JOC The Journal of Organic Chemistry

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DIBAL-Mediated Reductive Transformation of *trans*-Dimethyl Tartrate Acetonide into ε-Hydroxy α,β-Unsaturated Ester and Its Derivatives

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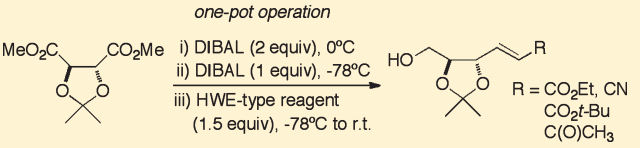
Supporting Information

ABSTRACT: Stepwise, selective DIBAL reduction of the acetonide diester derived from tartaric acid followed by the Horner−Emmons reaction effectively provided desymmetrized hydroxy mono-olefination products in a one-pot operation.

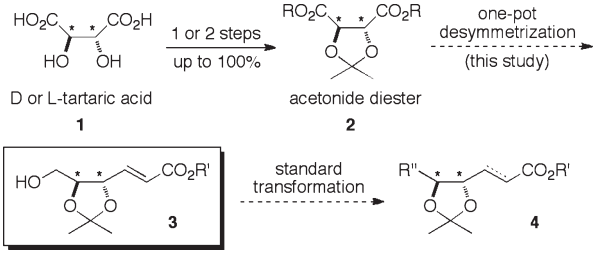


The D-(−)- and L-(+)-tartaric acids are well-known chiral molecules possessing two useful stereogenic centers. Both the natural (L) and unnatural (D) isomers are relatively inexpensive and widely available even on a bulk scale. Therefore, these molecules have continually been utilized as an important chiral starting material in various natural product synthesis.

Among a number of the derivatives, the acetonide protected diester **2**, easily prepared from the acid **1** by simple one- or two-step reactions (Scheme 1),[1] is often employed to lead to further symmetrical or unsymmetrical acetonides. In particular, a series of acetonide esters **4** including but not limited to **4a**−**e** (Figure 1) are frequently seen as chiral building blocks for the construction of a variety of synthetic intermediates in total synthesis.[2−8] However, there is no general, efficient path to access these compounds. Indeed, many of the literature routes require a long reaction sequence that includes redundant protection−deprotection and/or oxidation−reduction processes and often results in low overall yields (e.g., **4a**, five steps from dimethyl L-tartrate;[2] **4b**, seven steps from *cis*-2-butene-1,4-diol;[3] **4c**, six steps from L-tartaric acid;[4] **4d**, seven steps from L-tartaric acid;[5] **4e**, seven steps from L-arabitol,[6] etc.[7,8]). However, since all these acetonides **4** should technically be accessible from the common acetonide derivative **3** by means of a standard one-step chemical transformation currently available, compound **3** seems to be a highly versatile and potentially useful molecule (Scheme 1). Nonetheless, the synthesis of **3** has been rarely studied, and to the best of our knowledge, no practical route to **3** is yet available,[9] even though efficient approaches for *cis*-acetonide isomers of **3** have been well-established.[10] Thus, we envisioned that exploring a facile, single-pot transformation of acetonide diester **2** into **3** would be highly desirable, and furthermore, enable rapid access to **4** as well as to other useful analogues in just a few steps from tartaric acid **1** or, more conveniently, from a commercially available acetonide diester **2**.

A recent literature report[11] describes eight-step approach to **3** (**3a**) via a chiral diol **5** (Scheme 2). Although the starting D-mannitol is a very cheap material, the overall yield is disappointingly low (17%) (39% for the first four steps[12] and 44% for the second four steps[11]). Naturally, the diol intermediate **5** can be prepared from D-tartaric acid by two steps,[13] but the overall reaction efficiency (a total of six steps to **3a**) is still not satisfactory for this class of simple molecules.[14]

