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# Synthesis of Monoprotected 2-Alkylidene-1,3-Propanediols by an Unusual $S_N2'$ Mitsunobu Reaction

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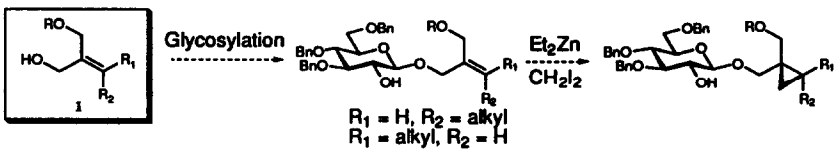
***Abstract:*** A simple and efficient route to monoprotected *E*- and *Z*-2-alkylidene-1,3-propanediols was developed. The key step involves an unusual regio- and stereoselective $S_N2'$ Mitsunobu reaction of substituted 3-hydroxy-2-methylenealkenoate.

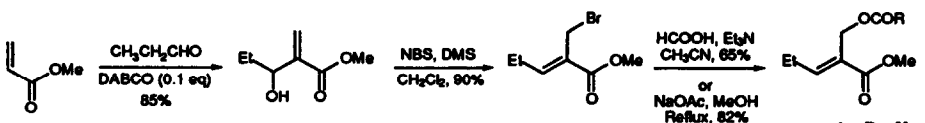
We recently reported that 3,4,6-tri-*O*-benzyl-D-glucose could be used as an efficient and practical chiral auxiliary for the cyclopropanation of variety of substituted allylic alcohols.[2] In connection with an ongoing synthetic program, we were interested in the unexplored cyclopropanation of protected 2-alkylidene-1,3-propanediols using our chiral auxiliary (Scheme 1).

**Scheme 1**

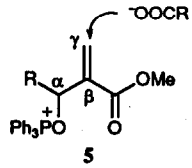



We were surprised to find very little investigation in the chemistry of the required 2-alkylidene-1,3-propanediol precursors **1**.[3] Furthermore, the few approaches available do not allow stereochemical control of the olefin and differentiation of the oxygenated positions: two essentials requirements in our system. The first approach we investigated was based on Hoffmann's protocol[4] that produces 2-bromomethyl-2-alkenoate **3** in 2 steps from methyl acrylate (Scheme 2). The bromide could be subsequently displaced with either ammonium formate[5] or NaOAc[6] to produce ester **4a** or **4b** , two suitable precursors to monoprotected diol **1**.[7]

**Scheme 2**




Based on the regioselectivity and stereoselectivity of the bromination reaction in these systems, we envisioned that under the Mitsunobu conditions,[8] the Michael acceptor nature of the oxophosphonium salt **5** derived from **2** should be increased and potential for γ-attack may be favored over α-attack (Figure 1).

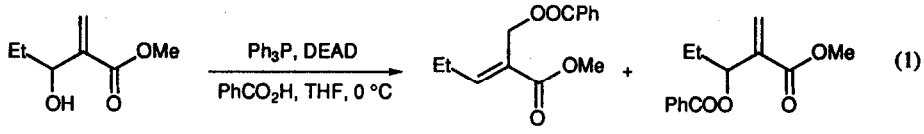



5

**Figure 1**

This would allow expedient preparation of a variety of derivatives of type **4** directly from **2**.

Although extremely rare, minor products derived from γ-attack have been observed in the Mitsunobu reaction of allylic systems.[9,10] Farina[9a] proposed, based on labeling experiments, that these products are generated by nucleophilic attack on the corresponding allylic cation formed via a $S_N1$ mechanism. To the best of our knowledge, no Mitsunobu reaction has been reported for an acyclic allylic alcohol bearing an ester group at the β-position.[11] When ester **2** was subjected to standard Mitsunobu conditions, the γ-attack product **4c** was isolated in 90% yield along with only 3% of the α-attack product **6** (eq 1). Furthermore, the olefin geometry was found to be *exclusively E*.[12]

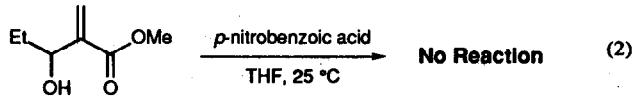



(1)

**2** **4c** (90%) **6** (3%)

The reaction conditions involving various carboxylic acids, solvents, and reaction conditions to favor γ- over α-attack are presented in Table 1. In all cases, the *E*-isomer was obtained as the only isolable double bond isomer. The first important thing to note is that stronger carboxylic acids, such as *p*-nitrobenzoic acid, favor normal Mitsunobu substitution (the ratio γ-:α-attack decreases, entry 1 and 3). This observation is consistent with Martin's and Bessodes' conclusion[13] regarding the effect of stronger carboxylic acids on the rate of the Mitsunobu inversion of hindered alcohols. Acetic acid produced a very high γ:α ratio, but a low yield was obtained due to the autodestruction of the reagents under the reaction conditions (entry 7). The very high γ selectivities observed for the bulky mesitoic acid could be explained by attack at the most accessible position (entry 8,9). In all cases, the yields and the selectivies were generally superior when THF was used as the solvent (entry 3,5,6). Interestingly, increasing the steric bulk of the R group not only suppressed α-attack, but it also considerably slowed down the γ-attack process (entry 10-11). In contrast to the less hindered ethyl analog (entry 3), the product resulting from α-attack could not be detected even when *p*-nitrobenzoic acid was used (entry 11).

