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# O-Alkylation versus C-alkylation under Mitsunobu conditions

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**Abstract**—A comparative study of the Mitsunobu reaction at C1 and C6 positions of mannose using bis(2,2,2-trifluoroethyl) malonate as nucleophile is disclosed. While C-alkylation was predominant at the C6 position, only O-alkylation occurred at the anomeric position of the carbohydrate. Some factors playing a role in the selectivity of the reaction are discussed and an inverse mechanism of the Mitsunobu reaction for the anomeric position is proposed.


## 1. Introduction

Since the first glycosylation method proposed by Koenigs and Knorr more than a century ago,[1] innovative synthetic transformations of sugars into glycoconjugates, besides enzymatic approaches, have attracted great attention.[2] Potential uses of O-linked glycoconjugates are substantial, i.e., they can constitute useful intermediates in carbohydrate chemistry for the synthesis of biologically active compounds involved in recognition processes. Therefore, the aglycone part of branched-chain sugars can be of various types. The necessity to develop simple synthetic tools that can be adapted for the preparation of diverse glycoconjugates is taking more and more importance. As part of our research on Mitsunobu reaction on carbohydrates, we have examined in a previous article the reactivity of bis(2,2,2-trifluoroethyl) malonate at the C6 position of mannose.[3] Due to the importance of glycosides and in search of developing new glycoconjugates for creating associative interactions between sugars and cells via liposomes,[4] we have explored the same reaction at the anomeric position of mannose. The choice of an activated malonate as nucleophile was motivated by many advantages such as: (a) a higher acidity than diethyl malonate[5] and (b) the branched chain is a useful intermediate in the synthesis of a variety of aglycon moieties. As hydroxyl groups in carbohydrates present different reactivities, the reaction of the activated malonate at C1 compared to the C6 position under Mitsunobu conditions was explored in detail.

## 2. Results and discussion

### 2.1. Mitsunobu reaction at the C1 position of suitable protected mannose

Compound **1**, prepared from commercially available peracetylated mannose,[6] served as starting material for the Mitsunobu reaction,[7] which was performed at room temperature using the redox couple triphenylphosphine/1,1′-(azodicarbonyl)dipiperidine ($PPh_3$/ADDP), bis(2,2,2-trifluoroethyl) malonate, and toluene as solvent. The different generated products are shown in Scheme 1. Though the activated malonate has been described as a nucleophile reacting via C-alkylation,[5] in our case, the expected *C*-alkylated compound as a result of the Mitsunobu reaction between the sugar hemiacetalic alcohol and the carbon nucleophile of the malonate was not observed. Instead, three types of *O*-alkylated compounds have been obtained.

- The first type is represented by four isomers: **2a**–**2d**. Their stereoisomerism is due to the anomeric configuration of the sugar and the geometric isomerism of the double bond.
- The second type is represented by compound **3**, which is formed by a combination of the protected mannose and a part of the activated malonate.
- The third type corresponds to compound **4**, which has the most surprising structure: two sugars linked to the same malonate residue.

*Keywords*: Mitsunobu reaction; Ambident nucleophile; C/O-Alkylation; Steric and electronic effects.
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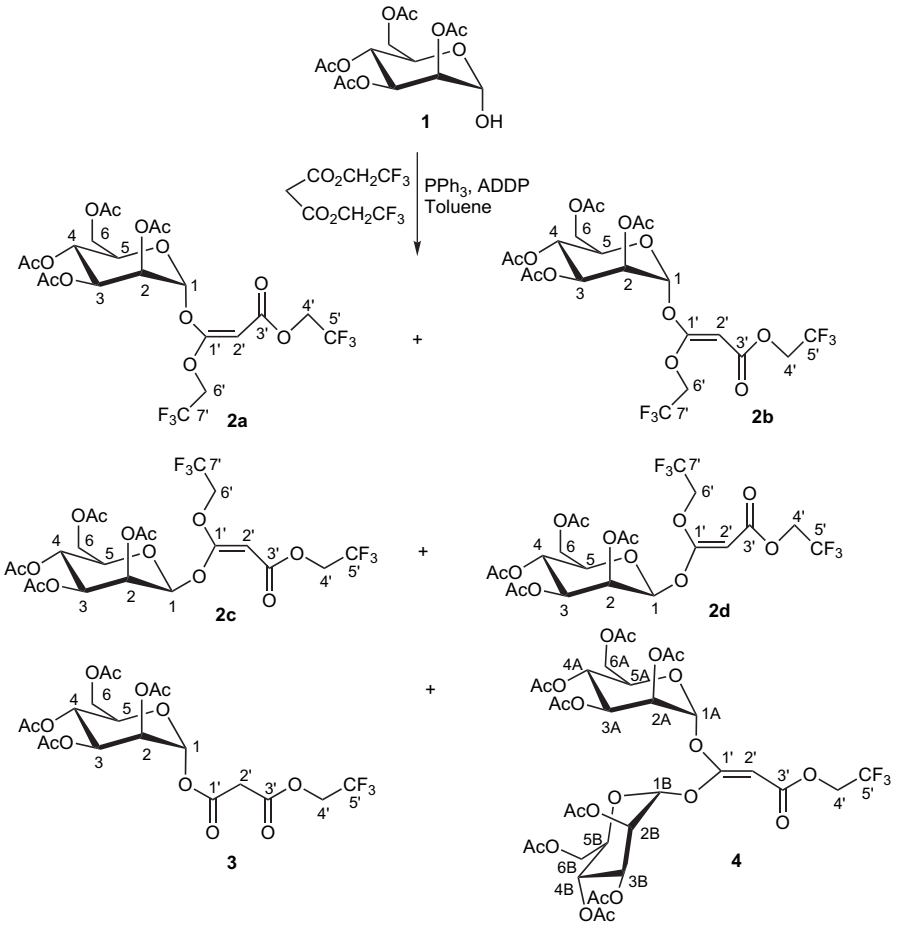



**Scheme 1**. Mitsunobu reaction at the C1 position of a protected mannose.

All of these compounds have been characterized by $^1$H NMR and mass spectrometry. The structure of compound **2a** was firmly established by X-ray crystallographic analysis and it proved to be α-anomer and (*Z*)-isomer (Fig. 1).

The other three isomers have very similar NMR spectra. They were identified using the $^1J$ coupling constant between C1 and H1 (Table 1). The analysis proves that **2b** is also an α-anomer (ca. 180 Hz) and that **2c** and **2d** are β-anomers (ca. 170 Hz).[8] Moreover, the coupling constant $^3J_{H1–H2}$ in $CDCl_3$ is bigger for the α-anomers **2a** and **2b** (between 1.9 and 2.1 Hz) than for the β-anomers **2c** and **2d** (1.3–1.4 Hz) (Table 2).