Scheme 1. Short Synthetic Approach to 3 and 4



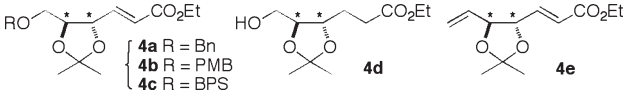
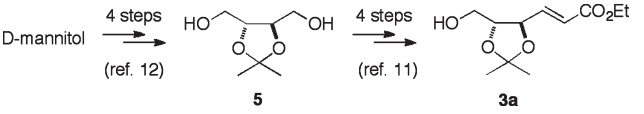


Figure 1. Series of acetonide esters **4a**−**e**

Scheme 2. Synthesis of 3a



Meanwhile, Seebach et al. employed a short-step approach to **3** (**3b**) starting from an acetonide diester **2** (**2a**) (Scheme 3).[15] Treatment of **2a** with 3 equiv of DIBAL reagent at −78 °C

Received: January 7, 2011
Published: April 29, 2011

followed by a Soxhlet extraction and further distillation afforded the corresponding lactol/hydroxyaldehyde **6** in 45% yield. Subsequently, Wittig olefination of **6** provided **3b** in 80%. While the overall yield was fair (36%)[16] and the obtained **3b** was a mixture of *E*/*Z* isomers with a partial epimerization at C4, this protocol still implies a potential feasibility for one-pot reductive transformation of diester **2** into **3** as described in Scheme 1.

To begin, the Seebach's protocol under various "single-pot" conditions, that is, without isolation of **6**, was initially examined. Even though the desired product **3b** was somewhat observed, the *E*/*Z* selectivity was, as expected, marginal (*E*/*Z* = ~6:4). In order to avoid this stereochemical drawback, the Wittig reagent was exchanged for a Horner−Wadsworth−Emmons (HWE) reagent, which is compatible with the use of DIBAL.[17] The use of $[(EtO)_2P(O)CHCOOEt]^-Na^+$ exclusively gave the desired *E*-isomer (*E*/*Z* = >25:1);[18] however, the yield of **3c** was disappointingly low (13%) (route A in Scheme 4), although, on the basis of the original Seebach protocol, the entire DIBAL addition temperature was initially maintained at −78 °C to prepare the lactol **6** via an organoaluminum intermediate **7**. Because of the poor reaction efficiency of route A, an alternative approach through a presumed hydroxy ester **8** was then explored by adding the first 2 equiv of DIBAL at rt (route B in Scheme 4).[19] Surprisingly, the applied route B conditions greatly improved the overall product yield of **3c** to 46%.

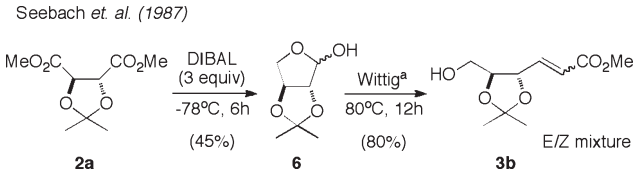
As summarized in Table 1, both route A and B conditions were further examined. Although the reaction yield was variable under different conditions, the route B (entries 4−10) still proved to be superior to route A (entries 1−3). Route B was highly solvent/temperature-dependent (entries 4−7), but much less subject to the ester substituent group (entries 6, 9, and 10). A faster DIBAL addition still gave the same results (entry 8). [Note: Not surprisingly, in the crude reaction mixture, two side products, (1) over-reduced diol acetonide **5** and (2) C_2-symmetrical α,β-unsaturated diester,[20] were always observed (the composition ratio of these depends on the reaction conditions). These were easily separated from product **3c** by column chromatography.]

The dependence of the reaction yield of **3c** on variations in the amount of DIBAL at two different temperatures (the first step at room temperature and the second step at −78 °C) was also investigated (Figure 2). The results indicate that the route B conditions, adding 2 equiv of DIBAL at rt (step 1) and another 1 equiv at −78 °C (step 2), are strictly required to maximize the yield of **3c**.

