73.8, 72.2, 72.0, 71.0, 70.9, 60.7, 27.9, 26.5, 26.4, 26.3, 26.3, 26.2, 9.7. IR: ν 2990, 2931, 2884, 1754, 1649, 1455, 1372, 1337, 1296, 1220, 1190, 1114, 1085, 1026, 976, 908, 888, 852, 817, 738, 668 cm$^{-1}$. FABMS: 443 (M+Li)$^+$.

**4.2.5. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)-4-phenylbutanoate (4e).** The product was obtained in 52% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41–7.15 (m, 5H), 5.22 (d, *J*=8 Hz, 1H), 4.76 (d, *J*=11.6 Hz, 1H), 4.39 (d, *J*=11.6 Hz, 1H), 4.30 (dd, *J*=5.2, 7.6 Hz, 1H), 4.23 (dd, *J*=1.6, 5.2 Hz, 1H), 4.15 (dd, *J*=2.8, 13.6 Hz, 1H), 4.10 (d, *J*=13.6 Hz, 1H), 3.99 (d, *J*=9.6 Hz, 1H), 3.98 (d, *J*=6.8 Hz, 1H), 3.87 (d, *J*=9.6 Hz, 1H), 2.82–2.69 (m, 2H), 2.12 (m, 2H), 1.55 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 172.8, 141.4, 137.6, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 126.2, 112.4, 112.2, 110.0, 109.9, 103.8, 103.8, 74.9, 74.0, 72.5, 72.4, 72.3, 72.3, 72.1, 71.2, 71.1, 71.0, 60.9, 60.9, 35.0, 34.8, 32.9, 32.8, 31.5, 31.4, 29.9, 28.1, 27.5, 27.4, 26.7, 26.5, 26.4, 26.3, 26.2, 25.6, 14.1. IR: ν 2987, 2933, 2873, 1754, 1604, 1496, 1454, 1383, 1372, 1296, 1220, 1191, 1168, 1113, 1086, 1066, 1028, 976, 912, 888, 850, 837, 810, 739, 699 cm$^{-1}$. FABMS: 519.2 (M+Li)$^+$.

**4.2.6. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-nitrobenzyloxy)acetate (3b).** This was prepared by the general esterification procedure using the alcohol **1** and *p*-nitrobenzyloxyacetic acid[86] **2b** to give **3b** as a greenish white solid (39%) and recovered alcohol **1** (33% recovery). Mp 84–86°C (dec.). $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.22 (apparent d, *J*=8.8 Hz, 2H), 7.56 (apparent d, *J*=8.8 Hz, 2H), 5.22 (d, *J*=8.0 Hz, 1H), 4.75 (s, 2H), 4.31 (d, *J*=16.4 Hz, 1H), 4.29 (d, *J*=13.2 Hz, 1H), 4.25 (dd, *J*=8.4, 2.4 Hz, 1H), 4.23 (d, *J*=16.4 Hz, 1H), 4.15 (dd, *J*=13.2, 2.4 Hz, 1H), 4.11 (d, *J*=13.2 Hz, 1H), 3.99 (d, *J*=9.2 Hz, 1H), 3.88 (d, *J*=9.6 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.37 (s, 6H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 169.7, 147.5, 144.8, 128.0, 123.6, 112.1, 109.7, 103.4, 74.6, 73.6, 72.0, 71.8, 71.2, 67.6, 60.5, 27.8, 26.3, 26.1, 26.0. IR: ν 2987, 2931, 1761, 1607, 1523, 1384, 1347, 1243, 1220, 1196, 1135, 1085, 1026, 976, 914, 885, 851, 818, 805, 740 cm$^{-1}$. FABMS *m/z* (% of base peak): 454.1 (M+H$^+$, 28), 438.0, (M+H−O$^+$, 88), 396.0 (M+H−$CH_3COCH_3^+$, 82), 243.1 (M−$OCOCH_2OR^+$, 48), 136.0 ($CH_2Ar^+$, 100). Anal. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09. Found: C, 55.80; H, 6.04; N, 3.09.

**4.2.7. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-nitrobenzyloxy)propionate (5a).** The product was obtained as an oil in 19% yield using alkylation Method C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.21 (apparent d, *J*=8.8 Hz, 2H), 7.56 (apparent d, *J*=8.8 Hz, 2H), 5.22–5.19 (d, *J*=8.0 Hz, 1H), 4.79 (d, *J*=12.4 Hz, 1H), 4.57–4.56 (d, *J*=12.4 Hz, 1H), 4.34–4.07 (m, 5H), 3.99–3.97 (d, *J*=9.6 Hz, 1H), 3.87–3.84 (d, *J*=9.2 Hz, 1H), 1.55 (s, 3H), 1.54 (d, *J*=6.8 Hz, 3H), 1.49 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 172.9, 147.7, 145.3, 128.3, 123.8, 112.3, 110.0, 103.8, 75.2, 74.9, 73.9,

72.2, 71.6, 70.9, 60.9, 28.0, 26.6, 26.5, 26.3, 18.9. IR: $\nu$ 2987, 2935, 2884, 1753, 1606, 1523, 1454, 1373, 1348, 1296, 1240, 1220, 1196, 1140, 1112, 1085, 1067, 1030, 976, 912, 888, 858, 821, 806, 739 $cm^{-1}$. FABMS *m/z* (% of base peak): 474.2 ($M+Li^+$, 53), 452.2 ($M-Me^+$, 15), 410.2 ($M+H-CH_3COCH_3^+$, 68), 243.2 ($M-OCOCH(Me)OR^+$, 36), 136.0 ($CH_2Ar^+$, 100). Anal. Calcd for $C_{22}H_{29}NO_{10}$: C, 56.53; H, 6.25; N, 3.00. Found: C, 56.81; H, 6.32; N, 3.02.

**4.2.8. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-methoxybenzyloxy)acetate (3c).** This was prepared by the general esterification procedure using the alcohol **1** and *p*-methoxybenzyloxyacetic acid[86] **2c** to give **3c** as a greenish white solid (92%). Mp 86°C (dec.). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.30 (apparent d, *J*=8.4 Hz, 2H), 6.88 (apparent d, *J*=8.8 Hz, 2H), 5.21 (d, *J*=7.6 Hz, 1H), 4.60 (d, *J*=11.2 Hz, 1H), 4.56 (d, *J*=11.2 Hz, 1H), 4.28 (dd, *J*=7.8, 5.0 Hz, 1H), 4.23 (dd, *J*=5.2, 1.2 Hz, 1H), 4.19 (d, *J*=16.8 Hz, 1H), 4.14 (dd, *J*=13.2, 2.4 Hz, 1H), 4.10 (d, *J*=16.4 Hz, 1H), 4.09 (d, *J*=13.2 Hz, 1H), 3.97 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=9.2 Hz, 1H), 3.81 (s, 3H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.3, 159.6, 129.9, 129.1, 113.9, 112.2, 109.8, 103.6, 74.7, 73.7, 73.0, 71.9, 70.8, 66.6, 60.6, 55.3, 27.9, 26.4, 26.3, 26.2. IR: $\nu$ 2988, 1931, 1761, 1613, 1514, 1455, 1384, 1302, 1250, 1221, 1195, 1114, 1085, 1032, 976, 914, 886, 851, 818, 805, 714 $cm^{-1}$. FABMS *m/z* (% of base peak): 437.2 ($M-H^+$, 64), 438 ($M^+$, 20), 423.0 (M−Me+, 46), 381.0 ($M+H-CH_3COCH_3^+$, 19), 244.0 ($M+H-OCOCH_2OR^+$, 80), 121.0 ($CH_2Ar^+$, 100). Anal. Calcd for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.15; H, 6.82.

**4.2.9. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-methoxybenzyloxy)propionate (6a).** The product was obtained as white crystals in 66% yield using alkylation Method C. Mp 121.5–123°C. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.30 (apparent d, *J*=8.4 Hz, 2H), 6.87 (apparent d, *J*=8.8 Hz, 1H), 5.22–5.19 (d, *J*=7.6 Hz, 1H), 4.70–4.65 (d, *J*=11.2 Hz, 1H), 4.39–4.38 (d, *J*=11.2 Hz, 1H), 4.31 (dd, *J*=7.8, 5.4 Hz, 1H), 4.23 (dd, *J*=5.2, 2.0 Hz, 1H), 4.15 (dd, *J*=13.4, 2.2 Hz, 1H), 4.11 (q, *J*=6.8 Hz, 1H), 4.10 (dd, *J*=13.2, 2.4 Hz, 1H), 3.99 (d, *J*=9.2 Hz, 1H), 3.86 (d, *J*=9.2 Hz, 1H), 3.79 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.46 (d, *J*=7.2 Hz, 3H), 1.39 (s, 3H), 1.35 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.3, 159.5, 129.9, 129.7, 113.9, 112.2, 109.8, 103.7, 74.8, 73.8, 73.7, 73.4, 72.0, 71.7, 71.0, 70.9, 60.7, 55.3, 27.9, 26.5, 26.4, 18.9. IR: $\nu$ 2987, 2937, 2825 (sh), 2050, 2003, 1901, 1748, 1612, 1587, 1514, 1489, 1467, 1449, 1375, 1344, 1316, 1300, 1251, 1221, 1179, 1137, 1112, 1085, 1063, 1028, 978, 914, 887, 865, 846, 824, 804, 767, 733, 686, 577 $cm^{-1}$. FABMS *m/z* (% of base peak): 459.3 ($M+Li^+$, 36), 437.2 ($M-Me^+$, 10), 243.2 ($M-OCOCH(Me)OR^+$, 36), 121.0 ($CH_2Ar^+$, 100). Anal. Calcd for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13. Found: C, 60.96; H, 6.94.

