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

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Abstract

Step-wise, 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 one-pot operation.

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),ⁱ 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**: 5 steps from dimethyl L-tartrate,ⁱⁱ **4b**: 7 steps from cis-2-butene-1,4-diol,ⁱⁱⁱ **4c**: 6 steps from L-tartaric acid,^{iv} **4d**: 7 steps from L-tartaric acid,^v **4e**: 7 steps from L-arabitol,^{vi} etc.^{vii,viii}). 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,^{ix} even though efficient approaches for cis-acetonide isomers of **3** have been well-established.^x 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**.

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

A recent literature^{xi} 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%) [the first four steps: 39%^{xii} and the second four steps: 44%^{xi}]. Naturally, the diol intermediate **5** can be prepared from D-tartaric acid by two steps,^{xiii} but the overall reaction efficiency (a total of six steps to **3a**) is still not satisfactory for this class of simple molecules.^{xiv}

Meanwhile, Seebach *et al.* employed a short-step approach to **3** (**3b**) starting from an acetonide diester **2** (**2a**) (Scheme 3).^{xv} Treatment of **2a** with 3 equivalents of DIBAL reagent at -78°C 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%)^{xvi} 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 to the use of DIBAL.^{xvii} The use of $[(\text{EtO})_2\text{P}(\text{O})\text{CHCOOEt}]^{-}\text{Na}^{+}$ exclusively gave the desired *E*-isomer (*E:Z* = > 25:1);^{xviii} however the yield of **3c** was disappointingly low (13%) (route A in Scheme 4), although, based on the original Seebach's protocol, the entire DIBAL addition temperature was initially maintained at -78°C to prepare the lactol **6** via an organo-aluminum intermediate **7**. Due to the poor reaction efficiency of route A, an alternative approach through a presumed hydroxyester **8** was then explored by adding the first two equivalents of DIBAL at r.t. (route B in Scheme 4).^{xix} 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). The 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,^{xx} 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 two equivalents of DIBAL at r.t. (step 1) and another one equivalent at -78°C (step 2), are strictly required to maximize the yield of **3c**.

All 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 successfully obtained **3c** 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% $\rightarrow$ 49% on a 1 mmol scale). More excitedly, even

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 very *E* stereoselective (*E*:*Z*=63:37). Again, the first-step DIBAL addition temperatures (0°C vs. r.t.) 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)^{xxi} successfully afforded **4a** in 75% yield.^{xxii} A silyl protecting group 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.^{xxiii} 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. ¹H 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 δ H 7.26 for the residual protons in CDCl₃), 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. ¹³C 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 δ C 77.0 for CDCl₃. 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 μ L, 1.0 mmol) in dry toluene (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 hours at 0°C by using a syringe pump. After stirring for 1 hour at 0°C, the resulting solution was placed in a dry-ice/acetone cooling bath (−78°C) and another one equivalent of DIBAL reagent (1.0 mL, 1.0 M solution in toluene, 1.0 mmol) was slowly added over a period of 1 hour. Following the addition of Horner-Emmons reagent that was separately prepared from triethyl phosphonoacetate (300 μ L, 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 2h and diluted with H₂O (2 mL). After the phase separation, the aqueous layer was extracted with Et₂O (2 $\times$ 15 mL). The combined organics were then dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by SiO₂ column chromatography (Hex/EtOAc = 3/1) to afford **3c** (113 mg, 49%) as a colorless oil.

(E)-Ethyl 3-[(4S,5S)-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (3c)— $[\alpha]_D^{20}$ −8.67 (*c* 1.43, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₀H₁₅O₅ 215.0919 [M-CH₃]⁺; found 215.0924.

(E)-tert-Butyl 3-[(4S,5S)-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** (125mg, 48%) as a colorless oil. $[\alpha]_D^{20}$ −6.69 (*c* 1.27, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₉O₅ 243.1232 [M-CH₃]⁺; found 243.1231.

(E)-4-[(4S,5S)-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** (105mg, 52%) as a colorless oil. $[\alpha]_D^{20}$ −9.23 (*c* 1.29, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₉H₁₃O₄ 185.0814 [M-CH₃]⁺; found 185.0813.

3-[(4S,5S)-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enitrile (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** [53mg (E-isomer) + 31mg (Z-isomer) = 84mg, 48%] as a colorless oil. (**E-isomer**): $[\alpha]_D^{20}$ −5.31 (*c* 1.28, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₈H₁₀NO₃ 168.0661 [M-CH₃]⁺; found