All of the entries and reactions discussed/shown so far were operated on a 1 mmol scale. The scalability was therefore examined. First, the reaction was run on a 10 mmol scale, and **3c** was successfully obtained in 44% yield. However, since the first-step DIBAL reduction was a slightly exothermic process that was not preferred for a large-scale operation, the addition temperature was lowered to 0 °C to be safe (Scheme 5). Interestingly, this modified condition somewhat improved the yield of **3c** (46% → 49% on a 1 mmol scale). More excitedly, even a 40 times larger scale reaction still afforded **3c** in 51% yield, which is essentially the same as the one obtained at 1 mmol reaction scale. Thus, the reaction proved to be scalable.

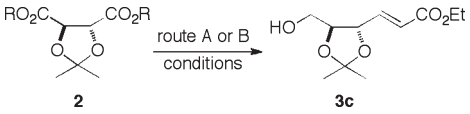
To explore the scope and limitations of this route B approach, other HWE-type reagents were accordingly employed (Scheme 6). All the cases worked well with similar efficiency and afforded corresponding olefins (**3d**, **3e**, and **3f**) in 46−52% yield, even though the α-cyano phosphonate reagent was not

Scheme 3. Synthesis of 3b



[a] $Ph_3P{=}CHCO_2Me$.

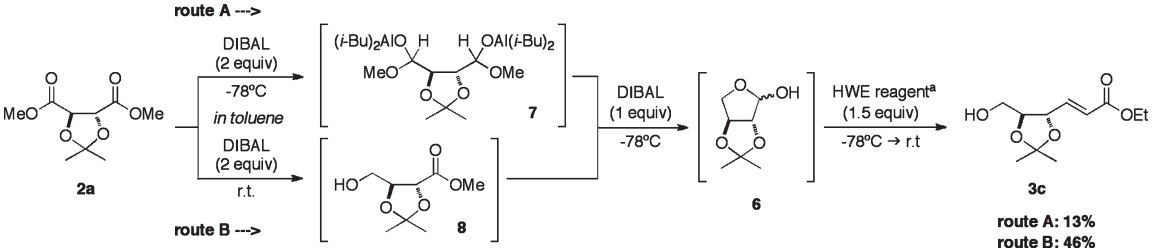
Table 1. Screening of Conditions for Routes A and B[a]



entry	2	reaction solvent	3c (%)
route A conditions			
1	R = Me	THF	19[b]
2	R = Me	THF	13
3	R = Me	toluene	13
route B conditions			
4	R = Me	THF	21
5	R = Me	hexane	25[c]
6	R = Me	toluene	46
7	R = Me	toluene	29[b]
8	R = Me	toluene	46[d]
9	R = Et	toluene	46
10	R = *i*-Pr	toluene	48

[a] Reaction conditions: **2** (1.0 mmol), DIBAL (1.0 M in toluene), DIBAL addition rate (1.0 mmol/h), solvent (4.0 mL), HWE reagent (1.5 mmol). [b] HWE reagent was added at r.t. [c] Used DIBAL (1.0 M in hexane). [d] DIBAL addition rate (2.0 mmol/h).

Scheme 4. One-Pot Transformation of 2a into 3c



[a] $[(EtO)_2P(O)CHCOOEt]^-Na^+$.