**4.2.10. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*p*-fluorobenzyloxy)acetate (3d).** Methyl glycolate. Glycolic acid (12.35 g, 163 mmol) and *p*-toluenesulfonic acid monohydrate (102 mg, 0.537 mmol) were dissolved in 100 mL dry MeOH. The mixture was heated to reflux in a heating mantle. After 2.5 h, the mixture was rotovapped to give a colorless liquid. The liquid was dissolved in $Et_2O$ (85 mL), washed with saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, rotovapped, and dried on the oil pump to give a pale green liquid (8.55 g, 59%). The material was pure by $^1H$ NMR and was used in subsequent reactions. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 4.18 (d, *J*=5.4 Hz, 2H), 3.81 (s, 3H), 2.34 (t, *J*=5.5 Hz, 1H, exchanges with $D_2O$).

*p*-Fluorobenzyloxyacetic acid (**2d**). In a two-neck flask a suspension of sodium hydride (60% in mineral oil, 590 mg, 14.8 mmol) was washed with hexanes (3×10 mL) and then dried under oil pump vacuum for 10 min. A solution of methyl glycolate (1.04 g, 11.6 mmol) in dry THF (10 mL) was added to the suspension of sodium hydride in dry THF (50 mL) over about 3 min. After 5 min *p*-fluorobenzyl bromide (2.17 mL, 17.3 mmol) was added dropwise over about 3 min. Tetrabutylammonium iodide (110 mg, 0.30 mmol) and DMPU (0.30 mL, 2.5 mmol) were added. The flask was insulated from light with aluminum foil and the mixture was stirred overnight. The reaction was followed by $^1H$ NMR. After stirring at rt for 14 h, the reaction mixture was heated in an oil bath to about 70°C. After stirring at this temperature for an additional 6 h, the reaction mixture was allowed to cool to rt. After 30 min the reaction was quenched by slow addition of saturated $NH_4Cl$ (10 mL). The layers were separated, and the solvent was removed from the organic layer. To the residue was added 1 M NaOH (50 mL) and the aqueous quench. After stirring at rt for 1 h, the aqueous layer was washed with $Et_2O$ (3×20 mL) and then cooled with crushed ice. Concentrated HCl was added until the pH was 1–2. The aqueous layer was extracted with DCM (3×20 mL). These combined organic extracts were dried ($MgSO_4$), filtered, and rotovapped to give a yellow liquid (1.0 g). $^1H$ NMR indicated that the liquid still contained some ester. To the liquid was added 4 M NaOH (40 mL). This suspension was heated to 60–70°C for 1 h, during which time it became a solution. After cooling at rt for 20 min, the aqueous layer was washed with DCM (3×20 mL) and then cooled with crushed ice. Concentrated HCl (16 mL) was added until the pH was 1–2. The aqueous layer was extracted with DCM (3×20 mL). These combined organic extracts were dried ($MgSO_4$), filtered, rotovapped, and dried on the oil pump to give **2d** as a yellow liquid which froze into white needles in the freezer (379 mg, 18%). Mp 44–45°C. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.37–7.32 (m, 2H), 7.09–7.03 (m, 2H), 4.62 (s, 2H), 4.14 (s, 2H). $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 175.3, 162.7 ($^1J_{C-F}$=246 Hz), 132.7, 130.0 ($^3J_{C-F}$=8 Hz), 115.5 ($^2J_{C-F}$=21 Hz), 72.7, 66.7. $^{19}F$ NMR ($CDCl_3$, 282 MHz): $\delta$ −114.7. IR: $\nu$ 3472–2919, 1731, 1604, 1511, 1433, 1223, 1155, 1116, 1016, 854, 821, 772, 660 $cm^{-1}$. FABMS *m/z* (% of base peak): 183.1 ($M-H^+$, 28).

The glycolate was prepared by the general esterification procedure using the alcohol **1** and *p*-fluorobenzyloxyacetic acid **2d** to give **3d** as a greenish white solid (84%). Mp 105°C. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.37–7.32 (m, 2H), 7.06–7.00 (m, 2H), 5.22 (d, *J*=7.8 Hz, 1H), 4.60 (s, 2H), 4.29 (dd, *J*=7.8, 5.3 Hz, 1H), 4.22 (d, *J*=12.0 Hz, 1H), 4.22 (ddd, *J*=11.1, 4.5, 1.2 Hz, 1H), 4.15 (d, *J*=12.8 Hz, 1H), 4.12 (d, *J*=2.4 Hz, 1H), 4.07 (d, *J*=5.1 Hz, 1H), 3.97 (d, *J*=9.3 Hz, 1H), 3.87 (d, *J*=9.3 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.1, 162.6 ($^1J_{C-F}$=246 Hz), 133.0, 129.9 ($^3J_{C-F}$=8 Hz), 115.4

($^2J_{C-F}$=22 Hz), 112.2, 109.8, 103.6, 74.7, 73.8, 72.6, 72.0, 71.1, 67.1, 60.7, 27.8, 26.4, 26.2. $^{19}$F NMR ($CDCl_3$, 282 MHz): $\delta$ −115.1. IR: $\nu$ 2990, 2931, 2884, 1759, 1602, 1509, 1455, 1373, 1222, 1196, 1127, 1084, 1026, 976, 914, 886, 855, 824, 818, 773, 738, 720, 668 cm$^{-1}$. FABMS *m/z* (% of base peak): 433.2 (M+Li$^+$, 44), 369.1 (M+H−$CH_3COCH_3^+$, 62), 243.1 (M−OCOCH$_2$OR$^+$, 20). Anal. Calcd for $C_{21}H_{27}FO_8$: C, 59.15; H, 6.38. Found: C, 59.44; H, 6.44.

**4.2.11. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*p*-fluorobenzyloxy)propionate (7a).** The product was obtained as a colorless oil in 75% yield using alkylation Method C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.37–7.34 (m, 2H), 7.05–7.00 (m, 2H), 5.22–5.19 (d, *J*=8.0 Hz, 1H), 4.67 (d, *J*=11.2 Hz, 1H), 4.40 (d, *J*=11.2 Hz, 1H), 4.30 (dd, *J*=8.0, 5.2 Hz, 1H), 4.23 (dd, *J*=5.4, 1.8 Hz, 1H), 4.16 (dd, *J*=13.6, 2.4 Hz, 1H), 4.11 (dd, *J*=13.2, 1.8 Hz, 1H), 4.10 (q, *J*=7.2 Hz, 1H), 3.99 (d, *J*=9.6 Hz, 1H), 3.87 (d, *J*=9.2 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.48 (d, *J*=6.4 Hz, 3H), 1.39 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.2, 162.8 ($^1J_{C-F}$=247 Hz), 133.6, 130.1 ($^3J_{C-F}$=8 Hz), 115.5 ($^2J_{C-F}$=22 Hz), 112.4, 110.0, 103.8, 75.0, 74.4, 74.0, 72.2, 71.5, 71.3, 60.9, 28.0, 26.6, 26.4, 19.0. $^{19}$F NMR ($CDCl_3$, 282 MHz): $\delta$ −115.4. IR: $\nu$ 3424, 2987, 2931, 1754, 1602, 1510, 1454, 1372, 1326, 1296, 1221, 1190, 1138, 1112, 1084, 1067, 1032, 975, 908, 885, 820 cm$^{-1}$. FABMS *m/z* (% of base peak): 447.2 (M+Li$^+$, 27), 425.2 (M−Me$^+$, 15), 383.2 (M+H−$CH_3COCH_3^+$, 84), 243.1 (M−OCOCH(Me)OR$^+$, 24). Anal. Calcd for $C_{22}H_{29}FO_8$: C, 59.99; H, 6.64. Found: C, 59.95; H, 6.61.

**4.2.12. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl methoxyacetate (3e).** This was prepared by the general esterification procedure using the alcohol **1** and methoxyacetic acid (Acros) to give **3e** as a yellowish green oil (74%) and recovered alcohol **1** (25% recovery). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.21 (d, *J*=8.0 Hz, 1H), 4.29 (dd, *J*=7.8, 5.4 Hz, 1H), 4.24 (ddd, *J*=5.4, 2.4, 1.2 Hz, 1H), 4.16 (d, *J*=16.4 Hz, 1H), 4.15 (dd, *J*=13.4, 2.6 Hz, 1H), 4.09 (d, *J*=13.2 Hz, 1H), 4.08 (d, *J*=16.8 Hz, 1H), 3.97 (d, *J*=9.6 Hz, 1H), 3.86 (d, *J*=9.6 Hz, 1H), 3.47 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.1, 112.2, 109.8, 103.6, 74.5, 73.8, 72.0, 71.0, 69.7, 60.7, 59.5, 27.9, 26.5, 26.3, 26.2. IR: $\nu$ 2988, 2936, 2825, 1764, 1454, 1373, 1221, 1192, 1129, 1085, 976, 913, 885, 850, 839, 804, 714, 668 cm$^{-1}$. FABMS *m/z* (% of base peak): 331.2 (M−H$^+$, 68), 317.2 (M−Me$^+$, 54), 275.2 (M+H−$CH_3COCH_3^+$, 100), 243.2 (M−OCOCH$_2$OR$^+$, 27). Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 54.14; H, 7.11.