In addition to the preceding arguments, the α-anomeric form of **2b** was also confirmed, in acetone-$d_6$, by the presence of a coupling constant of 0.7 Hz between the two protons H1 and H5, which are also present in **2a** but not in the two β-anomers **2c** and **2d**. Based on the values of the coupling constants $^3J_{H1–H2}$ and $^3J_{C1–H1}$, an α configuration was assigned for the sugars in compounds **3** and **4**.

On the other hand, $^1J_{C2'–H2'}$ is significantly different when *Z* and *E* isomers are compared (Table 1) allowing **2c** to be assigned a *Z* configuration as for compound **2a** and allowing **2b** and **2d** to be assigned an *E* configuration.

Two $–OCH_2CF_3$ groups are present in each of the four structures **2a**–**2d**; one belongs to an ether function and the other to an ester one. In $CDCl_3$, the NMR spectrum reveals two different $^3J_{H–F}$ coupling constants. The smaller one has a value inferior to 8 Hz, the other one is close to the value present in the malonate, an ester itself (Table 2). Based on these observations, the signals corresponding to the ether and to the ester fluorinated groups could be assigned, concluding that the $^3J_{H–F}$ of ether groups in compounds **2a**–**2d** is smaller than the value presented by the esters.

## 2.2. Mitsunobu reaction at the C6 position of suitable protected mannose

The difference in reactivity at the C1 and C6 hydroxy groups of carbohydrates is well known and has of course a significant influence on the Mitsunobu reaction. Concerning the C6 position, the Mitsunobu reaction applied at this center has been reported for the synthesis of thio-sugars.[9] We have previously described[3] a chain elongation of mannose by formation of a C–C bond at the C6 position of mannose. The obtained results at the anomeric position lead us to explore more precisely the by-products formed during the Mitsunobu reaction on the primary hydroxy group of this carbohydrate. Indeed, while the C-alkylation was predominant, 15% of *O*-alkylated compound has been obtained (Scheme 2). The activated malonate is an ambident nucleophile and the reactive intermediate is a composite of two resonance structures. It is therefore possible that, under certain conditions, either structure reacts to give *C*- or *O*-alkylated products.

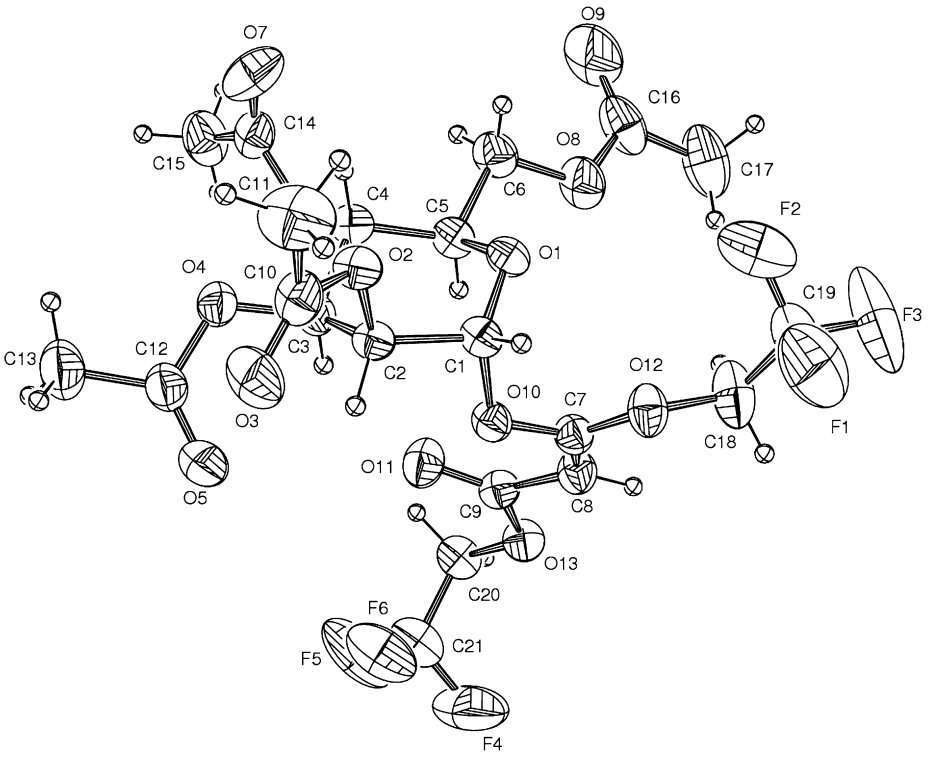



**Figure 1**. ORTEP drawing of **2a**.

The structures of the obtained compounds have been assigned after the analysis of their $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra, and the results are presented in Tables 3 and 4.