dx.doi.org/10.1021/jo200019j |J. Org. Chem. 2011, 76, 4669–4674

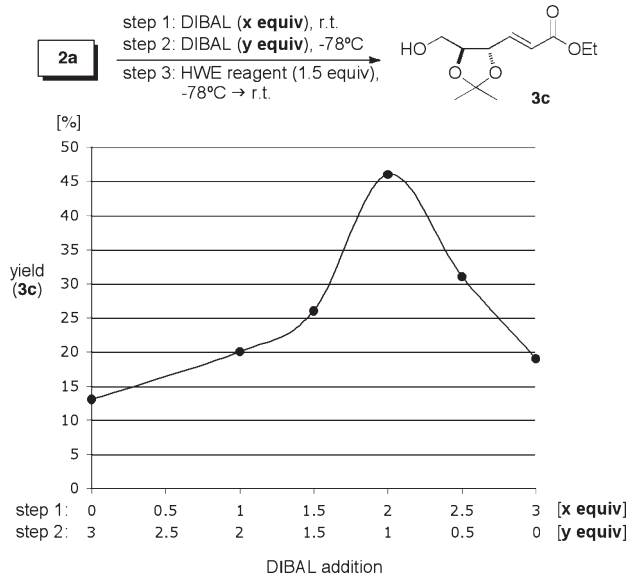
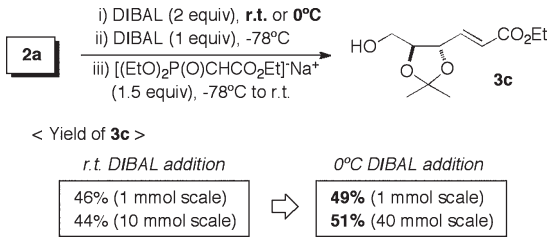
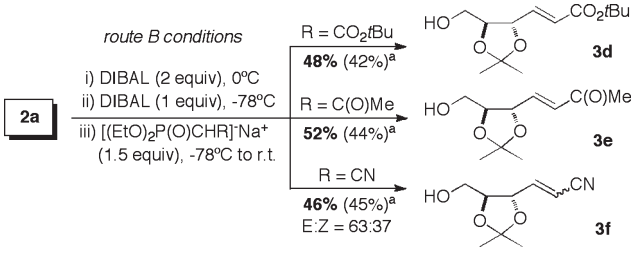


Figure 2. Dependence of the yield of **3c** on the amounts of DIBAL at the first and second steps.

Scheme 5. Testing Scalability (1 mmol vs 40 mmol)



Scheme 6. Different Phosphonate Reagents

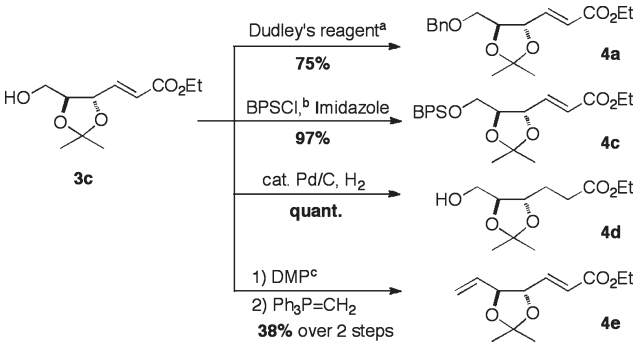


[a] Yields in parentheses were obtained when the first-step DIBAL addition was operated at room temperature.

very *E* stereoselective (*E*/*Z* = 63:37). Again, the first-step DIBAL addition temperatures (0 °C vs rt) affected the product yields. Substrate generality besides diester **2** was also explored. Unfortunately, when dimethyl succinate and dimethyl glutarate were tested, the route B conditions did not give desired olefins in an effective manner (only 15% and 26% yield, respectively). Thus, the presence of the conformational constraint imparted by the acetonide group seems to be important.

Finally, one-step transformation of compound **3** into **4** was investigated (Scheme 7). Benzylation of **3c** by employing Dudley's reagent (2-benzyloxy-1-methylpyridinium triflate)[21] successfully afforded **4a** in 75% yield.[22] A silyl protecting group

Scheme 7. Transformation of 3 into 4



[a] 2-Benzyloxy-1-methylpyridinium triflate. [b] *tert*-Butylchlorodiphenylsilane. [c] Dess–Martin periodinane.

was also cleanly introduced on the hydroxyl group of **3c** in 97%. Pd/C-catalyzed hydrogenation quantitatively converted **3c** into the reduced ester **4d**. One-pot transformation of **3c** into **4e** was also attempted; however, the yield of **4e** was consistently low (<20%). Therefore, following DMP oxidation of **3c**, the aldehyde was isolated as a crude product and then used for the next Wittig olefination. This stepwise approach improved the yield to 38%, which is comparable to the reported ones.[23] These results strongly support that the now more readily available **3** can play an important role as a versatile intermediate for organic synthesis. In addition, the number of reaction steps to access **4** through our newly established approach are less than half those of literature protocols. Thus, even though the reaction yield from **2** to **3** is fair (up to 52%), these new routes to **4** are still highly competitive and useful from the aspect of overall synthetic efficiency.