**4.2.13. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-methoxypropionate (8a).** The product was obtained as white crystals in 75% yield using alkylation Method C. Mp 81–85°C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.20–5.17 (d, *J*=7.8 Hz, 1H), 4.31 (dd, *J*=8.0, 5.2 Hz, 1H), 4.23 (dd, *J*=5.2, 1.6 Hz, 1H), 4.15 (dd, *J*=13.6, 2.4 Hz, 1H), 4.10 (d, *J*=13.6 Hz, 1H), 4.0–3.9 (m, 1H), 3.95 (dd, *J*=6.6 Hz, 1H), 3.85–3.82 (d, *J*=9.2 Hz, 1H), 3.41 (s, 3H), 1.60–1.34 (m, 15H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.1, 112.3, 109.9, 103.8, 74.9, 73.9, 72.1, 71.1, 60.8, 57.9, 28.0, 26.6, 26.5, 26.4, 18.7. IR: $\nu$ 2988, 2939, 2889, 2825, 1755, 1737, 1454, 1451, 1373, 1264, 1237, 1220, 1189, 1127, 1113, 1084, 1066, 1041, 976, 914, 886, 854, 845, 820, 806, 800 cm$^{-1}$. FABMS *m/z* (% of base peak): 353.2 (M+Li$^+$, 62), 331.2 (M−Me$^+$, 72), 289.1 (M+H−$CH_3COCH_3^+$, 100), 243.2 (M−OCOCH(Me)OR$^+$, 33). Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.73; H, 7.66.

**4.2.14. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (methoxymethoxy)acetate (3f).** Benzyl (methoxymethoxy)acetate. Benzyl glycolate[87] (2.77 g, 16.7 mmol) was dissolved in 20 mL dry THF at rt. *i*-Pr$_2$NEt (4.7 mL, 27 mmol) and iodomethyl methyl ether (2.1 mL, 25 mmol) were added. The mixture fumed and formed white precipitate upon the addition of the iodide. After stirring at rt for 3.5 h, the mixture was heated to reflux. After 22 h, 25 mL ice-cold saturated $K_2CO_3$ was added to the reaction mixture. The mixture was extracted with EtOAc (3×25 mL). The combined DCM extracts were washed with saturated NaCl (10 mL), dried ($MgSO_4$), and rotovapped to give a brown semi-solid. The liquid was separated on a flash silica column (1:10 EtOAc/hexanes to 1:8 EtOAc/hexanes). Fractions were combined, rotovapped, and dried on the oil pump to give the product as a yellow liquid (2.97 g, 85%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$7.37 (s, 5H), 5.21 (s, 2H), 4.72 (s, 2H), 4.21 (s, 2H), 3.39 (s, 2H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 169.8, 135.4, 128.4, 128.3, 96.2, 66.3, 64.1, 55.5. IR: $\nu$ 3033, 2952, 2896, 2825, 1758, 1498, 1456, 1404, 1364, 1279, 1194, 1152, 1121, 1062, 1015, 920, 841, 818, 804, 753, 698 cm$^{-1}$. FABMS *m/z* (% of base peak): 211.1 (M+H$^+$, 100).

(Methoxymethoxy)acetic acid (**2f**). The ester (204 mg, 0.971 mmol) from above was dissolved in ~5 mL EtOAc. The flask was evacuated and flushed with $N_2$ three times. $Pd(OH)_2$ (23 mg) was added to the solution. The flask was evacuated and flushed with $H_2$ (balloon pressure) three times. The mixture was stirred at rt for 2 h. The mixture was filtered through a pad of packed Celite. The Celite was washed with ~40 mL EtOAc. The filtrate was rotovapped and dried on the oil pump to give **2f** as a yellow liquid (96 mg, 82%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 10.52 (s, 1H), 4.74 (s, 2H), 4.24 (s, 2H), 3.43 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 175.7, 96.5, 64.0, 56.0. IR: $\nu$ 3449, 1734, 1605, 1428, 1215, 1151, 1114, 1055 cm$^{-1}$. FABMS *m/z* (% of base peak): 120.0 (M$^+$, 13). Anal. Calcd for $C_4H_8O_4$: C, 40.00; H, 6.71. Found: C, 39.86; H, 6.85.

The glycolate was prepared by the general esterification procedure using the alcohol **1** and methoxymethoxyacetic acid **2f** to give **3f** as a yellow oil (771 mg, 31%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.20 (d, *J*=7.6 Hz, 1H), 4.72 (s, 2H), 4.30 (d, *J*=16.8 Hz, 1H), 4.29 (dd, *J*=8.0, 5.6 Hz, 1H), 4.24 (ddd, *J*=6.8, 1.2, 1 Hz, 1H), 4.20 (d, *J*=16.8 Hz, 1H), 4.14 (dd, *J*=13.4, 2.2 Hz, 1H), 4.09 (d, *J*=13.6 Hz, 1H), 3.97 (d, *J*=9.3 Hz, 1H), 3.85 (d, *J*=9.3 Hz, 1H), 3.40 (s, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.0, 112.3, 109.9, 103.6, 96.6, 74.8, 73.8, 71.9, 71.0, 64.3, 60.7, 55.9, 27.9, 26.5, 26.4, 26.2. IR: $\nu$ 3624, 3530, 2990, 2931, 2884, 2825, 1764, 1737, 1455, 1384, 1373, 1243, 1220, 1196, 1149, 1120, 1085, 1061, 979, 920, 885, 850, 808, 720 cm$^{-1}$. FABMS *m/z* (% of base peak): 369.3 (M+Li$^+$, 44), 347.2 (M−Me$^+$, 43), 305.2 (M+H−$CH_3COCH_3^+$, 100), 243.2

($M-OCOCH_2OR^+$, 52). Anal. Calcd for $C_{16}H_{26}O_9$: C, 53.03; H, 7.23. Found: C, 53.25; H, 7.32.

**4.2.15. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(methoxymethoxy)propionate (9a).** The product was obtained in 65% yield using alkylation Method C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.18–5.14 (d, $J$=8.4 Hz, 1H), 4.70 (q, $J$=7.1 Hz, 2H), 4.29 (dd, $J$=7.8, 5.0 Hz, 1H), 4.23 (dd, $J$=5.6, 1.8 Hz, 1H), 4.14 (dd, $J$=13.6, 2.4 Hz, 1H), 4.09 (d, $J$=13.6 Hz, 1H), 3.96 (d, $J$=9.2 Hz, 1H), 3.85 (d, $J$=9.2 Hz, 1H), 3.39 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.48 (d, $J$=7.2 Hz, 3H), 1.40 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.0, 112.3, 109.8, 103.8, 96.3, 75.0, 74.0, 71.9, 71.8, 70.9, 60.7, 56.0, 27.9, 26.6, 26.2, 18.7. IR: $\nu$ 2987, 2937, 2891, 2826, 1758, 1454, 1373, 1326, 1296, 1221, 1190, 1156, 1126, 1085, 1026, 976, 915, 886, 852, 810, 765, 750, 654, 626 cm$^{-1}$. FABMS $m/z$ (% of base peak): 383.2 ($M+Li^+$, 72), 361.2 ($M-Me^+$, 20), 319.2 ($M+H-CH_3COCH_3^+$, 69), 243.2 ($M-OCOCH(Me)OR^+$, 34). Anal. Calcd for $C_{17}H_{28}O_9$: C, 54.25; H, 7.50. Found: C, 54.38; H, 7.51.

**4.2.16. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (benzyloxymethoxy)acetate (3g).** Methyl (benzyloxymethoxy)acetate. NaI (84 mg, 0.56 mmol) was dissolved in 25 mL dry THF at 0°C. Methyl glycolate (2.50 g, 27.8 mmol), $i$-$Pr_2NEt$ (10 mL, 57.5 mmol), and benzyl chloromethyl ether[88] (8.65 g, 55.3 mmol) were added. The mixture was left to stir, with warming to rt. After 45 h, the reaction mixture was poured into 30 mL ice-cold saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with 4×25 mL EtOAc. The combined organic layers were washed with 10 mL saturated NaCl, dried ($MgSO_4$), and rotovapped to give a yellow liquid. It was separated on a flash silica column (1:10 EtOAc/hexanes to 1:4 EtOAc/hexanes). Fractions were combined, rotovapped, and dried on the oil pump to give the ester as a pale yellow liquid (4.524 g, 77%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.34 (s, 5H), 4.85 (s, 2H), 4.65 (s, 2H), 4.23 (s, 2H), 3.76 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.3, 137.4, 128.2, 127.7, 127.6, 94.4, 69.6, 64.2, 51.6. IR: $\nu$ 3037, 2953, 2896, 1758, 1737, 1498, 1454, 1437, 1383, 1285, 1215, 1170, 1122, 1063, 1028, 931, 844, 824, 814, 742, 699 cm$^{-1}$. FABMS $m/z$ (% of base peak): 211.0 ($M+H^+$, 60). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.57; H, 6.69.