**Table 1**. $^{13}C$ NMR parameters of compounds **2a–d**, **3**, and **4** in $CDCl_3$

| | **2a** (α*Z*) | **2c** (β*Z*) | **2b** (α*E*) | **2d** (β*E*) | **3** | **4** | |
|---|---|---|---|---|---|---|---|
| | | | | | | A[a] | B[a] |
| C1 | 95.30 | 94.96 | 96.76 | 96.19 | 91.59 | 95.51 | 96.16 |
| C2 | 68.26 | 67.31 | 67.91 | 67.46 | 67.89 | 68.33 | 68.15 |
| C3 | 68.42 | 70.10 | 68.21 | 69.73 | 68.45 | 68.20 | 68.05 |
| C4 | 65.10 | 65.61 | 65.09 | 65.51 | 65.13 | 65.50 | 65.69 |
| C5 | 71.06 | 73.33 | 70.76 | 73.30 | 70.89 | 71.18 | 70.44 |
| C6 | 61.93 | 62.07 | 61.88 | 62.07 | 61.80 | 61.64 | 62.31 |
| C1′ | 162.86 | 162.46 | 163.21 | 163.22 | 162.80 | 162.17 | |
| C2′ | 75.61 | 75.68 | 75.80 | 75.06 | 40.50 | 77.78 | |
| C3′ | 164.36 | 164.70 | 164.30 | 165.28 | 164.27 | 163.58 | |
| C4′ | 59.81 | 59.57 | 59.76 | 59.69 | 61.14 | 60.07 | |
| C5′ | 123.20 | 123.18 | 123.18 | 123.19 | 122.52 | 123.97 | |
| C6′ | 66.24 | 65.83 | 64.89 | 64.56 | — | — | |
| C7′ | 121.82 | 122.03 | 122.35 | 122.32 | — | — | |
| Me-2[b] | 20.64 | 20.50 | 20.46 | 20.35 | 20.49 | 20.63 | 20.48 |
| Me-3[b] | 20.64 | 20.51 | 20.58 | 20.44 | 20.53 | 20.55 | 20.65 |
| Me-4[b] | 20.73 | 20.62 | 20.63 | 20.49 | 20.57 | 20.75 | 20.72 |
| Me-6[b] | 20.82 | 20.64 | 20.68 | 20.58 | 20.62 | 20.86 | 20.73 |
| C=O(2)[b] | 169.72 | 169.54 | 169.52 | 169.49 | 169.46 | 169.67 | 169.66 |
| C=O(3)[b] | 169.74 | 169.84 | 169.70 | 169.76 | 169.58 | 169.72 | 169.72 |
| C=O(4)[b] | 169.77 | 170.25 | 169.91 | 170.05 | 169.83 | 169.79 | 169.77 |
| C=O(6)[b] | 170.54 | 170.53 | 170.51 | 170.56 | 170.54 | 170.50 | 170.50 |
| $J_{C1-H1}$[c] | 182.3 | 170.7 | 180.5 | 167.2 | 178.5 | 180.4 | 181.9 |
| $J_{C2'-H2'}$[c] | 165.1 | 165.1 | 166.7 | 166.7 | — | 166.6 | |
| $J_{C4'-F5'}$ | 36.4 | 36.2 | 36.6 | 36.4 | 37.0 | 36.6 | |
| $J_{C5'-F5'}$ | 277.4 | 277.0 | 277.4 | 277.0 | 277.4 | 277.4 | |
| $J_{C6'-F7'}$ | 37.7 | 37.4 | 37.3 | 37.0 | — | — | |
| $J_{C7'-F7'}$ | 277.7 | 277.6 | 278.5 | 278.4 | — | — | |

[a] The chemical shifts of these sugar moieties can be interchanged.
[b] The signals of these groups have not been assigned.
[c] These parameters were determined in acetone-$d_6$.

## 2.3. Proposed mechanisms and comparative discussions for the two Mitsunobu reactions

Ambident nucleophiles used under Mitsunobu reaction have shown to afford compounds of competitive alkylation (e.g., N/O, N/S, C/O competitive alkylations have already been described).[7,10] Attempts to alkylate enolates by means of the Mitsunobu reaction gave compounds with exclusive C- or O-alkylations or mixtures of *C*- and *O*-alkylated products.[7,11,12] In 1995, Ramesh and Balasubramanian reported a failed attempt to C-alkylate the anomeric position of a glycal moiety with an ambident nucleophile, but a mixture of α- and β-*O*-alkylated compounds was obtained instead of getting *C*-alkylated product.[13]

In the case of our compounds, the Mitsunobu reaction at the primary alcohol of mannose gave predominantly *C*-alkylated compounds, while the same reaction, applied to the anomeric hydroxy group, gave an *O*-alkylated mixture. While studying the effects that could play a role in the selectivity of the alkylation, two factors attracted our attention: (a) the steric hindrance and (b) the hardness and softness of the reaction centers.

(a) First, it appears difficult to conclude on the role of steric effects since opposite results have been reported. Indeed, in 1997, Shing et al. described the alkylation of Meldrum's acids by allylic alcohols under Mitsunobu conditions and proved that primary alcohols gave *C*-alkylated compounds, while secondary alcohols gave *O*-alkylated or a mixture containing predominately *O*-alkylated products.[12] This difference in reactivity was in part assigned to the steric hindrance of the allylic alcohol itself. In contrast, in 2001, studying the structural