168.0662. (**Z-isomer**): $[\alpha]_D^{20}$ 7.50 (*c* 0.96, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₈H₁₀NO₃ 168.0661 [M-CH₃]⁺; 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 hours at 0 °C by using a syringe pump. After stirring for 1 hour at the same temperature, the resulting solution was placed in a dry-ice/acetone cooling bath (−78 °C) and another one equivalent of DIBAL reagent (40.0 mL, 1.0 M solution in toluene, 40.0 mmol) was slowly added over a period of 1 hour. 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 hours (−78 °C to r.t.). The mixture was then quenched with saturated Rochelle's salt solution (80 mL) at 0 °C and vigorously stirred for 2 hours at r.t. After diluting with H₂O (80 mL), the biphasic mixture was separated. The separated aqueous layer was extracted with Et₂O (2 × 100 mL). The combined organics were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by SiO₂ 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 C₂-symmetrical α,β -unsaturated diester (7% yield, 780mg), 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 μ L, 0.5 mmol) in benzotrifluoride (2 mL) was added 2-benzyloxy-1-methylpyridinium triflate^{xxi} (349 mg, 1 mmol) and MgO (40 mg, 1 mmol). The reaction mixture was stirred at 83 °C. After stirring 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 SiO₂ 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.^{xxiv}; $[\alpha]_D^{20}$ = −23.2 (*c* 1.00, CHCl₃), [lit.^{xxiv} $[\alpha]_D^{20}$ = −23.4 (*c* 1.0, CHCl₃)]; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 μ L, 0.5 mmol) in DMF (5 mL) was added *tert*-butylchlorodiphenylsilane (133 μ L, 0.51 mmol) and imidazole (68 mg, 1 mmol). The reaction mixture was stirred at 0 °C for 10 h, then stirring overnight at room temperature. After the phase separation, the aqueous layer was extracted with Et₂O (2 × 15 mL). The combined organics were then washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by SiO₂ 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.^{iv}; $[\alpha]_D^{20}$ = −1.88 (*c* 3.41, CHCl₃), [lit.^{iv} $[\alpha]_D^{20}$ = −1.8 (*c* 3.4, CHCl₃)]; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 μ L, 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 atmosphere 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 SiO₂ 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.^{xxv}; [α]_D²⁰ = −24.7 (*c* 2.60, CHCl₃), [lit.^{xxvi} [α]_D²³ = −24.1 (*c* 2.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 CH₂Cl₂ (8 mL). After stirring 2.5 h at r.t., the reaction mixture was quenched with sat. NaHCO₃ (5 mL) and sat. Na₂S₂O₃ (5 mL) and vigorously stirred for 10 min. After the phase separation, the aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 10 mL). The combined organics were then dried over Mg₂SO₄ 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 μ L, 2.5 M solution in hexane, 0.9 mmol) dropwise. After stirring for 30 min, a solution of the aldehyde in dry THF (5 mL) was added slowly over 10 min. After stirring for 1 h, the cooling bath was removed and the resulting mixture was stirred for 1 h at r.t. After quenching with half sat. NH₄Cl (15 mL), the separated aqueous layer was extracted with Et₂O (2 $\times$ 15 mL). The combined organics were washed with brine, dried over MgSO₄, 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.^{vi}; [α]_D²⁰ = +9.48 (*c* 0.52, CHCl₃), [lit. [α]_D²⁰ = +14.8 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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.

Supplementary Material

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- xiv. Although we attempted to explore two-step direct transformation of **5** into **3** by employing an oxidation of diol **5** followed by the Horner-Emmons olefination via a lactol intermediate, the desired product **3a** was not observed. Major problem of this route was the first oxidation step. Even though several oxidation conditions were carefully screened (*e.g.* DMP, TEMPO, and Parikh-Doering conditions, *etc.*), the corresponding lactol intermediate was hardly obtained.

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- xvi. Among the distilled fractions of **6**, only the second one was used for the next Wittig olefination (ref. 15). Thus the actual overall yield may be lower than 36%.
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¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 142.0, 123.9, 111.0, 79.9, 61.0, 27.0, 14.4.

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- xxii. 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**.
- xxiii. The overall yield of our 3-step route from **2a** to **4e** is 19% [51% (**2a** → **3c**) and 38% (**3c** → **4e**)]. Literature approaches: 21% over 7 steps from **2a** (Sarabia, Francisco; Sanchez-Ruiz, A. *J. Org. Chem.* 2005; 70:9514. [PubMed: 16268627]); 37% over 7 steps from L-arabitol (ref. 6); 20% over 6 steps from D-mannitol (Chou C-Y, Hou D-R. *J. Org. Chem.* 2006; 71:9887. [PubMed: 17168616]).
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Figure 1.
A Series of Acetonide Esters **4a–e**

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

Scheme 1.
Short Synthetic Approach to **3** and **4**

Scheme 2.
Synthesis of **3a**

Seebach *et. al.* (1987)

Scheme 3.
Synthesis of **3b**
^a $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$.

Scheme 4. One-Pot Transformation of **2a** into **3c**^a[(EtO)₂P(O)CHCOOEt]⁻Na⁺

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

Scheme 6.

Different phosphonate reagents

^aYields in parenthesis were obtained when the first-step DIBAL addition was operated at room temperature.

Scheme 7. Transformation of **3** into **4**^a2-benzyloxy-1-methylpyridinium triflate, ^b *tert*-butylchlorodiphenylsilane, ^c Dess-Martin periodinane

Table 1

Screening of Route A and B conditions^a

entry	2	reaction solvent	3c (%)
route A conditions			
1	R = Me	THF	19^b
2	"	"	13
3	"	toluene	13
route B conditions			
4	R = Me	THF	21
5	"	hexane	25^c
6	"	toluene	46
7	"	"	29^b
8	"	"	46^d
9	R = Et	"	46
10	R = <i>i</i> -Pr	"	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).