(Benzyloxymethoxy)acetic acid (**2g**). The ester (1.01 g, 4.80 mmol) from above was dissolved in 5 mL THF, 5 mL deionized $H_2O$, and 3 mL 4 M NaOH. After stirring vigorously at rt for 30 min, the mixture was extracted with 2×15 mL $Et_2O$. The aqueous layer was cooled with ice and then acidified with 10% citric acid and ~0.5 mL concentrated HCl (pH <2 by pH paper). The aqueous layer was extracted with 4×25 mL $Et_2O$. These combined $Et_2O$ layers were washed with 10 mL saturated NaCl, dried ($MgSO_4$), filtered, rotovapped, and dried on the oil pump to give **2g** as a colorless oil (914 mg, 97% yield). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.35 (s, 5H), 4.87 (s, 2H), 4.67 (s, 2H), 4.27 (s, 2H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 175.8, 137.3, 128.6, 128.0, 94.6, 70.1, 64.1. IR: $\nu$ 3436, 3032, 2897, 1760, 1732, 1497, 1454, 1433, 1384, 1249, 1209, 1170, 1120, 1062, 1028, 938, 908, 824, 742, 698 cm$^{-1}$. FABMS $m/z$ (% of base peak): 197.0 ($M+H^+$, 56). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.93; H, 5.99.

The glycolate was obtained by the general esterification procedure using the alcohol **1** and benzyloxymethoxyacetic acid **2g** to give **3g** as a green oil (85%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.35 (s, 5H), 5.20 (d, $J$=7.6 Hz, 1H), 4.86 (s, 2H), 4.66 (s, 2H), 4.35 (d, $J$=16.8 Hz, 1H), 4.28 (dd, $J$=7.6, 5.2 Hz, 1H), 4.25 (d, $J$=16.4 Hz, 1H), 4.23 (dd, $J$=2.8, 1.2 Hz, 1H), 4.14 (dd, $J$=13.6, 2.4 Hz, 1H), 4.09 (d, $J$=13.2 Hz, 1H), 3.94 (d, $J$=9.6 Hz, 1H), 3.83 (d, $J$=9.6 Hz, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 170.1, 137.6, 128.6, 128.1, 128.0, 112.3, 109.9, 103.7, 94.8, 74.7, 73.9, 72.0, 71.1, 70.2, 64.5, 60.7, 27.9, 26.5, 26.5, 26.3. IR: $\nu$ 2986, 2934, 2889, 1763, 1496, 1455, 1373, 1220, 1198, 1167, 1114, 1085, 1063, 1028, 976, 913, 884, 849, 805, 739, 699 cm$^{-1}$. FABMS $m/z$ (% of base peak): 445.3 ($M+Li^+$, 52), 423.3 ($M-Me^+$, 26), 381.3 ($M+H-CH_3COCH_3^+$, 72), 351.2 ($M+H-CH_3COCH_3-CH_2O^+$, 47), 243.2 ($M-OCOCH_2OR^+$, 100). Anal. Calcd for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.53; H, 6.91.

**4.2.17. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxymethoxy)propionate (10a).** The product was obtained in 68% yield using alkylation Method C. Mp 82–83.5°C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.37–7.35 (m, 5H), 5.19–5.13 (d, $J$=8.0 Hz, 1H), 4.85–4.81 (m, 2H), 4.68–4.61 (m, 2H), 4.34 (q, $J$=6.8 Hz, 1H), 4.27 (dd, $J$=7.8, 5.4 Hz, 1H), 4.22–4.20 (m, 1H), 4.13 (dd, $J$=13.2, 2.6 Hz, 1H), 4.07 (d, $J$=13.6 Hz, 1H), 3.84 (d, $J$=9.6 Hz, 1H), 3.77 (d, $J$=9.6 Hz, 1H), 1.54 (s, 3H), 1.48 (d, $J$=7.6 Hz, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.0, 137.8, 128.6, 128.2, 128.0, 112.3, 109.9, 130.8, 96.4, 94.4, 75.0, 74.0, 72.0, 71.8, 70.9, 70.2, 60.7, 28.0, 26.6, 26.2, 18.8. IR: $\nu$ 2987, 2937, 2890, 1760, 1454, 1373, 1221, 1167, 1123, 1114, 1084, 1026, 976, 912, 886, 852, 805, 738, 699 cm$^{-1}$. FABMS $m/z$ (% of base peak): 459.3 ($M+Li^+$, 53), 437.2 ($M-Me^+$, 38), 395.2 ($M+H-CH_3COCH_3^+$, 48), 365.2 ($M+H-CH_3-COCH_3-CH_2O^+$, 24), 243.2 ($M-OCOCH(Me)OR^+$, 100). Anal. Calcd for $C_{23}H_{32}O_9$: C, 61.05; H, 7.13. Found: C, 61.30; H, 7.00.

**4.2.18. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*t*-butyldimethylsilyloxy)acetate (3h).** The glycolate was obtained by the general esterification procedure using alcohol **1** and (*t*-butyldimethylsilyloxy)acetic acid[89] **2h** to give **3h** (49%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.17 (d, $J$=7.5 Hz, 1H), 4.39–4.21 (m, 4H), 4.14 (dd, $J$=2.4, 13.8 Hz, 1H), 4.08 (d, $J$=13.2 Hz, 1H), 3.96 (d, $J$=9.6 Hz, 1H), 3.85 (d, $J$=8.7 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 171.7, 112.3, 109.9, 103.8, 74.9, 74.0, 72.0, 70.9, 61.8, 60.7, 28.0, 26.6, 26.5, 26.4, 26.0, 25.9, −5.3. IR: $\nu$ 2990, 2931, 2860, 1768, 1461, 1378, 1369, 1255, 1220, 1142, 1086, 973, 914, 885, 853, 836, 779 cm$^{-1}$. FABMS: 439.1 ($M+Li^+$). Anal. Calcd for $C_{20}H_{36}O_8Si$: C, 55.53; H, 8.39. Found: C, 55.35; H, 8.39.

**4.2.19. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyloxy)propionate (11a).** The product was obtained in 76% yield using alkylation Method

B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.13 (d, $J$=7.2 Hz, 1H), 4.39 (dd, $J$=7.5, 14.1 Hz, 1H), 4.28 (m, 1H), 4.21 (m, 1H), 4.14 (dd, $J$=2.1, 13.2 Hz, 1H), 4.08 (d, $J$=14.1 Hz, 1H), 3.96 (d, $J$=9.6 Hz, 1H), 3.83 (d, $J$=9.6 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.45 (d, $J$=6.6 Hz, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 174.3, 112.3, 109.8, 103.9, 74.9, 73.9, 72.1, 70.9, 68.6, 60.8, 28.0, 26.7, 26.6, 26.4, 26.0, 21.9, 18.5, −4.7, −5.2. IR: $\nu$ 2987, 2933, 2888, 2857, 1768, 1740, 1472, 1383, 1372, 1254, 1220, 1143, 1086, 1068, 1030, 976, 914, 887, 837, 810, 780, 668 cm$^{-1}$. FABMS: 445.1 (M−H$^+$). Anal. Calcd for $C_{21}H_{38}O_8Si$: C, 56.48; H, 8.58. Found: C, 56.61; H, 8.63.

**4.2.20. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyloxy)-4-pentenoate (11b).** The product was obtained in 78% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.90–5.80 (m, 1H), 5.17–5.08 (m, 3H), 4.33–4.26 (m, 2H), 4.21 (dd, $J$=1.6, 5.2 Hz, 1H), 4.13 (dd, $J$=2.4, 13.2 Hz, 1H), 4.08 (d, $J$=9.9 Hz, 1H), 3.95 (d, $J$=9.2 Hz, 1H), 3.84 (d, $J$=9.2 Hz, 1H), 2.51 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.2, 133.5, 118.5, 112.3, 109.8, 103.9, 74.8, 73.9, 72.3, 72.0, 71.0, 60.8, 40.2, 28.0, 26.7, 26.5, 26.4, 25.9, 18.5, −4.7, −5.2. IR: $\nu$ 3080, 3987, 2932, 2887, 2838, 1765, 1738, 1643, 1472, 1462, 1434, 1384, 1372, 1296, 1220, 1140, 1086, 1044, 976, 913, 888, 836, 810, 779, 737, 668, 626 cm$^{-1}$. FABMS: 471.0 (M−H$^+$). Anal. Calcd for $C_{23}H_{40}O_8Si$ (472.64); C, 58.45; H, 8.57. Found: C, 58.47; H, 8.57.