**Table 2**. $^{1}H$ and $^{19}F$ NMR parameters of compounds **2a–d**, **3**, and **4** in $CDCl_3$ and acetone-$d_6$

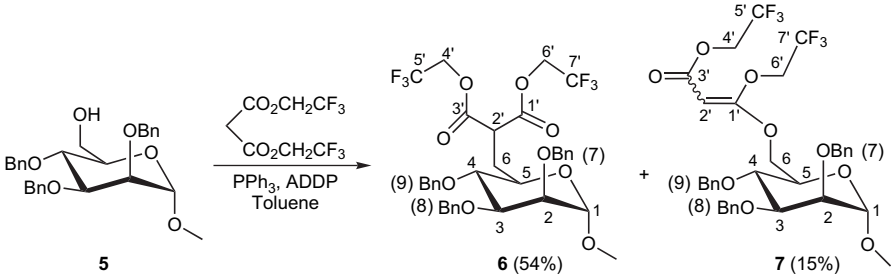
| | **2a** (αZ) | | **2c** (βZ) | | **2b** (αE) | | **2d** (βE) | | **3** | **4** | | Malonate |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $CDCl_3$ | Acetone | $CDCl_3$ | Acetone | $CDCl_3$ | Acetone | $CDCl_3$ | Acetone | $CDCl_3$ | $CDCl_3$ | | $CDCl_3$ |
| | | | | | | | | | | A[a] | B[a] | |
| H1 | 5.89 | 5.99 | 5.62 | 6.02 | 5.51 | 5.75 | 5.25 | 5.76 | 6.12 | 5.83 | 5.52 | — |
| H2 | 5.49 | 5.47 | 5.71 | 5.68 | 5.39 | 5.55 | 5.60 | 5.73 | 5.27 | 5.46 | 5.39 | — |
| H3 | 5.61 | 5.57 | 5.16 | 5.35 | 5.32 | 5.43 | 5.16 | 5.34 | 5.28 | 5.62 | 5.28 | — |
| H4 | 5.41 | 5.36 | 5.29 | 5.24 | 5.34 | 5.32 | 5.26 | 5.23 | 5.35 | 5.44 | 5.31 | — |
| H5 | 4.33 | 4.34 | 3.75 | 4.03 | 4.00 | 4.24 | 3.89 | 4.24 | 4.07 | 4.28 | 4.05 | — |
| H6a | 4.31 | 4.22 | 4.25 | 4.25 | 4.32 | 4.30 | 4.25 | 4.27 | 4.27 | 4.29 | 4.33 | — |
| H6b | 4.09 | 4.06 | 4.22 | 4.14 | 4.14 | 4.14 | 4.28 | 4.20 | 4.11 | 4.18 | 4.10 | — |
| H2′ | 4.61 | 4.96 | 4.62 | 4.80 | 4.98 | 4.91 | 4.81 | 4.88 | 3.62[b] 3.60[b] | 4.96 | | 3.61 |
| H4′a | 4.58 | 4.68 | 4.46 | 4.61 | 4.51 | 4.63 | 4.50 | 4.62 | 4.61 | 4.59 | | 4.55 |
| H4′b | 4.53 | 4.66 | 4.44 | 4.61 | 4.45 | 4.61 | 4.46 | 4.62 | 4.57 | 4.48 | | 4.55 |
| H6′a | 4.33 | 4.88 | 4.37 | 4.85 | 4.60 | 5.02 | 4.55 | 4.74 | — | — | | — |
| H6′b | 4.31 | 4.80 | 4.33 | 4.79 | 4.58 | 4.97 | 4.46 | 4.72 | — | — | | — |
| Me-2[c] | 2.22 | 2.16 | 2.26 | 2.20 | 2.22 | 2.16 | 2.22 | 2.19 | 2.18 | 2.21 | 2.19 | — |
| Me-3[c] | 2.10 | 2.07 | 2.07 | 2.05 | 2.10 | 2.07 | 2.12 | 2.08 | 2.09 | 2.11 | 2.08 | — |
| Me-4[c] | 2.10 | 2.01 | 2.07 | 2.02 | 2.10 | 2.03 | 2.11 | 2.05 | 2.05 | 2.08 | 2.07 | — |
| Me-5[c] | 2.03 | 1.97 | 2.04 | 1.97 | 2.06 | 1.98 | 2.07 | 2.00 | 2.00 | 2.02 | 2.02 | — |
| F-5′ | −73.66 | [d] | −73.89 | [d] | −73.94 | [d] | −74.21 | [d] | −73.64 | −73.64 | | −74.38 |
| F-7′ | −73.48 | [d] | −73.74 | [d] | −73.78 | [d] | −73.75 | [d] | — | — | | — |
| $J_{H1–H2}$ | 1.9 | 1.8 | 1.3 | 1.3 | 2.1 | 1.9 | 1.4 | 1.3 | 1.9 | 1.9 | 2.0 | — |
| $J_{H1-H5}$ | [e] | 0.7 | [e] | [e] | [e] | 0.7 | [e] | [e] | [e] | [e] | [e] | — |
| $J_{H2–H3}$ | 3.4 | 3.6 | 3.3 | 3.5 | 3.1 | 3.5 | 3.4 | 3.4 | 3.5 | 3.5 | 3.1 | — |
| $J_{H3–H4}$ | 10.2 | 10.2 | 9.9 | 10.0 | 10.0 | 10.2 | 9.5 | 9.9 | 9.1 | 10.2 | 9.8 | — |
| $J_{H4–H5}$ | 10.2 | 10.2 | 10.0 | 10.0 | 10.0 | 10.2 | 9.4 | 10.0 | 10.2 | 10.0 | 10.2 | — |
| $J_{H5–H6a}$ | 4.8 | 5.3 | 6.1 | 5.9 | 6.6 | 6.3 | 7.7 | 7.2 | 5.0 | 4.7 | 6.4 | — |
| $J_{H5–H6b}$ | 2.4 | 2.4 | 2.5 | 2.6 | 2.3 | 2.1 | 2.5 | 2.4 | 2.4 | 2.5 | 2.4 | — |
| $J_{H6a–H6b}$ | −12.5 | −12.4 | −12.4 | −12.3 | −12.4 | −12.0 | −12.2 | −12.1 | −12.5 | −12.5 | −12.3 | — |
| $J_{H4′a–H4′b}$ | −12.8 | −11.9 | −12.7 | [f] | −12.6 | −12.6 | −12.6 | [f] | −12.6 | −12.8 | | — |
| $J_{H4′a–F5′}$[g] | 8.5 | 8.9 | 8.7 | 9.0 | 8.5 | 9.0 | 8.5 | 9.0 | 8.3 | 8.6 | | 8.3 |
| $J_{H6′a–H6′b}$ | −11.3 | −13.0 | −11.4 | −11.9 | −12.6 | −13.0 | −12.8 | −12.7 | — | — | | — |
| $J_{H6′a–F7′}$[h] | 7.5 | 8.2 | 7.8 | 8.3 | 8.0 | 8.5 | 8.0 | 8.6 | — | — | | — |

[a] The chemical shifts of these sugar moieties can be interchanged.
[b] AB system with $J(2′a,2′b)=-16.4$ Hz.
[c] The signals of these groups have not been assigned.
[d] Not measured in this solvent.
[e] Not observed.
[f] Not measured (coupling constant between isochronous protons).
[g] $J(H4′a–F5′)=J(H4′b–F5′)$.
[h] $J(H6′a–F7′)=J(H6′b–F7′)$.

effects in the Mitsunobu reaction of calix[4]arene with benzylic and allylic alcohols, Wang and Gutsche reported a greater tendency for the primary than for the secondary alcohols to yield products of O-alkylation.[10b]

(b) However, we believe that the difference in hardness or softness of the reaction centers has also to be considered. Pearson's hard and soft acids and bases theory[14] has been often employed in order to explain the C/O selectivity in enolate ion alkylation.[12,15] While the C-alkylation is favored by soft alkylating agents, the O-alkylation becomes preponderant when the hardness of the alkylating agent increases. Thus, the bigger the carbocationic character of the electrophilic atom involved in the reaction, the greater the chance for the oxygen to react. Otherwise said, the greater the $S_N1$ character of the reactions, the greater the chance for the reaction to undergo an oxygen attack.[10b]

In Figure 2, among the two oxyphosphonium salts **9** and **10**, the intermediate **10** has a greater tendency to undergo




