Practical One-Pot Synthesis of Protected L-Glyceraldehyde Derivatives

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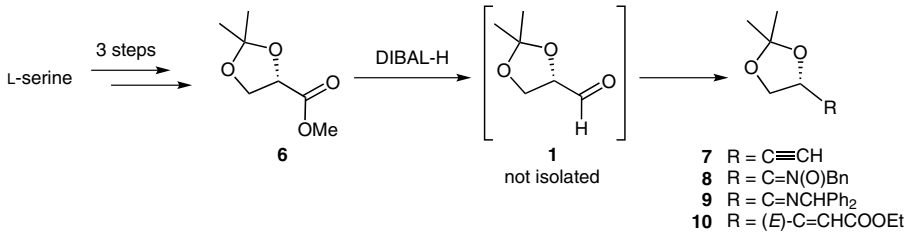
Received: 17.01.2012; Accepted after revision: 09.03.2012

PSP No 230

Abstract: A large-scale, simple, economic, and safe procedure for the preparation of L-glyceraldehyde acetonide under conditions, which allow its direct transformation (one-pot) into the desired products (acetylene, imine, nitrone, unsaturated ester) is reported. L-Glyceraldehyde acetonide is obtained from the corresponding ester, which is readily available from L-serine.

Key words: L-glyceraldehyde acetonide, L-glyceraldehyde derivatives, aldehydes, nitrones, acetylenes



Scheme 1

O,*O*-Ketals of L-glyceraldehyde, particularly the isopropylidene derivative **1** (Figure 1), represent valuable substrates in target-oriented synthesis.[1–12] There are several well-known methods for its preparation. Aldehyde **1** can be obtained, by analogy to its D-enantiomer,[13] from L-mannitol following a two-step procedure involving formation of diacetal followed by a glycolic cleavage.[6] Considering the high price of the substrate, such a method certainly has only a limited value.

Other methods use inexpensive and readily available ascorbic acid (**2**) as the substrate. There are several ways of its transformation into **1**. Substrate **2** can be hydrogenated to L-gulono-1,4-lactone (**3**)[14] (Figure 1), the side chain hydroxyl groups protected with isopropylidene group, and then the 5,6-*O*,*O*-isopropylidene derivative subjected to $NaIO_4$ degradation to provide **1**.[15]

The 5,6-*O,O*-isopropylidene group can be introduced into ascorbic acid (**2**) prior to hydrogenation of the double bond. Subsequently, compound **4** is reduced with $NaBH_4$, hydrolyzed, and oxidized with lead tetraacetate,[3,16] or alternatively, the product is reduced with $LiAlH_4$ and then oxidized with $NaIO_4$.[16,17] Compound **4** can be also subjected to oxidative degradation (30% H_2O_2) to afford 3,4-*O*-isopropylidene-L-threonic acid (**5**) (Figure 1), which subsequently is subjected to hypochloric acid promoted decarbonylation to provide **1**.[18,19]

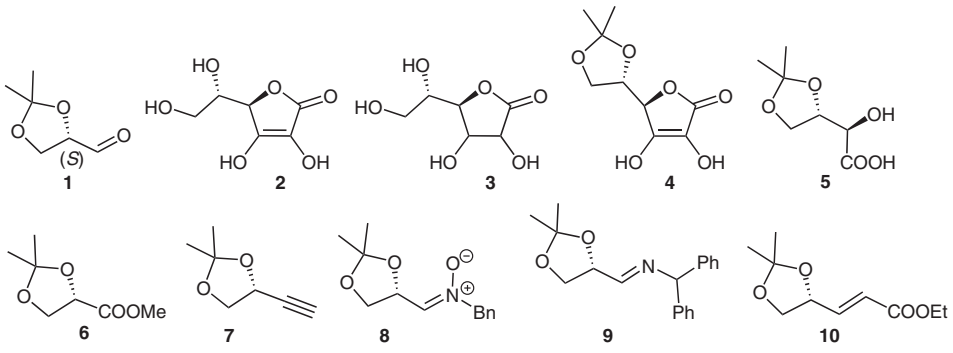


Figure 1 Structures of compounds **1**–**10**

SYNTHESIS 2012, 44, 2695–2698
Advanced online publication: 26.06.2012
DOI: 10.1055/s-0031-1291136; Art ID: SS-2012-T0054-PSP

The major drawback of all methods based on ascorbic acid is related to the formation of the final acetonide of L-glyceraldehyde **1** in dilute water solution. The numerous applications of **1** in target-oriented synthesis usually require an anhydrous product. To obtain such a product, laborious extraction of **1** is necessary reducing substantially the overall yield of the procedure. Generally, it is strongly recommended to avoid any aqueous workup during the glyceraldehyde synthesis due to the fact that it is able to form a stable hydrate. Moreover, the reactions must be carried out under restricted pH conditions because **1** is prone to racemization or deprotection under basic or acidic condition, respectively.