**4.2.21. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldimethylsilyloxy)-3-phenylpropionate (11c).** The product was obtained in 89% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.25 (m, 5H), 5.16 (d, $J$=8.1 Hz, 1H), 4.41 (dd, $J$=3.6, 8.7 Hz, 1H), 4.28 (dd, $J$=5.1, 7.2 Hz, 1H), 4.21 (dd, $J$=1.5, 5.1 Hz, 1H), 4.15 (dd, $J$=2.1, 13.8 Hz, 1H), 4.08 (d, $J$=13.2 Hz, 1H), 3.92 (d, $J$=9.3 Hz, 1H), 3.73 (d, $J$=9.6 Hz, 1H), 3.12 (dd, $J$=3.6, 13.8 Hz, 1H), 2.93 (dd, $J$=8.7, 14.1 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.80 (s, 6H), −0.09 (s, 3H), −0.23 (s, 3H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.2, 137.5, 130.2, 128.3, 126.8, 112.2, 109.8, 103.8, 74.8, 73.9, 73.8, 72.0, 71.1, 60.8, 42.0, 28.0, 26.6, 26.5, 26.4, 25.8, 18.4, −5.2, −5.6. IR: $\nu$ 2990, 2931, 2860, 1764, 1736, 1490, 1456, 1372, 1251, 1220, 1128, 1086, 976, 938, 903, 888, 845, 810, 779, 699 cm$^{-1}$. FABMS: 529.1 (M+Li$^+$).

**4.2.22. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (*t*-butyldiphenylsilyloxy)acetate (3i).** The glycolate was obtained by the general esterification procedure using the alcohol **1** and (*t*-butyldiphenylsilyloxy)acetic acid[90] to give **3i** (79%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.72–7.67 (m, 4H), 7.44–7.37 (m, 6H), 5.15 (d, $J$=7.2 Hz, 1H), 4.40 (d, $J$=16.8 Hz, 1H), 4.24 (d, $J$=16.8 Hz, 1H), 4.24–4.18 (m, 2H), 4.10 (dd, $J$=1.5, 13.8 Hz, 1H), 4.05 (d, $J$=13.2 Hz, 1H), 3.92 (d, $J$=9.6 Hz, 1H), 3.68 (d, $J$=9 Hz, 1H), 1.55 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.09 (s, 9H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 171.0, 135.8, 135.7, 133.0, 132.8, 130.1, 130.1, 128.0, 112.2, 109.8, 103.7, 74.9, 73.9, 71.9, 70.7, 62.2, 60.6, 28.0, 26.9, 26.7, 26.6, 26.2, 19.5. IR: $\nu$ 3071, 2987, 2932, 2857, 1770, 1740, 1472, 1428, 1383, 1372, 1297, 1221, 1197, 1140, 1113, 1085, 1067, 1028, 976, 914, 881, 849, 822, 800, 741, 702, 609 cm$^{-1}$. FABMS: 563.4 (M+Li$^+$).

**4.2.23. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyloxy)propionate (12a).** The product was obtained in 83% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.70–7.66 (m, 4H), 7.47–7.33 (m, 6H), 5.08 (d, $J$=7.2 Hz, 1H), 4.33 (dd, $J$=6.6, 13.8 Hz, 1H), 4.24–4.18 (m, 2H), 4.11 (dd, $J$=2.1, 13.8 Hz, 1H), 4.05 (d, $J$=14.1 Hz, 1H), 3.85 (d, $J$=9.6 Hz, 1H), 3.49 (d, $J$=9.6 Hz, 1H), 1.54 (s, 3H), 1.45 (s, 3H), 1.43 (d, $J$=6.6 Hz, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.10 (s, 9H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.7, 136.1, 135.9, 133.8, 133.1, 130.0, 127.9, 112.2, 109.8, 103.7, 74.9, 73.9, 71.7, 70.6, 69.0, 60.6, 28.0, 27.0, 26.8, 26.7, 26.2, 21.9, 19.4. IR: $\nu$ 3071, 2987, 2932, 2857, 1764, 1740, 1472, 1428, 1372, 1221, 1189, 1135, 1112, 1085, 1066, 1026, 975, 911, 887, 866, 823, 785, 740, 702, 608 cm$^{-1}$. FABMS: 577.5 (M+Li$^+$).

**4.2.24. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyloxy)-4-pentenoate (12b).** The product was obtained in 88% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.69–7.66 (m, 4H), 7.45–7.33 (m, 6H), 5.90–5.77 (m, 1H), 5.18–5.03 (m, 3H), 4.38 (t, $J$=5.1 Hz, 1H), 4.27 (dd, $J$=2.1, 13.8 Hz, 1H), 4.22–4.16 (m, 2H), 4.04 (d, $J$=13.8 Hz, 1H), 3.82 (d, $J$=9.3 Hz, 1H), 3.49 (d, $J$=9.3 Hz, 1H), 2.46 (t, $J$=6.6, 5.8 Hz, 2H), 1.52 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.10 (s, 9H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 172.4, 136.2, 136.1, 133.6, 133.1, 132.8, 130.0, 127.9, 118.7, 112.2, 109.7, 103.7, 74.9, 74.0, 72.4, 71.7, 70.7, 60.6, 40.0, 28.1, 27.1, 26.9, 26.8, 26.7, 19.6. IR: $\nu$ 3072, 2990, 2931, 2861, 1766, 1738, 1472, 1372, 1243, 1220, 1136, 1113, 1086, 1030, 996, 976, 912, 887, 862, 824, 740, 702 cm$^{-1}$. FABMS: 603.5 (M+Li$^+$).

**4.2.25. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(*t*-butyldiphenylsilyloxy)-3-phenylpropionate (12c).** The product was obtained in 88% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.61–7.53 (m, 2H), 7.43–7.17 (m, 13H), 5.00 (d, $J$=7.2 Hz, 1H), 4.54 (t, $J$=5.9 Hz, 1H), 4.14–4.03 (m, 3H), 3.99 (d, $J$=13.2 Hz, 1H), 3.66 (d, $J$=9.3 Hz, 1H), 3.07 (d, $J$=9.6 Hz, 1H), 3.02 (s, 1H), 3.00 (d, $J$=1.5 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 1.04 (s, 9H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 172.2, 136.8, 136.3, 136.0, 133.4, 133.0, 130.3, 130.0, 129.9, 128.3, 127.8, 126.8, 112.1, 109.7, 103.5, 74.7, 73.9, 73.7, 71.5, 70.5, 60.6, 41.8, 27.9, 27.0, 26.9, 26.6, 26.2. IR: $\nu$ 2990, 2931, 2860, 1766, 1731, 1455, 1384, 1372, 1214, 1113, 1085, 1032, 973, 886, 853, 818, 773, 738, 701, 668 cm$^{-1}$. FABMS: 653.3 (M+Li$^+$).

**4.2.26. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (triethylsilyloxy)acetate (3j).** A solution of **3a** in EtOAc was stirred in the presence of $H_2$ (balloon pressure) and 20% $Pd(OH)_2$/C overnight. $Pd(OH)_2$ was removed by filtration through Celite. The crude product (1.52 g, 5.84 mmol) was dissolved in anhydrous pyridine (15 mL), and triethylsilyl chloride (1.1 mL, 6.5 mmol) was added dropwise at 0°C. The reaction mixture was stirred at rt

overnight. Pyridine was removed on the rotovap. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Upon removing solvent, the residue was purified by flash chromatography on a silica gel column (hexanes/ethyl acetate) to afford **3j** as an oil (2.08 g, 82%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.18 (d, $J$=7.7 Hz, 1H), 4.35 (d, $J$=16.8 Hz, 1H), 4.30–4.22 (m, 3H), 4.14 (dd, $J$=2.1, 13.6 Hz, 1H), 4.08 (d, $J$=13.2 Hz, 1H), 3.96 (d, $J$=9.3 Hz, 1H), 3.85 (d, $J$=9.5 Hz, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 0.98 (t, $J$=7.8 Hz, 9H), 0.65 (dd, $J$=7.6, 15.6 Hz, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 171.6, 112.3, 109.9, 103.8, 74.9, 74.0, 72.0, 70.8, 61.4, 60.7, 28.0, 26.6, 26.3, 6.8, 4.5. IR: $\nu$ 2990, 2954, 2884, 1768, 1737, 1455, 1384, 1372, 1221, 1196, 1142, 1086, 1067, 976, 887, 852, 816, 794, 745 cm$^{-1}$. FABMS: 439.1 (M+Li$^+$). Anal. Calcd for $C_{20}H_{36}O_8Si$: C, 55.53; H, 8.39. Found: C, 55.69; H, 8.39.

**4.2.27. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triethylsilyloxy)propionate (13a).** The product was obtained in 77% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.14 (d, $J$=5.7 Hz, 1H), 4.39 (dd, $J$=4.8, 9.9 Hz, 1H), 4.27 (dd, $J$=3.9, 6.0 Hz, 1H), 4.22 (dd, $J$=1.5, 3.9 Hz, 1H), 4.14 (dd, $J$=1.8, 10.2 Hz, 1H), 4.08 (d, $J$=10.2 Hz, 1H), 3.97 (d, $J$=6.9 Hz, 1H), 3.83 (d, $J$=6.9 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H), 1.46 (d, $J$=5.4 Hz, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.97 (t, $J$=6.6 Hz, 9H), 0.63 (dd, $J$=5.7, 11.7 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 174.2, 112.2, 109.8, 103.8, 74.8, 73.9, 71.9, 70.8, 68.0, 60.7, 27.9, 26.6, 26.5, 26.3, 21.9, 6.8, 4.7. IR: $\nu$ 2990, 2943, 2884, 2731, 1764, 1624, 1459, 1414, 1372, 1325, 1296, 1221, 1190, 1140, 1086, 1018, 977, 912, 889, 865, 850, 836, 812, 786, 746, 674, 626, 514 cm$^{-1}$. FABMS: 453.1 (M+Li$^+$). Anal. Calcd for $C_{21}H_{38}O_8Si$ (446.61); C, 56.48; H, 8.58. Found: C, 56.24; H, 8.50.