**Scheme 2**. Mitsunobu reaction at the C6 position of appropriate protected mannose.

**Table 3**. $^{1}$H NMR parameters of compounds **6** and **7** in $CDCl_3$

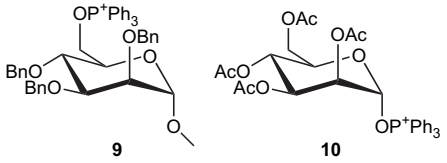
| | **6**[a,b] | **7**[a,c] |
|---|---|---|
| H1 | 4.64 | 4.72 |
| H2 | 3.80 | 3.83 |
| H3 | 3.87 | 3.94 |
| H4 | 3.72 | 4.10 |
| H5 | 3.61 | 3.84 |
| H6a | 2.22 | 4.48 |
| H6b | 2.64 | 4.58 |
| H2′ | 3.89 | 4.44 |
| H4′a | 4.52[d] | 4.39 |
| H4′b | 4.55[d] | 4.45 |
| H6′a | 4.53[d] | 4.25 |
| H6′b | 4.53[d] | 4.36 |
| H7a | 4.63 | 4.67 |
| H7b | 4.63 | 4.67 |
| H8a | 4.72 | 4.70 |
| H8b | 4.78 | 4.78 |
| H9a | 4.68 | 4.71 |
| H9b | 4.99 | 5.01 |
| OMe | 3.30 | 3.36 |
| $J_{H-H2}$ | 1.9 | 1.9 |
| $J_{H2-H3}$ | 3.0 | 3.0 |
| $J_{H3-H4}$ | 9.2 | 9.4 |
| $J_{H4-H5}$ | 9.4 | 9.6 |
| $J_{H5-H6a}$ | 2.7 | 2.0 |
| $J_{H5-H6b}$ | 10.1 | 5.2 |
| $J_{H6a-H6b}$ | −14.2 | −11.4 |
| $J_{H6a-H2'}$ | 5.2 | — |
| $J_{H6b-H2'}$ | 9.3 | — |
| $J_{H4'a-H4'b}$ | −12.6 | −12.8 |
| $J_{H4'a-F5'}$ | 8.3 | 8.7 |
| $J_{H4'b-F5'}$ | 8.3 | 8.6 |
| $J_{H6'a-H6'b}$ | [e] | −11.6 |
| $J_{H6'a-F7'}$ | 8.3 | 7.9 |
| $J_{H6'b-F7'}$ | 8.3 | 7.8 |
| $J_{H7a-H7b}$ | [e] | [e] |
| $J_{H8a-H8b}$ | −12.3 | −12.2 |
| $J_{H9a-H9b}$ | −11.0 | −11.2 |

[a] Phenyl hydrogen signals of benzyl groups are between 7.28 and 7.42 ppm.
[b] $\delta(CF_3)=-73.70$ and $-73.74$ ppm.
[c] $\delta(CF_3)=-73.69$ and $-73.71$ ppm.
[d] These signals cannot be assigned.
[e] Not measured (coupling constant between isochronous protons).

**Table 4**. $^{13}$C parameters of compounds **6** and **7** in $CDCl_3$

| | **6** | **7** |
|---|---|---|
| C1 | 99.19 | 99.22 |
| C2 | 75.19 | 74.66 |
| C3 | 80.02 | 80.20 |
| C4 | 78.21 | 74.14 |
| C5 | 68.92 | 70.41 |
| C6 | 30.95 | 69.78 |
| C1′ | 166.88[a] | 163.51 |
| C2′ | 47.87 | 71.44 |
| C3′ | 167.15[a] | 167.78 |
| C4′ | 61.03 | 59.20 |
| C5′ | 122.55 | 123.39 |
| C6′ | 61.03 | 65.33 |
| C7′ | 122.55 | 122.25 |
| C7[b] | 72.13 | 72.10 |
| C8[b] | 72.87 | 72.86 |
| C9[b] | 74.56 | 75.08 |
| $J_{C4'-F5'}$ | 37.30 | 36.00 |
| $J_{C5'-F5'}$ | 277.40 | 277.54 |
| $J_{C6'-F7'}$ | 37.30 | 37.05 |
| $J_{C7'-F7'}$ | 277.40 | 277.42 |

[a] These values can be interchanged.
[b] For OBn groups, methylene chemical shifts are only given.



9 10

**Figure 2**. Reaction intermediates activated as oxyphosphonium salts.

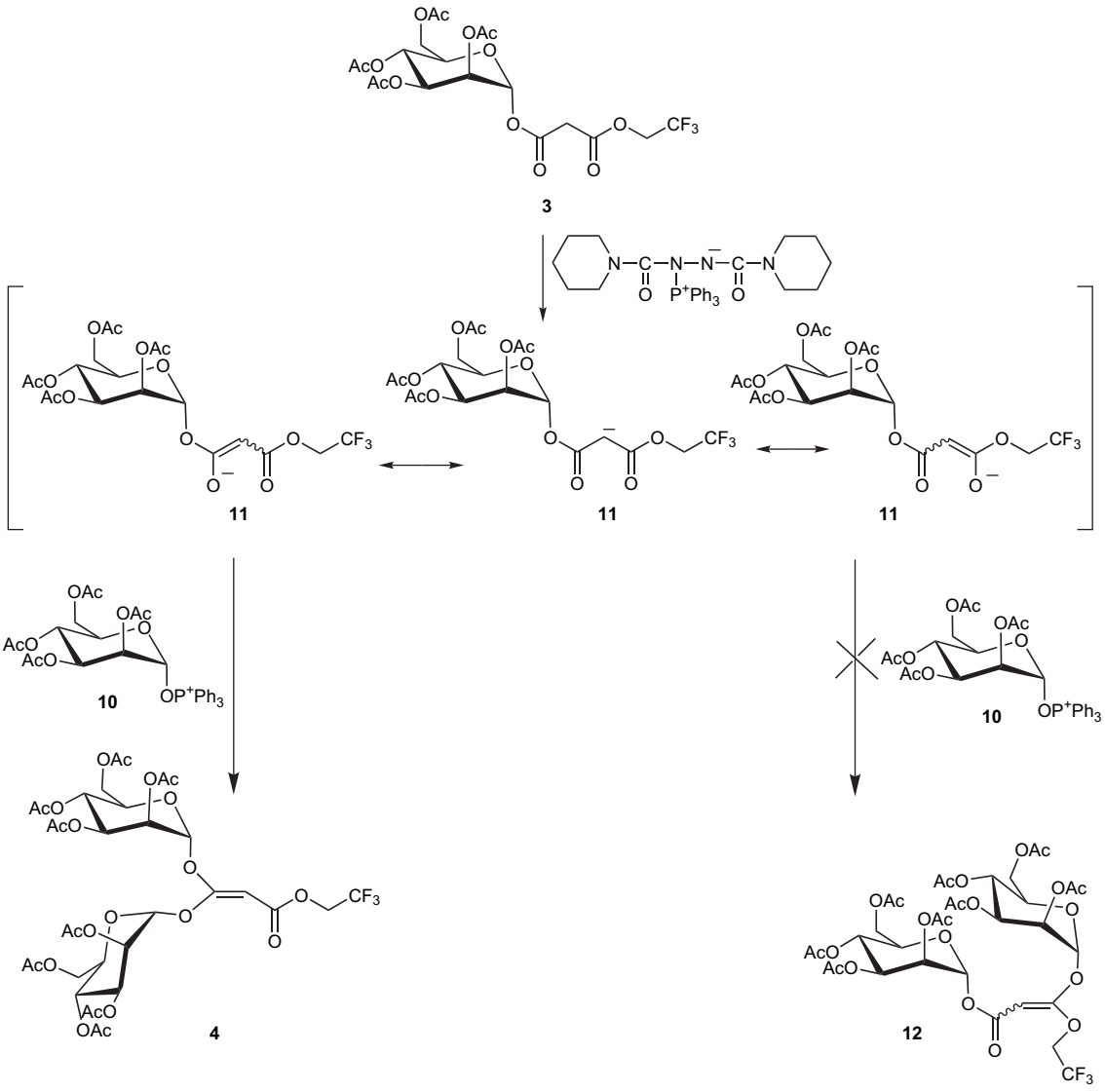
a carbocationic state, because the compound formed in this case after $OPPh_3$ elimination is stabilized by electronic delocalization of the cyclic oxygen. This would explain the tendency of the hemiacetalic alcohol to lead to *O*-alkylated compounds, while the primary alcohol undergoes reactions through an $S_N^2$ type of mechanism, thereby affording predominantly *C*-alkylated products. Meanwhile, the formation of a carbocationic intermediate after $OPPh_3$ elimination from compound **9** explains the formation of both α and β structures starting from the α-anomer only.