Two additional control experiments clearly showed that both the oxophosphonium moiety *and* the ester group were essential for obtaining high yield of the product resulting from γ-attack. Treatment of allylic alcohol **2** with *p*-nitrobenzoic acid in THF at 25 °C led to complete recovery of starting material (eq 2).

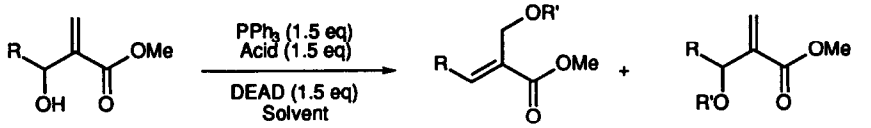



(2)

**2**

Furthermore, replacement of the methyl ester by a protected primary alcohol produced only the Mitsunobu inversion product with no trace of the desired allylic transposition product (eq 3).

**Table 1.**

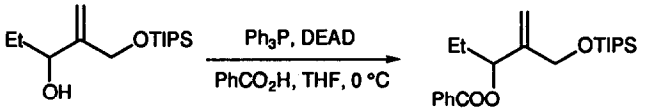



**2** (R = Et)
**7** (R = *i*-Pr)

**4** (R = Et)
**8** (R = *i*-Pr)

| Entry | R | Acid | Solvent | Temp (time) | γ:α ratio[a] | Yield | Major Product |
|---|---|---|---|---|---|---|---|
| 1 | Et | Benzoic | THF | 0 °C (15 min) | 30:1 | 90%[b] | **4c**, R' = Bz |
| 2 | Et | Benzoic | THF | -30 °C (2 h) | >50:1 | 80%[c] | **4c**, R' = Bz |
| 3 | Et | *p*-nitrobenzoic | THF | 0 °C (15 min) | 10:1 | 86%[b] | **4d**, R' = PNBz[d] |
| 4 | Et | *p*-nitrobenzoic | THF | -40 °C (2 h) | 25:1 | 85%[b] | **4d**, R' = PNBz |
| 5 | Et | *p*-nitrobenzoic | $CH_2Cl_2$ | 0 °C (5 h) | 5:1 | 60%[c] | **4d**, R' = PNBz |
| 6 | Et | *p*-nitrobenzoic | Toluene | 0 °C (15 min) | 9:1 | 60%[c] | **4d**, R' = PNB |
| 7 | Et | acetic | THF | 0 °C (4 h) | >50:1 | 50%[c] | **4b**, R' = Ac |
| 8 | Et | mesitoic[e] | THF | 0 °C (15 min) | >50:1 | 76%[b] | **4e**, R' = Mes[f] |
| 9 | Et | mesitoic | THF | -40 °C (1 h) | >50:1 | 75%[c] | **4e**, R' = Mes |
| 10 | *i*-Pr | *p*-nitrobenzoic | THF | -40 °C (2 h) | ---- | 0%[g] | ---- |
| 11 | *i*-Pr | *p*-nitrobenzoic | THF | 0 °C (1 h) | >50:1 | 80%[c] | **8**, R' = PNBz |

[a]Determined by 400 MHz $^1$H NMR of the crude product. [b]Isolated yield of analytically pure product. [c]Yield was evaluated by $^1$H NMR. [d]PNBz: *p*-nitrobenzoyl. [e]mesitoic: 2,4,6-trimethylbenzoic. [f]Mes: 2,4,6-trimethylbenzoyl. [g]Starting material was recovered unchanged.




**Only** (3)

With the Mitsunobu adducts in hand, the synthesis of the monoprotected diols **10** and **12** was completed as described in Scheme 3. The prefered starting material for the sequence was the *p*-nitrobenzoate ester **4d** since transesterification of **4c** with $K_2CO_3$ in $CH_3OH$ at 0 °C produced *ca.* 25% of methyl ether resulting the $S_N2'$ displacement of the benzoate by the methoxide ion. In contrast, the corresponding *p*-nitrobenzoate was smoothly cleaved under these conditions to produce alcohol **9**. A subsequent protection and reduction afforded the desired *Z*-isomer **10** in 73% overall yield for the 3 steps. The synthesis of the *E*-isomer **12** was equally accessible simply by starting with the mesitoate **4e**. Chemoselective reduction of the methyl ester followed by silylation and cleavage of the mesitoate ester produced the *E*-isomer **12** in 67% overall yield for the 3 steps.

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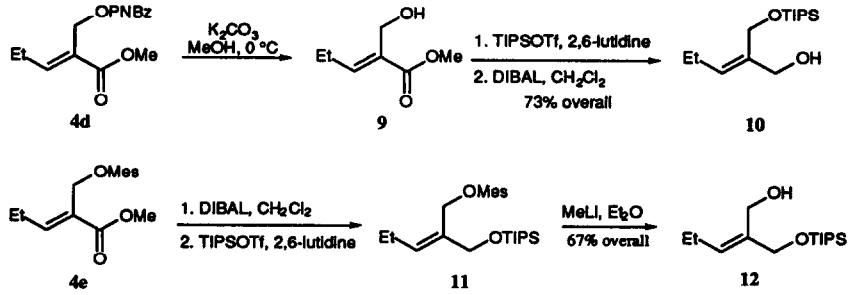
**Scheme 3**

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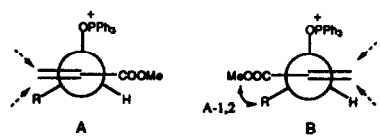


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