**4.2.28. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triethylsilyloxy)-4-pentenoate (13b).** The product was obtained in 71% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.91–5.81 (m, 1H), 5.18–5.09 (m, 3H), 4.33 (dd, $J$=5.2, 6.8 Hz, 1H), 4.28 (dd, $J$=6.6, 8.4 Hz, 1H), 4.21 (dd, $J$=2.0, 5.6 Hz, 1H), 4.14 (dd, $J$=2.8, 13.6 Hz, 1H), 4.08 (d, $J$=13.2 Hz, 1H), 3.96 (d, $J$=9.6 Hz, 1H), 3.84 (d, $J$=9.2 Hz, 1H), 2.52 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 0.96 (t, $J$=7.6 Hz, 9H), 0.62 (dd, $J$=7.6, 15.6 Hz, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.2, 133.4, 118.4, 112.2, 109.8, 103.9, 74.9, 74.0, 72.0, 72.0, 71.0, 60.8, 40.2, 28.0, 26.7, 26.6, 26.4, 6.9, 4.8. IR: $\nu$ 3079, 2987, 2954, 2878, 1763, 1738, 1642, 1457, 1415, 1383, 1372, 1296, 1240, 1220, 1190, 1139, 1114, 1086, 1067, 1043, 1030, 1004, 976, 912, 888, 850, 832, 810, 745, 676, 626, 514 cm$^{-1}$. FABMS: 471.0 (M−H$^+$). Anal. Calcd for $C_{23}H_{40}O_8Si$ (472.64); C, 58.45; H, 8.53. Found: C, 58.70; H, 8.58.

**4.2.29. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 3-phenyl-2-(triethylsilyloxy)propionate (13c).** The product was obtained in 75% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.25 (m, 5H), 5.15 (d, $J$=7.8 Hz, 1H), 4.44 (dd, $J$=3.9, 8.3 Hz, 1H), 4.27 (dd, $J$=5.2, 7.6 Hz, 1H), 4.21 (m, 1H), 4.14 (dd, $J$=2.2, 13.4 Hz, 1H), 4.07 (d, $J$=13.4 Hz, 1H), 3.92 (d, $J$=9.4 Hz, 1H), 3.72 (d, $J$=8.7 Hz, 1H), 3.11 (dd, $J$=3.7, 13.4 Hz, 1H), 2.95 (dd, $J$=8.3, 13.5 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.83 (t, $J$=7.83 Hz, 9H), 0.46 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.3, 137.4, 130.1, 128.3, 126.8, 112.2, 109.8, 103.8, 74.8, 73.9, 73.3, 71.9, 71.0, 60.7, 41.9, 28.0, 26.6, 26.6, 26.3, 6.8, 4.5. IR: $\nu$ 3064, 3030, 2987, 2955, 2877, 1764, 1737, 1605, 1496, 1455, 1415, 1383, 1372, 1296, 1240, 1220, 1191, 1128, 1086, 1067, 1043, 1030, 976, 910, 888, 852, 811, 774, 743, 699, 668, 626 cm$^{-1}$. FABMS: 529.0 (M+Li$^+$). Anal. Calcd for $C_{27}H_{42}O_8Si$: C, 62.04; H, 8.10. Found: C, 62.01; H, 8.05.

**4.2.30. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triethylsilyloxy)butanoate (13d).** The product was obtained in 83% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.14 (d, $J$=7.8 Hz, 1H), 4.29–4.20 (m, 3H), 4.14 (dd, $J$=1.8, 13.5 Hz, 1H), 4.08 (d, $J$=13.4 Hz, 1H), 3.97 (d, $J$=9.3 Hz, 1H), 3.84 (d, $J$=9.3 Hz, 1H), 1.79 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 0.99 (t, $J$=4.2 Hz, 3H), 0.97 (t, $J$=8.0 Hz, 9H), 0.63 (dd, $J$=7.8, 15.6 Hz, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.8, 112.2, 109.7, 103.9, 74.9, 73.9, 72.9, 72.0, 70.8, 60.7, 28.9, 28.0, 26.6, 26.5, 26.3, 9.4, 6.9, 4.8. IR: $\nu$ 2986, 2956, 2878, 1760, 1736, 1460, 1415, 1383, 1372, 1326, 1296, 1240, 1221, 1190, 1140, 1114, 1086, 1069, 1028, 976, 910, 888, 848, 810, 743, 669, 626 cm$^{-1}$. FABMS: 466.9 (M+Li$^+$). Anal. Calcd for $C_{22}H_{40}O_8Si$: C, 57.36; H, 8.75. Found: C, 57.22; H, 8.74.

**4.2.31. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 4-phenyl-2-(triethylsilyloxy)butanoate (13e).** The product was obtained in 61% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.18 (m, 5H), 5.18 (d, $J$=7.6 Hz, 1H), 4.36 (t, $J$=5.2 Hz, 1H), 4.29 (dd, $J$=5.2, 8.0 Hz, 1H), 4.22 (dd, $J$=1.6, 5.2 Hz, 1H), 4.15 (dd, $J$=2.0, 13.6 Hz, 1H), 4.09 (d, $J$=13.2 Hz, 1H), 3.98 (d, $J$=9.2 Hz, 1H), 3.85 (d, $J$=9.2 Hz, 1H), 2.74 (m, 2H), 2.07 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.97 (t, $J$=8 Hz, 9H), 0.64 (dd, $J$=10.4, 18.4 Hz, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.6, 141.9, 128.7, 128.5, 126.0, 112.2, 109.8, 103.9, 74.9, 73.9, 72.0, 71.4, 71.1, 60.8, 37.6, 31.0, 28.0, 26.6, 26.5, 26.4, 6.9, 4.8. IR: $\nu$ 3063, 3029, 2987, 2955, 2877, 1760, 1737, 1604, 1497, 1455, 1415, 1383, 1372, 1326, 1296, 1240, 1220, 1187, 1155, 1129, 1086, 1066, 1029, 976, 911, 888, 850, 931, 804, 744, 700, 669, 626 cm$^{-1}$. FABMS: 542.9 (M+Li$^+$). Anal. Calcd for $C_{28}H_{44}O_8Si$: C, 62.66; H, 8.26. Found: C, 62.68; H, 8.12.

**4.2.32. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triethylsilyloxy)heptanoate (13f).** The product was obtained in 58% yield using alkylation Method B. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.14 (d, $J$=7.8 Hz, 1H), 4.29–4.20 (m, 3H), 4.14 (dd, $J$=2.0, 13.5 Hz, 1H), 4.05 (d, $J$=13.4 Hz, 1H), 3.97 (d, $J$=9.3 Hz, 1H), 3.84 (d, $J$=9.2 Hz, 1H), 1.73 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.43–1.30 (m, 6H), 1.40 (s, 3H), 1.33 (s, 3H), 0.96 (t, $J$=8.0 Hz, 9H), 0.89 (t, $J$=6.5 Hz, 3H), 0.62 (dd, $J$=7.6, 15.6 Hz, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$174.0, 112.2, 109.8, 103.9, 74.9, 74.0, 72.0, 70.8, 60.8, 35.7, 31.8, 28.0, 26.7, 26.6, 26.4, 24.6, 22.7, 14.2, 6.9, 4.8. IR: $\nu$ 2987, 2955, 2876, 1761, 1736, 1458, 1416, 1382, 1372, 1296, 1240, 1220, 1190, 1140, 1114, 1030, 976, 912, 888, 851, 838, 810, 744, 668 cm$^{-1}$. FABMS: 500.9 (M−H$^+$). Anal. Calcd for $C_{25}H_{46}O_8Si$: C, 59.73; H, 9.22. Found: C, 59.95; H, 9.31.

**4.2.33. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 3-naphthalen-2-yl-2-(triethylsilyloxy)propionate (13g).** The product was obtained in 71% yield using alkylation Method B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82–7.70 (m, 4H), 7.45–7.39 (m, 3H), 5.15 (d, $J$=7.8 Hz, 1H), 4.54 (dd, $J$=3.9, 7.8 Hz, 1H), 4.24 (dd, $J$=5.2, 7.6 Hz, 1H), 4.18 (s, 1H), 4.10 (d, $J$=1.5 Hz, 1H), 4.06 (d, $J$=13.2 Hz, 1H), 3.90 (d, $J$=9.3 Hz, 1H), 3.74 (d, $J$=9.3 Hz, 1H), 3.27 (dd, $J$=4.1, 13.6 Hz, 1H), 3.13 (dd, $J$=8.0, 13.4 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 0.80 (t, $J$=7.8 Hz, 9H), 0.45 (m, 6H). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 173.2, 134.9, 133.6, 132.6, 128.8, 128.3, 127.8, 126.0, 125.5, 112.2, 109.8, 103.8, 74.8, 73.9, 73.3, 72.0, 71.1, 60.8, 42.2, 27.9, 26.6, 26.5, 26.4, 6.8, 4.6. IR: $\nu$ 2990, 2954, 2872, 1760, 1731, 1455, 1372, 1220, 1190, 1124, 1085, 973, 888, 853, 817, 740 cm$^{-1}$. FABMS: 579.0 (M+Li$^+$). Anal. Calcd for $C_{31}H_{44}O_8Si$: C, 65.01; H, 7.74. Found: C, 65.13; H, 7.81.