The product **3** arose from a transesterification reaction. Such processes under Mitsunobu conditions have been already described.[16] In 1975, Bittner et al. reported the mono- and bis-transesterification of diethylmalonate with methanol in the presence of $PPh_3$/DEAD as redox couple. The betaine adduct formed by the azodicarboxylate with $PPh_3$ is described as a bifunctional catalyst, activating both the alcohol and the carbonyl part of the ester. Since this kind of reaction is characterized by equilibrium states at all the steps of its mechanism, it is a reversible reaction. In order to have complete transesterification, the alcohol or the malonate must be in great excess. As our reaction was carried out with little excess of malonate (2 equiv reporting to the sugar), the transesterification was not complete. Actually, in the reaction mixture protected mannose was found to be present at almost 30% even after 15 h of reaction.

Concerning compound **4**, it could arise most probably by a second Mitsunobu reaction on compound **3** (Scheme 3). Compound **3** possesses in its structure an active methylene site, which can be deprotonated under Mitsunobu conditions to give the enolate **11**. This enolate reacted via oxygen as discussed above. It could have generated, by attack at the activated sugar **10**, two structural isomers: **4** and **12**. The structure of compound **4** was assigned after careful studies of the NMR spectra. Analyzing the coupling constant $^{3}J_{H-F}$, we identified that the $-OCH_2CF_3$ group corresponds to an ester and not to an ether functional group (Table 2). Moreover, the chemical shifts of the two carbon anomers are quite similar and they are displayed in a region of the $^{13}$C NMR spectrum typical in our compounds for anomeric carbons linked to ether functional groups (Table 1). These arguments led us to the conclusion that compound **4** corresponds to the structure given in Scheme 3.

It is worth noting that an α predominant structure was identified for the sugars, which are present in the obtained compounds (Table 5). We have attributed the α configuration to the anomeric effect[17] and to the neighboring acetate participation.[18]

Analyzing the *O*-alkylated mixture obtained at the anomeric position of protected mannose, we thought that temperature




**Scheme 3**. Mitsunobu-type mechanism proposed for the formation of compound **4**.

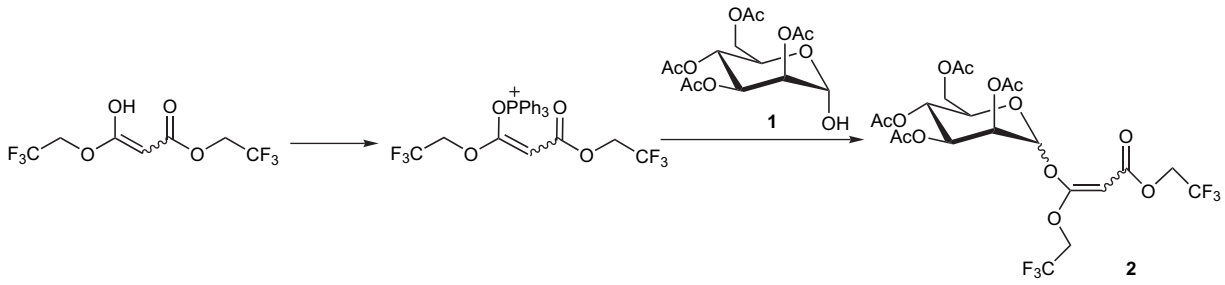
might play a role in the selectivity of the reaction. Therefore, a Mitsunobu reaction as described in Scheme 2 was realized at −15 °C, and, interestingly, only transesterification reaction took place and no 'Mitsunobu products' were identified (Table 5). This proves that the transesterification is a more reactive pathway under these conditions than the Mitsunobu reaction itself. At room temperature, very little progress has been seen by letting the reaction to run from 30 min to 15 h. The most significant observation, which can be deduced from Table 5 is the decrease in the concentration of product **3** with time and temperature augmentation, parallel to a Mitsunobu product increase. So the product **3** can be an intermediate in the synthesis of other compounds (Scheme 3).

**Table 5**. Relative percentages of the obtained compounds[a]

| Reaction conditions | **1** | **3** | Identified Mitsunobu compounds | | | | | Non-identified compounds |
|---|---|---|---|---|---|---|---|---|
| | | | **2a** (α*Z*) | **2b** (α*E*) | **2c** (β*Z*) | **2d** (β*E*) | **4** (αα*E*) | |
| 30 min/−15 °C | 67 | 33 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 min/25 °C | 29 | 23 | 17 | 3 | 6 | 6 | 6 | 10 |
| 15 h/25 °C | 27 | 18 | 16 | 5 | 5 | 9 | 7 | 13 |
| 13 h/25 °C[b] | 73 | 0 | 0 | 0 | 0 | 0 | 23 | 4 |

[a] These values were measured on $^{13}C$ NMR spectra of the crude reaction mixture in the anomeric carbon area (90–100 ppm). Thus, non-identified compounds are compounds with this type of carbon only.

[b] This reaction was realized with compounds **1** and **3** as starting materials under Mitsunobu conditions (compound **1**: 1 equiv, compound **3**: 0.5 equiv, $PPh_3$: 2 equiv, ADDP: 2 equiv).




**Scheme 4**. Malonate activation as oxyphosphonium salt.

In order to confirm that **3** is an active intermediate, it was isolated by carrying out the reaction at −15 °C, as under these conditions it is the only obtained product. The isolated compound **3** was resubjected to a Mitsunobu reaction with the starting sugar **1**. It revealed the formation of compound **4** and full consumption of compound **3** as confirmed by NMR and mass spectroscopies (Table 5).

The formation of product **3** proves that under Mitsunobu conditions, compound **1** can act as a nucleophile. Meanwhile, the malonate exists in the form of a keto–enol equilibrium. If the enolic form of the malonate can be activated as an oxyphosphonium salt, it is conceivable to imagine for the anomeric position an inversed mechanism of the Mitsunobu reaction (Scheme 4). The sugar and the malonate would change roles, the sugar being the nucleophile, which attacks the activated malonate. This type of attack would explain the formation of exclusive *O*-alkylated compounds at the anomeric position.