In summary, applying a unique, stepwise DIBAL addition sequence to *trans*-dimethyl tartrate acetonide **2a** most effectively gave the corresponding lactol intermediate **6** that was subsequently exposed to various Horner–Wadsworth–Emmons reagents to provide γ-hydroxy mono-olefination products. This simple protocol now enables a rapid access to a number of useful chiral acetonide derivatives such as **3** and **4** starting from readily available tartaric acid.

EXPERIMENTAL SECTION

Materials and Methods. All experiments were performed in flame-dried glassware fitted with rubber septa under argon atmosphere. Toluene was dried by passing through activated alumina. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 300 or 500 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δH 7.26 for the residual protons in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 75 or 125 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δC 77.0 for $CDCl_3$. Infrared spectral data are reported in units of cm^{-1}. Analytical TLC was performed on silica gel plates using UV light and/or potassium permanganate stain followed by heating. Flash column chromatography was performed on silica gel 60A (32–63D).

General Procedure for the Synthesis of 3 (3c) on a 1.0 mmol Scale. Into a solution of **2a** (183 μL, 1.0 mmol) in dry toluene

dx.doi.org/10.1021/jo200019j |*J. Org. Chem.* 2011, 76, 4669–4674

(4.0 mL) under argon atmosphere was added DIBAL reagent (2.0 mL, 1.0 M solution in toluene, 2.0 mmol) slowly over a period of 2 h at 0 °C by using a syringe pump. After being stirred for 1 h at 0 °C, the resulting solution was placed in a dry ice/acetone cooling bath (−78 °C) and another 1 equiv of DIBAL reagent (1.0 mL, 1.0 M solution in toluene, 1.0 mmol) was slowly added over a period of 1 h. Following the addition of Horner−Emmons reagent that was separately prepared from triethyl phosphonoacetate (300 μL, 1.5 mmol) and NaH (60 mg, 60% in mineral oil, 1.5 mmol) in dry toluene (2 mL), the reaction mixture was stirred overnight (−78 °C to r.t.) and quenched with saturated Rochelle's salt solution (2 mL). The resulting mixture was vigorously stirred for 2 h and diluted with H_2O (2 mL). After the phase separation, the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organics were then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 3/1) to afford **3c** (113 mg, 49%) as a colorless oil.

(*E*)-Ethyl 3-[(4*S*,5*S*)-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (3c): $[\alpha]^{20}_D$ −8.67 (*c* 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 5.8, 15.6 Hz, 1H), 6.14 (d, *J* = 15.6 Hz, 1H), 4.53 (m, 1H), 4.21 (q, *J* = 6.0 Hz, 2H), 3.87 (m, *J* = 7.8 Hz, 2H), 3.68 (m, *J* = 6.9 Hz, 1H), 2.70 (brs, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.30 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 143.8, 122.8, 110.0, 80.7, 76.0, 60.7, 60.6, 26.9, 26.7, 14.1; IR spectra (neat) 1727, 3480; HRMS (EI) calcd for $C_{10}H_{15}O_5$ 215.0919 $[M - CH_3]^+$, found 215.0924.