**4.2.34. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl (triisopropylsilyloxy)acetate (3k).** Benzyl (triisopropylsilyloxy)acetate. Benzyl glycolate[87] (1.66 g, 10.0 mmol) and triethylamine (3.0 mL, 21.3 mmol) were dissolved in dry DCM (15 mL) at rt. After 15 min triisopropyl trifluoromethanesulfonate (3.6 mL, 13.4 mmol) was added quickly. The mixture bubbled and became warm. The pale green solution was stirred at rt overnight. After 22 h the reaction mixture (red in color) was washed with 10 mL ice-cold saturated $NaHCO_3$ and 10 mL saturated NaCl, dried ($MgSO_4$), filtered, and rotovapped to give red liquid (4.21 g). The liquid was dissolved in DCM and separated on a flash silica column (1:6 EtOAc/hexanes, ~0.5% $Et_3N$). Fractions were combined, rotovapped, and dried on the oil pump to give the ester as a yellow liquid (3.088 g, 96%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.35 (s, 5H), 5.18 (s, 2H), 4.36 (s, 2H), 1.15–1.03 (m, 21H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 171.3, 135.7, 128.5, 128.4, 128.3, 66.4, 62.1, 17.8, 12.0. IR: $\nu$ 3034, 2943, 2865, 1765, 1735, 1498, 1464, 1443, 1385, 1366, 1281, 1267, 1208, 1194, 1147, 1071, 1044, 996, 967, 919, 882, 834, 823, 809, 796, 748, 694, 661, 644 cm$^{-1}$. FABMS $m/z$ (% of base peak): 323.1 (M+H$^+$, 13). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.90; H, 9.51.

(Triisopropylsilyloxy)acetic acid (**2k**). Hydrogenolysis of the ester above according to the procedure for **2f** gave the acid **2k** in quantitative yield. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 9.3 (br s, 1H), 4.28 (s, 2H), 1.19–1.00 (m, 21H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 175.3, 61.6, 17.7, 12.3. FABMS $m/z$ (% of base peak): 233.2 (M+H$^+$, 21). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.90; H, 10.57.

The glycolate was prepared by the general esterification procedure using the alcohol **1**and triisopropylsilyloxyacetic acid **2k** to give **3k** as a green oil (87% yield) and recovered alcohol **1** (9% recovery). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.18 (d, $J$=7.6 Hz, 1H), 4.43 (d, $J$=16.4 Hz, 1H), 4.36 (d, $J$=16.8 Hz, 1H), 4.27 (dd, $J$=7.8, 5.4 Hz, 1H), 4.22 (dd, $J$=5.6, 1.8 Hz, 1H), 4.13 (dd, $J$=13.8, 2.2 Hz, 1H), 4.08 (d, $J$=13.6 Hz, 1H), 3.96 (d, $J$=9.2 Hz, 1H), 3.85 (d, $J$=9.6 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.13–1.05 (m, 21H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 171.4, 112.2, 109.8, 103.8, 74.8, 73.9, 72.0, 70.7, 62.0, 60.7, 28.0, 26.5, 26.3, 18.0, 12.1. IR: $\nu$ 2986, 2942, 2892, 2867, 2120, 1770, 1738, 1463, 1383, 1372, 1326, 1297, 1241, 1221, 1198, 1146, 1114, 1086, 1068, 1030, 977, 916, 883, 855, 816, 798, 748, 682, 668 cm$^{-1}$. FABMS $m/z$ (% of base peak): 481.4 (M+Li$^+$, 60), 473.4 (M−H$^+$, 31), 459.4 (M−Me$^+$, 34), 417.3 (M+H−$CH_3COCH_3^+$, 78), 243.2 (M−$OCOCH_2OR^+$, 100). HRFABMS: Calcd for $C_{23}H_{42}O_8SiLi$ (M+Li)$^+$: 481.2809. Found: 481.2810.

**4.2.35. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(triisopropylsilyloxy)propionate (14a).** The product was obtained as white needles in 70% yield using alkylation Method C. Mp 77–79°C (dec). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 5.14 (d, $J$=8.0 Hz, 1H), 4.50 (q, $J$=6.8 Hz, 1H), 4.27 (dd, $J$=7.8, 5.4 Hz, 1H), 4.21 (dd, $J$=5.4, 1.0 Hz, 1H), 4.14 (dd, $J$=13.4, 2.6 Hz, 1H), 4.08 (d, $J$=13.2 Hz, 1H), 3.96 (d, $J$=9.2 Hz, 1H), 3.83 (d, $J$=9.2 Hz, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.49 (d, $J$=5.6 Hz, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.18–1.05 (m, 21H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 174.3, 112.2, 109.8, 103.9, 74.9, 73.9, 72.1, 70.8, 68.7, 60.8, 28.0, 26.6, 26.5, 26.4, 22.4, 18.1, 12.3. IR: $\nu$ 2990, 2942, 2867, 1765, 1736, 1455, 1372, 1220, 1190, 1141, 1086, 1067, 976, 885, 820 cm$^{-1}$. FABMS $m/z$ (% of base peak): 495.4 (M+Li$^+$, 34), 487.4 (M−H$^+$, 24), 473.4 (M−Me$^+$, 46), 431.4 (M+H−$CH_3COCH_3^+$, 67), 243.2 (M−$OCOCH(Me)OR^+$, 100). Anal. Calcd for $C_{24}H_{44}O_8Si$: C, 58.99; H, 9.08. Found: C, 58.85; H, 9.10.

**4.2.36. 1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranos-3-yl (benzyloxy)acetate (15).** 1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranose. This compound was prepared by a procedure modified from the literature.[91] A solution of 3-pentanone (84 mL, 790 mmol), trimethyl orthoformate (42 mL, 329 mmol), and *p*-toluenesulfonic acid monohydrate (280 mg, 1.5 mmol) in 100 mL MeOH was heated in an oil bath to ~76°C. After 3 h, the bath temperature was increased to ~95°C, and the head temperature rose to 62°C. After 2.5 h at this bath temperature, the head temperature started to fall. The mixture was allowed to cool at rt for 20 min. More 3-pentanone (200 mL, 1880 mmol) was added, and the mixture was cooled in an ice bath. After 10 min D-fructose (ground to a powder, 26.9 g, 149 mmol) and $HClO_4$ (70%, 0.1 mL) were added. After stirring in the ice bath for 4.5 h, the reaction was quenched with $Et_3N$ (5 mL). After 15 min deionized water (25 mL) was added, and the mixture was stirred vigorously. After 10 min stirring at rt, the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and rotovapped to give a clear pale green liquid (45.4 g). After overnight storage in the freezer, the crude product was dissolved in EtOAc and rotovapped again (42.2 g). The mixture was separated on a flash silica column (1:6 to 1:2 $Et_2O$/hexanes). Fractions were combined, rotovapped, and dried on the oil pump to give the product as a light pale yellow oil (25.1 g, 53%). $^1$H (400 MHz, $CDCl_3$) and $^{13}$C NMR (75 MHz, $CDCl_3$) spectra agreed with those in the literature.[91]

The glycolate was prepared by the general esterification procedure using the alcohol above and benzyloxyacetic acid **2a** to give **15** as a pale yellow oil (4.45 g, 70%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.38–7.30 (m, 5H), 5.23 (d, $J$=7.6 Hz, 1H), 4.64 (s, 2H), 4.32 (dd, $J$=7.4, 5.4 Hz, 1H), 4.24 (dd, $J$=6.4, ~1 Hz, 1H), 4.22 (d, $J$=16.8 Hz, 1H), 4.11

(d, $J$=16.8 Hz, 1H), 4.10 (d, $J$=15.4 Hz, 1H), 4.07 (m, 1H), 3.95 (d, $J$=9.2 Hz, 1H), 3.84 (d, $J$=8.8 Hz, 1H), 1.84–1.59 (m, 8H), 0.98–0.83 (m, 12H). $^{13}$C NMR ($CD_3OD$, 75.5 MHz): $\delta$ 171.7, 138.5, 129.4, 129.2, 129.0, 117.5, 114.8, 104.7, 75.8, 74.9, 74.2, 73.1, 72.7, 67.9, 61.9, 31.0, 30.7, 29.7, 8.8, 8.7, 8.1. IR: $\nu$ 2966, 2919, 2872, 1760, 1455, 1378, 1349, 1273, 1185, 1128, 1088, 1044, 972, 918, 855, 824, 739, 697 cm$^{-1}$. FABMS $m/z$ (% of base peak): 466.2 ($M+H^+$, 36). Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.64; H, 7.81. Found: C, 64.65; H, 7.78.