## 3. Conclusions

The present paper reports a comparative study of the Mitsunobu reaction realized at C1 and C6 positions of suitably protected mannose, using the bis(2,2,2-trifluoroethyl) malonate as a pronucleophile. The different generated products show that at the C6 position, the malonate was mainly *C*-alkylated, while at the anomeric position only O-alkylation compounds were identified. In this case, the protected mannose may play the role of the nucleophile and finally, an inverse mechanism of the Mitsunobu reaction for the anomeric position is proposed.

## 4. Experimental

### 4.1. General methods

Triphenylphosphine was recrystallized from boiling ethanol. ADDP was purchased from Aldrich Chemical, Inc. All reactions were monitored by thin-layer chromatography with pre-coated silica gel ($SiO_2$) plates (E. Merck, Silica gel 60 $F_{254}$). Compounds were visualized by spraying the TLC plates with diluted 10% aqueous sulfuric acid solution or anisaldehyde solution, followed by heating at 150 °C. Proton spectra have been recorded on a Bruker DRX-400 spectrometer working at 400.13 MHz for $^1$H and 100.62 MHz for $^{13}$C. Two solvents ($CDCl_3$ and acetone-$d_6$) were used in order to facilitate the analysis of complex spin systems. Chemical shifts are reported relative to $CHCl_3$ ($\delta$=7.26 ppm in $^1$H NMR spectrum and $\delta$=77.00 ppm in $^{13}$C NMR spectrum) and to acetone ($\delta$=2.05 ppm in $^1$H NMR spectrum). Coupling constants ($J$) are measured in hertz. Assignments given for the NMR spectra are based on COSY, HMQC, and C13GD pulse sequences. Non-first-order spectra have been calculated and simulated with gNMR (Cherwell Publishing) and NMRSIM (Bruker) softwares. The numbering system of structures is not conventional. It was chosen so that a given carbon keeps the same label during the course of the various reactions, for an easier understanding of NMR parameters gathered in the tables. The electrospray ionization spectra were obtained on a Waters 2614 Micromass ZQ mass spectrometer in positive ($ESI^+$) and negative ($ESI^-$) modes. The melting point was measured on BUCHI 510 micromelting point apparatus.

### 4.2. General procedure for Mitsunobu reaction[3]

To a mixture of sugar (1 equiv), bis(2,2,2-trifluoroethyl) malonate (1.2 equiv), and triphenylphosphine (2 equiv) in toluene (3 mL) was added ADDP (2 equiv) in three equal fractions over 30 min. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was filtered and the precipitate was washed with a small volume of toluene. The yellow filtrate was concentrated in vacuo and directly purified by silica gel column chromatography.

**4.2.1. Reaction at the C1 position of mannose.** The general Mitsunobu reaction procedure was applied to 2.57 g (7.37 mmol) of sugar, 2.37 g (8.85 mmol) of bis(2,2,2-trifluoroethyl) malonate, 3.87 g (14.76 mmol) of triphenylphosphine in 22 mL of toluene, and 3.72 g of ADDP (14.76 mmol). The crude product concentrated in vacuo was purified by separation on successive silica gel column chromatographies. Firstly, a rough chromatography was realized using petroleum ether/ethyl acetate, 70/30 v/v, as eluant and four fractions containing compounds **2**–**4** as mixtures were obtained.

- Fraction 1 was a mixture of compounds **2a** and **2b** ($R_f$=0.58, petroleum ether/ethyl acetate: 50/50 v/v).
- Fraction 2 was a mixture of compounds **2c** and **2d** ($R_f$=0.50, petroleum ether/ethyl acetate: 50/50 v/v).
- Fraction 3 was a mixture of compounds **3**, **2c**, and **2d** (compound **3**: $R_f$=0.44, petroleum ether/ethyl acetate: 50/50 v/v).
- Fraction 4 was a mixture of compounds **4** and **1** (compound **4**: $R_f$=0.27, petroleum ether/ethyl acetate: 50/50 v/v).

Afterward, by further purifications of these fractions, compound **2a** was obtained as white crystals and the other compounds as gums or oils:

- *Compound* **2a** contained in fraction 1 was recrystallized from diisopropyl ether or from a mixture of petroleum ether/diethyl ether, 60/40 v/v, and the residue obtained after some repeated recrystallizations was chromatographed on silica gel (petroleum ether/diethyl ether: 40/60 v/v), in order to obtain *compound* **2b**.
- *Compounds* **2c** and **2d** from fraction 2 were separated by successive chromatographies (petroleum ether/diethyl ether: 40/60 v/v, hexanes/diethyl ether: 30/70 v/v).
- *Compound* **3** from fraction 3 was purified by column chromatography (petroleum ether/diethyl ether: 40/60 v/v).
- *Compound* **4** from fraction 4 was purified by column chromatography (petroleum ether/diethyl ether: 20/80 v/v).

**4.2.2. 2,2,2-Trifluoroethyl (2*Z*)-3-[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)oxy]-3-(2,2,2-trifluoroethoxy)acrylate (2a).** $R_f$: 0.63 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 621 [M+Na]$^+$, 637 [M+K]$^+$, (ESI$^-$/MeOH) *m/z*: 633 [M+Cl]$^-$; mp=118–120 °C.

**4.2.3. 2,2,2-Trifluoroethyl (2*E*)-3-[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)oxy]-3-(2,2,2-trifluoroethoxy)acrylate (2b).** $R_f$: 0.58 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 621 [M+Na]$^+$, 637 [M+K]$^+$, (ESI$^-$/MeOH) *m/z*: 633 [M+Cl]$^-$.

**4.2.4. 2,2,2-Trifluoroethyl (2*Z*)-3-[(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)oxy]-3-(2,2,2-trifluoroethoxy)acrylate (2c).** $R_f$: 0.49 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 621 [M+Na]$^+$, 637 [M+K]$^+$, (ESI$^-$/MeOH) *m/z*: 633 [M+Cl]$^-$.

**4.2.5. 2,2,2-Trifluoroethyl (2*E*)-3-[(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)oxy]-3-(2,2,2-trifluoroethoxy)acrylate (2d).** $R_f$: 0.44 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 621 [M+Na]$^+$, 637 [M+K]$^+$, (ESI$^-$/MeOH) *m/z*: 633 [M+Cl]$^-$.

**4.2.6. 2,2,2-Trifluoroethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl malonate (3).** $R_f$: 0.54 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 539 [M+Na]$^+$, (ESI$^-$/MeOH) *m/z*: 515 [M−H]$^-$.