(*E*)-*tert*-Butyl 3-[(4*S*,5*S*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (3d). The title compound was prepared according to the general procedure. Column chromatography (Hex/EtOAc = 3/1) yielded **3d** (125 mg, 48%) as a colorless oil: $[\alpha]^{20}_D$ −6.69 (*c* 1.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 6.2, 15.8 Hz, 1H), 6.07 (dd, *J* = 1.2, 15.8 Hz, 1H), 4.46 (m, 1H), 3.84 (m, 2H), 3.64 (m, 1H), 2.34 (brs, 1H), 1.46 (s, 9H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 142.4, 124.8, 109.9, 80.74, 80.73, 76.0, 60.6, 27.9, 26.8, 26.7; IR spectra (neat) 1710, 3469; HRMS (EI) calcd for $C_{12}H_{19}O_5$ 243.1232 $[M - CH_3]^+$, found 243.1231.

(*E*)-4-[(4*S*,5*S*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-2-one (3e). The title compound was prepared according to the general procedure (note: the HWE reagent was prepared in dry THF (2 mL) instead of dry toluene (2 mL) due to the poor solubility). Column chromatography (Hex/EtOAc = 7/3 to 6/4) yielded **3e** (105 mg, 52%) as a colorless oil: $[\alpha]^{20}_D$ −9.23 (*c* 1.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 6.2, 15.9 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 4.52 (m, 1H), 3.86 (m, 2H), 3.69 (brs, 1H), 2.78 (brs, 1H), 2.28 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 142.5, 131.1, 110.0, 80.8, 76.2, 60.7, 27.4, 26.8, 26.6; IR spectra (neat): 1679, 3546; HRMS (EI) calcd for $C_9H_{13}O_4$ 185.0814 $[M - CH_3]^+$, found 185.0813.

3-[(4*S*,5*S*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-prop-2-enenitrile (3f). The title compound was prepared according to the general procedure (note: the HWE reagent was prepared in dry THF (2 mL) instead of dry toluene (2 mL) due to the poor solubility). Column chromatography (Hex/EtOAc = 7/3 to 6/4) yielded **3f** [53 mg (E-isomer) + 31 mg (Z-isomer) = 84 mg, 48%] as a colorless oil. ***E*-Isomer**: $[\alpha]^{20}_D$ −5.31 (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 4.8, 16.2 Hz, 1H), 5.75 (dd, *J* = 1.5, 16.2 Hz, 1H), 4.51 (m, 1H), 3.84 (m, 2H), 3.68 (m, 1H), 2.39 (brs, 1H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 116.7, 110.4, 100.7, 80.3, 76.2, 60.7, 26.8, 26.5; IR spectra (neat) 2230, 3475; HRMS (EI) calcd for $C_8H_{10}NO_3$ 168.0661 $[M - CH_3]^+$, found 168.0662. ***Z*-Isomer**: $[\alpha]^{20}_D$ 7.50 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 8.3, 11.1 Hz, 1H), 5.53 (d, *J* = 11.1 Hz, 1H), 4.81 (m, 1H), 3.89 (m, 2H), 3.76 (m, 1H), 2.16 (brs, 1H), 1.47 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 114.8, 111.0, 102.3, 80.8, 75.6, 61.1, 26.8, 26.6; IR spectra (neat) 2227, 3485; HRMS (EI) calcd for $C_8H_{10}NO_3$ 168.0661 $[M - CH_3]^+$, found 168.0659.

Experimental Procedure for the Synthesis of 3c on a 40.0 mmol Scale. Into a solution of **2a** (7.33 mL, 40.0 mmol) in dry toluene (160 mL) under argon atmosphere was added DIBAL reagent (80.0 mL, 1.0 M solution in toluene, 80.0 mmol) slowly over a period of 2 h at 0 °C by using a syringe pump. After being stirred for 1 h at the same temperature, the resulting solution was placed in a dry ice/acetone cooling bath (−78 °C), and another 1 equiv of DIBAL reagent (40.0 mL, 1.0 M solution in toluene, 40.0 mmol) was slowly added over a period of 1 h. Following the addition of Horner−Emmons reagent (over 20 min) that was separately prepared from triethyl phosphonoacetate (12.0 mL, 60.0 mmol) and NaH (2.40 g, 60% in mineral oil, 60.0 mmol) in dry toluene (80 mL), the reaction mixture was stirred for ∼12 h (−78 °C to rt). The mixture was then quenched with saturated Rochelle's salt solution (80 mL) at 0 °C and vigorously stirred for 2 h at rt. After dilution with H_2O (80 mL), the biphasic mixture was separated. The separated aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 3/1) to afford **3c** (4.68 g, 51%) as a colorless oil. [Note: Two side products, diol **5** (∼5% yield by NMR) and C_2-symmetrical α,β-unsaturated diester (7% yield, 780 mg), in the crude mixture were easily separated due to the large differences in polarity [R_f (Hex/EtOAc = 3/1) 0.43 for the diester, 0.14 for **3c**, and ∼0 for diol **5**].]