**4.2.37. 1,2:4,5-Di-*O*-isopentylidene-β-D-fructopyranos-3-yl 2-(benzyloxy)propionate (16).** The product was obtained as an oil in 71% yield using alkylation Method C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.38–7.27 (m, 5H), 5.25–5.20 (d, $J$=8.4 Hz, 1H), 4.72 (d, $J$=11.6 Hz, 1H), 4.42 (d, $J$=11.6 Hz, 1H), 4.34 (dd, $J$=7.8, 5.8 Hz, 1H), 4.25 (dd, $J$=5.6, 1 Hz, 1H), 4.16–4.07 (m, 3H), 3.97 (d, $J$=9.2 Hz, 1H), 3.84 (d, $J$=9.2 Hz, 1H), 1.87–1.58 (m, 8H), 1.48 (d, $J$=6.4 Hz, 3H), 0.98–0.86 (m, 12H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 173.3, 137.7, 128.6, 128.2, 128.0, 116.4, 113.9, 103.7, 74.7, 74.2, 73.9, 72.4, 72.1, 71.7, 61.1, 30.4, 29.9, 29.0, 28.9, 19.0, 8.7, 7.9. IR: $\nu$ 2978, 2884, 1758, 1462, 1373, 1349, 1260, 1174, 1130, 1114, 1090, 1044, 975, 922, 848, 835, 822, 748, 698 cm$^{-1}$. FABMS $m/z$ (% of base peak): 485.3 ($M+Li^+$, 42), 449.3 ($M-Et^+$, 63), 393.3 ($M-Et_2CO^+$, 100), 299.2 ($M-OCOCH(Me)OR^+$, 58). Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.52; H, 8.15.

### 4.3. General procedure for the removal of the *O*-protecting group and cleavage of the auxiliary

To a solution of ester **13** (PG=TES) in THF/pyridine (1:1) was added several drops of HF–pyridine. This mixture was stirred at room temperature for 10 min. Distilled water then was added. The mixture was extracted with DCM (4×). The combined organic layers were washed with brine and dried ($MgSO_4$). Upon removing solvent, the residue was purified by flash chromatography (elution with hexanes/EtOAc) or used directly for the next step.

The residue obtained above (**17**) was dissolved in THF/MeOH/$H_2O$ (2:2:1, v/v). To this was added LiOH (2 equiv.). The reaction was monitored by TLC. When the reaction was complete, THF and methanol were removed on the rotovap. The aqueous solution was extracted with $Et_2O$ to remove the auxiliary. After the aqueous phase had been acidified with 10% HCl, it was extracted with DCM (3×) and the combined organic layers were dried ($MgSO_4$). Solvent was removed to afford the pure free acid **18**.

### 4.4. Determination of the de values

All reported yields and de values were based on isolated product. Determinations of de values were made by comparing the HPLC trace or the $^1$H NMR spectrum of the product to a standard that was racemic at the α-position. These pseudo-racemic standards were prepared by a different synthetic route (see below). Pseudo-racemic standards were prepared for alkylated compounds **4a–e**, **11b**, **12b**, **13a**, and **16**; the de's for the remainder of the alkylated compounds were determined by analogies in their $^1$H NMR spectra to those of the pseudo-racemic standards.

Representative procedure for preparation of the standards that were racemic at the α-center. Pseudo-racemic 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranos-3-yl 2-(benzyloxy) propionate (**4a**). Racemic (2-benzyloxy)propionic acid was prepared by alkylating benzyloxyacetic acid **2a** with MeI in the presence of LDA according to a literature procedure[92] (11%). The pseudo-racemic standard was prepared by the general esterification procedure using the alcohol **1** and racemic 2-(benzyloxy)propionic acid to give pseudo-racemic standard **4a** (84%).

### 4.5. The modified Cevalier's method for checking racemization during deprotection or hydrolysis

The method was carried out as described in the literature[78] with the following modifications: 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDC)/$Et_3N$ were substituted for DCC and the hydrochloride salt of H-Ala-OMe was used directly in the coupling. To verify the identification of diastereomers by $^1$H NMR, pseudo-racemic standards of **19a,b** were prepared using the racemic benzyloxy acids,[92] followed by hydrogenolysis with $Pd(OH)_2$.

### 4.6. Crystal structure of 3a

*Data Collection*. The sample was mounted on the end of a glass fiber using a small amount of silicon grease and transferred to the diffractometer. The sample was maintained at a temperature of −125°C using a nitrogen cold stream. All X-ray measurements were made on an Enraf–Nonius CAD4-MACH diffractometer. The unit cell dimensions were determined by a fit of 24 well centered reflections and their Friedel pairs with $33°<2\theta<36°$. A quadrant of unique data and their Bijvoet pairs were collected using the ω scan mode in a non-bisecting geometry. The adoption of a non-bisecting scan mode was accomplished by offsetting $\psi$ by 20° for each data point collected. This was done to minimize the interaction of the goniometer head with the cold stream. The Bijvoet pairs were collected using the negative $\theta$ position for the $-h\ -k\ -l$ reflection. This was done so that the X-ray pathlength through the crystal was identical for each pair. Three standard reflections were measured every 4800 s of X-ray exposure time. Scaling the data was accomplished using a 5 point smoothed curved routine fit to the intensity check reflections. The intensity data was corrected for Lorentz and polarization effects. No absorption correction was applied to the data.

*Structure solution and refinement*. The data were reduced using routines from the NRCVAX[93] set of programs. The structure was solved using SIR92.[94] All of the non-H atom positions were recovered from the initial E-map. All hydrogen atom positions were derived from difference Fourier maps. Hydrogen atom positional and isotropic displacement parameters were allowed to refine in the least squares refinement. The structure was refined using full matrix least-squares based on F. All non-H atoms were allowed to refine with anisotropic displacement parameters (ADPs). The calculated structure factors

included corrections for anomalous dispersion from the usual tabulation.[95] A secondary extinction correction was included in the final refinements. The anomalous scattering signal for **3a** was weak which prevented the direct determination of the absolute structure. Therefore, the absolute structure for the sample was set using the absolute configuration around atom C4 which was known to be *S*.

*Results*. Crystal system: monoclinic. Space group: $P2_1$. Unit cell: $a$=12.8625(10) Å, $b$=5.5705(3) Å, $c$=4.5033(7) Å. $Z$=2. A total of 4452 reflections were collected of which 4015 were unique ($R_{merge}$=0.010). $R$=0.027, $R_w$=0.033, GOF=1.47 for 3791 reflections above $1.0\sigma(I)$.

Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC 182697). Copies of the data can be obtained, free of charge, on the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

### 4.7. Crystal structure of 4c

*Data Collection*. The sample was mounted on the end of a glass fiber using a small amount of silicon grease and transferred to the diffractometer. The sample was maintained at a temperature of −125°C using a nitrogen cold stream. All X-ray measurements were made on an Enraf–Nonius CAD4-MACH diffractometer. The unit cell dimensions were determined by a fit of 25 well centered reflections and their Friedel pairs with $31°<2\theta<36°$. A quadrant of unique data and their Bijvoet pairs were collected using the ω scan mode in a non-bisecting geometry. The adoption of a non-bisecting scan mode was accomplished by offsetting $\psi$ by 20° for each data point collected. This was done to minimize the interaction of the goniometer head with the cold stream. The Bijvoet pairs were collected using the negative $\theta$ position for the $-h\ -k\ -l$ reflection. This was done so that the X-ray pathlength through the crystal was identical for each pair. Three standard reflections were measured every 4800 s of X-ray exposure time. Scaling the data was accomplished using a 5 point smoothed curved routine fit to the intensity check reflections. The intensity data was corrected for Lorentz and polarization effects. No absorption correction was applied to the data. During the data collection, the low temperature device developed a problem of excessive ice build up. This may have affected the quality of the data slightly.

*Structure solution and refinement*. The data were reduced using routines from the NRCVAX[93] set of programs. The structure was solved using SIR92.[94] All of the non-H atom positions were recovered from the initial E-map. All hydrogen atom positions were introduced at idealized positions. Hydrogen atom positional parameters were allowed to refine in the least squares refinement, and the isotropic displacement parameters were allowed to ride on the parent carbon atom. The structure was refined using full matrix least-squares based on F. All non-H atoms were allowed to refine with anisotropic displacement parameters (ADPs). The calculated structure factors included corrections for anomalous dispersion from the usual tabulation.[95] A secondary extinction correction was included in the final refinements. The anomalous scattering signal for **4c** was weak which prevented the direct determination of the absolute structure. Therefore, the absolute structure for the sample was set using the absolute configuration around atom C4 which was known to be *S*.

*Results*. Crystal system: monoclinic. Space group: $P2_1$. Unit cell: $a$=8.0120(5) Å, $b$=14.1477(8) Å, $c$=11.7213(8) Å. $Z$=2. A total of 4678 reflections were collected, of which 4479 were unique ($R_{merge}$=0.013). $R$=0.035, $R_w$=0.046, GOF=1.39 for 3975 reflections greater than $1.0\sigma(I)$.

Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC 182698). Copies of the data can be obtained, free of charge, on the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

## Acknowledgments

The authors thank the American Heart Association (Grant 9740117 N) for funding. The authors also wish to thank the National Science Foundation for the funding (Grant 9509532) used to purchase the X-ray diffractometer. C. E. B. gratefully acknowledges a graduate fellowship from the Burroughs Wellcome Fund.

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