**4.2.7. 2,2,2-Trifluoroethyl 3,3-bis[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)oxy] acrylate (4).** $R_f$: 0.23 (petroleum ether/$Et_2O$: 10/90 v/v); MS: (ESI$^+$/MeOH) *m/z*: 864 [M+$NH_4$]$^+$, 869 [M+Na]$^+$, 1716 [2 M+Na]$^+$, (ESI$^-$/MeOH) *m/z*: 881 [M+Cl]$^-$.

**4.2.8. Reaction at the C6 position of mannose.** The general Mitsunobu reaction procedure was applied to 0.50 g (1.08 mmol) of sugar, 0.35 g (1.29 mmol) of bis(2,2,2-trifluoroethyl) malonate, 0.57 g (2.15 mmol) of triphenylphosphine in 3.3 mL of toluene, and 0.54 g of ADDP (2.15 mmol). The purification was achieved by column chromatography on silica gel (petroleum ether to petroleum ether/diethyl ether: 85/15 v/v) to afford compounds **6** and **7** as transparent oils.

**4.2.9. α-D-*manno*-Octopyranosiduronic acid methyl 6,7-dideoxy-2,3,4-tris-*O*-(phenylmethyl)-7-[(2,2,2-trifluoroethoxy)carbonyl]-2,2,2-trifluoroethyl ester (6).** $R_f$: 0.47 (petroleum ether/$Et_2O$: 60/40 v/v); SM: (ESI$^+$/MeOH) *m/z*: 737 [M+Na]$^+$, (ESI$^-$/MeOH) *m/z*: 713 [M−H]$^-$.

**4.2.10. 2,2,2-Trifluoroethyl [2Z(*E*)]-3-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside)-3-(2,2,2-trifluoroethoxy)acrylate (7).** $R_f$: 0.40 (petroleum ether/$Et_2O$: 60/40 v/v); SM: (ESI$^+$/MeOH) *m/z*: 737 [M+Na]$^+$, (ESI$^-$/MeOH) *m/z*: 713 [M−H]$^-$.

## 5. X-ray crystal structure determination of 2a

$C_{21}H_{24}F_6O_{13}$, $M_r$=598.40, monoclinic, $P2_1$, $a$=8.9725(2), $b$=9.7445(2), $c$=31.1935(6) Å, $V$=2727.3(1) Å$^3$, $Z$=2, $D_x$=1.457 mg m$^{-3}$, $\lambda$ (Mo Kα)=0.71073 Å, $\mu$=1.45 cm$^{-1}$, $F(000)$=1232, $T$=293 K. The sample (0.24×0.24×0.10 mm) was studied on a Bruker AXS X8-APEX II with graphite monochromatized Mo Kα radiation. The cell parameters were obtained with 30 frames (psi rotation: 1° per frame). The data collection[19] ($2\theta_{max}$=54°, phi scan frames via 1.0° phi rotation and 20 s per frame, range *hkl*: $h$ −10, 11; $k$ −12, 10; $l$ −38, 38) gave 36,215 reflections. The data lead to 5414 independent reflections from which 4254 independent reflections with $I>2.0\sigma(I)$. The structure was solved with SIR-97,[20] which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms may be found with a Fourier difference. The whole structure was refined with SHELX97[21] by the full-matrix least-square techniques (use of $F$ square magnitude; $x$, $y$, $z$, $\beta_{ij}$ for C, O and F atoms, $x$, $y$, $z$ in riding mode for H atoms; 362 variables and 4254 observations with $I>2.0\sigma(I)$; calcd $w=1/[\sigma 2(F_0^2)+(0.08P)^2+0.11P]$ where $P=(F_0^2+2F_c^2)/3$ with the resulting $R$=0.041, $R_w$=0.119 and $S_w$=0.998, $\Delta\rho<0.26$ eÅ$^{-3}$.

Atomic scattering factors are from International Tables for X-ray Crystallography.[22] ORTEP views were realized with PLATON98.[23]

Crystallographic data (excluding structural factors) for the structure of compound **2a** has been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 646510.

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## References and notes

1. Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957–981.
2. Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624 and references therein.
3. Clavel, C.; Barragan-Montero, V.; Montero, J.-L. *Tetrahedron Lett.* **2004**, *45*, 7465–7467.

4. Barragan, V.; Menger, F. M.; Caran, K.; Vidil, C.; Morere, A.; Montero, J.-L. *Chem. Commun.* **2001**, 85–86.
5. Takacs, J. M.; Xu, Z.; Jiang, X.-T.; Leonov, A. P.; Theriot, G. C. *Org. Lett.* **2002**, *4*, 3843–3845.
6. D-Mannose pentaacetate of 10 g (25.62 mmol, 1 equiv) was dissolved in 10 mL of methylene chloride followed by the addition of 8.94 mL (102.47 mmol, 4 equiv) of morpholine. After complete consumption of the starting material (1.5 h), the reaction mixture was diluted with ethyl acetate and washed successively with 2 N HCl and 5% $NaHCO_3$ aqueous solutions, water, and brine, and then dried ($Na_2CO_3$), filtered, and concentrated. The structure of the reaction product was confirmed by NMR and mass spectrometries. The pure desired α-compound was obtained as the only reaction product and it was used in the Mitsunobu reaction without further purification.
7. Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.
8. Bock, K.; Pederson, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.
9. Besson, T.; Al Neirabeyeh, M.; Viaud, M.-C.; Rollin, P. *Synth. Commun.* **1990**, *20*, 1631–1639.
10. (a) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819–2822; (b) Wang, J.; Gutsche, C. D. *Struct. Chem.* **2001**, *12*, 267–274.
11. Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *13*, 1279–1282.
12. Shing, T. K. M.; Li, L.-H.; Narkunan, K. *J. Org. Chem.* **1997**, *62*, 1617–1622.
13. Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron* **1995**, *51*, 255–272.
14. Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.
15. Damoun, S.; Van de Woude, G.; Chocho, K.; Geerlings, P. *J. Phys. Chem. A* **1999**, *103*, 7861–7866.
16. Bittner, S.; Barneis, Z.; Felix, S. *Tetrahedron Lett.* **1975**, *44*, 3871–3874.
17. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983.
18. Goodman, L. *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 109–175.
19. *Bruker SMART (version 5.611) and SAINT+ (version 6.45)*; Bruker AXS: Madison, WI, 2003.
20. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1998**, *31*, 74–77.
21. Sheldrick, G. M. *SHELX97. Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
22. *International Tables for X-ray Crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992; Vol. C.
23. Spek, A. L. *PLATON. A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 1998.