One-Step Transformation of 3 into 4. *Benzylation of **3c** into **4a**.* Into a solution of **3c** (103 μL, 0.5 mmol) in benzotrifluoride (2 mL) were added 2-benzyloxy-1-methylpyridinium triflate[21] (349 mg, 1 mmol) and MgO (40 mg, 1 mmol). The reaction mixture was stirred at 83 °C. After being stirred for 66 h, the resulting reaction mixture was then filtered through Celite with EtOAc and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 10/1) to give the compound **4a** as a colorless oil (120 mg, 75%). This product spectroscopically matched that of the known compound:[24] $[\alpha]^{20}_D$ = −23.2 (*c* 1.00, $CHCl_3$) [lit.[24] $[\alpha]^{20}_D$ = −23.4 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5 H), 6.90 (dd, *J* = 5.4, 15.8 Hz, 1H), 6.09 (dd, *J* = 1.5, 15.8 Hz, 1H), 4.60 (s, 2H), 4.43 (ddd, *J* = 1.5, 5.4, 8.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.96 (dt, *J* = 4.8 8.4 Hz, 1H), 3.63 (d, *J* = 4.8 Hz, 2H),1.46 (s, 3H), 1.44 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.0, 137.7, 128.4, 127.8, 127.7, 122.6, 110.2, 79.6, 77.4, 73.6, 69.3, 60.6, 26.9, 26.7, 14.2.

*Silyl Protection of **3c** into **4c**.* Into a solution of **3c** (103 μL, 0.5 mmol) in DMF (5 mL) were added *tert*-butylchlorodiphenylsilane (133 μL, 0.51 mmol) and imidazole (68 mg, 1 mmol). The reaction mixture was stirred at 0 °C for 10 h and then stirred overnight at room temperature. After the phase separation, the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organics were then washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 20/1) to afford **4c** (228 mg, 97%) as a colorless oil. This product spectroscopically matched that of the known compound:[4] $[\alpha]^{20}_D$ = −1.88 (*c* 3.41, $CHCl_3$) [lit.[4] $[\alpha]^{20}_D$ = −1.8 (*c* 3.4, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.71 (m, 4 H), 7.43−7.41 (m, 6H), 6.97 (dd, *J* = 5.7, 15.8 Hz, 1H), 6.14 (d, *J* = 15.8 Hz, 1H), 4.62 (t, *J* = 5.7 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.88−3.85 (m, 3H), 1.47 (s, 3H), 1.45 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 9H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.4, 135.60, 135.57, 132.9, 129.9, 129.8, 127.8, 127.7, 122.1, 109.9, 80.7, 77.5, 63.1, 60.5, 26.9, 26.8, 19.2, 14.2.

*Hydrogenation of **3c** into **4d**.* Into a solution of **3c** (103 μL, 0.5 mmol) in MeOH (5 mL) was added 5% palladium on charcoal anhydrous (12 mg, 10 wt %). The mixture was stirred under a hydrogen atomosphere at room temperature for 4 h. The reaction mixture was then filtered through Celite with EtOAc and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 3/1) to give the compound **4d** as a

colorless oil (117 mg, quantitative). This product spectroscopically matched that of the known compound:[25] $[\alpha]^{20}_D$ = −24.7 (*c* 2.60, $CHCl_3$) [lit.[26] $[\alpha]^{23}_D$ = −24.1 (*c* 2.6, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.2 Hz, 2H), 3.86 (dt =7.5, 3.6 Hz, 1H), 3.74 (m, 2H), 3.62 (m, 1H), 2.53−2.36 (m, 3H), 1.92 (m, 1H), 1.81 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 108.8, 81.0, 76.1, 61.8, 60.5, 30.6, 27.9, 27.2, 26.9, 14.1.

DMP Oxidation/Wittig Olefination of ***3c*** *into* ***4e***. Dess−Martin periodinane (467 mg, 1.1 mmol) was added to a solution of **3c** (230 mg, 1.0 mmol) in CH_2Cl_2 (8 mL). After being stirred 2.5 h at rt, the reaction mixture was quenched with satd $NaHCO_3$ (5 mL) and satd $Na_2S_2O_3$ (5 mL) and vigorously stirred for 10 min. After the phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were then dried over Mg_2SO_4 and concentrated in vacuo. The crude aldehyde was immediately used for the next reaction. Into a suspension of methyltriphenylphosphonium bromide (356 mg, 1.0 mmol) in dry THF (10 mL) at −78 °C (acetone/dry ice) was added *n*-BuLi (360 μL, 2.5 M solution in hexane, 0.9 mmol) dropwise. After the mixture was stirred for 30 min, a solution of the aldehyde in dry THF (5 mL) was added slowly over 10 min. After the mixture was stirred for 1 h, the cooling bath was removed and the resulting mixture was stirred for 1 h at rt. After quenching with half-saturated NH_4Cl (15 mL), the separated aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified with silica gel column chromatography (Hex/EtOAc = 95/5) to afford 85 mg colorless oil (38%). This product spectroscopically matched that of the known compound:[6] $[\alpha]^{20}_D$ = +9.48 (*c* 0.52, $CHCl_3$) [lit. $[\alpha]^{20}_D$ = +14.8 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 5.4, 15.6 Hz, 1H), 6.12 (dd, *J* = 1.2, 15.6 Hz, 1H), 5.83 (ddd, *J* = 7.2, 10.2, 17.1 Hz, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.31 (d, *J* = 10.2 Hz, 1H), 4.28−4.10 (m, 4H), 1.47 (s, 3H), 1.45 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 143.0, 133.8, 123.1, 120.1, 110.2, 82.3, 80.1, 60.8, 27.2, 27.0, 14.4.

■ ASSOCIATED CONTENT

Supporting Information. Copy of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The project described was supported by Grant No. 5P20RR021929 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The University of Mississippi also supported this research.

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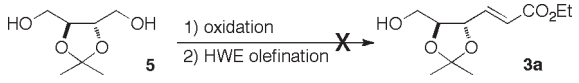

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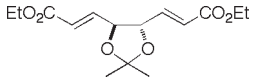

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 1.8, 3.6, 15.9 Hz, 2H), 6.14 (d, *J* = 15.6 Hz, 2H), 4.28−4.30 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 4H), 1.47 (s, 6H), 1.30 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 142.0, 123.9, 111.0, 79.9, 61.0, 27.0, 14.4.

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(22) Due to the presumed sensitivity of **3c** to both acidic and basic benzylation conditions, the neutral Dudley's protocol was therefore selected. Another neutral, silver oxide promoted benzylation condition was not very effective for **3c**.

(23) The overall yield of our three-step route from **2a** to **4e** is 19% [51% (**2a** → **3c**) and 38% (**3c** → **4e**)]. Literature approaches: 21% over seven steps from **2a** (Sarabia, Francisco; Sanchez-Ruiz, A. *J. Org. Chem.* **2005**, *70*, 9514); 37% over seven steps from L-arabitol (ref 6); 20% over six steps from D-mannitol (Chou, C.-Y.; Hou, D.-R. *J. Org. Chem.* **2006**, *71*, 9887).

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