Herein, we report a practical method for the synthesis of crude **1** based on the transformation of relatively cheap L-serine. The key advantage of the proposed procedure is the ability to use directly the solution of the freshly formed aldehyde **1** without its prior isolation and purification (one-pot approach for synthesis).

Following known procedures,[20–22] L-serine can be transformed into the acetonide of methyl dihydroxypropanoate **6** (Scheme 1) in a three-step sequence that involves the displacement of the amino group to form a hydroxyl group (with retention of configuration, through the respective diazonium intermediate) followed by the esterification and acetal formation.

According to our protocol, compound **6** can be reduced with DIBAL-H, or other modified hydrides to provide **1**. This procedure provides ketals of L-glyceraldehyde in an organic solvent, usually in dichloromethane, toluene, or hexane, in good yield and ready to be used in subsequent transformations without purification. The yield of crude aldehyde **1** is ca. 90% (based on GC). For comparison, procedures based on ascorbic acid derivative **4** provide crude product **1** in 95%,[15b] whereas, the transformation of L-threonic acid salts **5** give only 60–75% of crude **1**.[18,19] Although reported yields of aldehyde **1** are high, the efficiency of isolation of the product from a solution is rather moderate, ca. 50–55%. This is because all of the known syntheses of L-glyceraldehyde are performed in aqueous or aqueous/organic solution, which makes isolation of the product from the post-reaction mixture troublesome. There are two factors responsible for that. As mentioned in the introduction, the product **1** forms a stable hydrate, which increases its solubility in water and, in consequence, complicates extractive workup. Additionally, L-glyceraldehyde acetonide is a relatively volatile compound, so removal of organic solvent(s) from the solution must be performed under restricted pressure conditions.[15b,18,19] On the other hand, conducting the synthesis in an anhydrous organic solvent enables to overcome the above-mentioned difficulties and simplifies handling of the aldehyde **1**; moreover, the procedure allows to use a solution of **1** directly for further transformations, which is the key advantage of the described method.

Additionally, our method does not require restricted pH control that usually creates a problem, especially during large-scale preparation.[15b,18,19] Moreover, compound **6** seems to be the most suitable starting material from the point of view of the atom economy. If one calculates the mass balance of substrates and product **1**, in the case of compound **6**, only ~18% of material is transformed into useless by-products whereas in the cases of **4** and **5** (for calcium salt), ~40% and ~33% of material is wasted, respectively.

The general suitability of the proposed procedure is further demonstrated by the direct formation of acetylene **7**, nitrone **8**, imine **9**, and α,β-unsaturated ester **10** (Figure 1) from compound **1**. These compounds **7**–**10** were selected considering their usefulness in target-oriented synthesis. In particular, the acetylene **7**, substrate for the synthesis of ezetimibe, a powerful cholesterol inhibitor,[23] can be obtained by treatment of **1** in dichloromethane solution with the Bestmann–Ohira reagent (dimethyl 1-diazo-2-oxopropylphosphonate)[24,25] in the presence of anhydrous methanol and anhydrous potassium carbonate. The *N*-benzyl nitrone **8**[26,27] can be prepared by treatment of a solution of **1** with *N*-benzylhydroxylamine, whereas the imine **9**[28] can be obtained by reacting **1** with diphenylmethylamine, while the ester **10** can be obtained by treatment of **1** with ethyl triphenylphosphorylideneacetate[29] or triethyl phosphonoacetate.[15]

To conclude, we have described a large-scale, simple, economic, and safe procedure for the preparation of L-glyceraldehyde acetonide (**1**) under conditions which allow for its direct transformation (one-pot) into desired products (acetylene, imine, nitrone, unsaturated ester). Aldehyde **1** is obtained from ester **6**, which is readily available from L-serine.

All reagents were used as purchased from commercial suppliers without further purification. Anhydrous CH_2Cl_2 was obtained by distillation over CaH_2 and anhydrous MeOH was purchased from Aldrich. NMR spectra were recorded on Varian 200 and 400 MHz spectrometers using $CDCl_3$ with TMS as the internal standard. Chemical shifts are reported as δ values in ppm and coupling constants are in hertz. Infrared spectra were obtained on an FT-IR-1600 Perkin-Elmer spectrophotometer. The optical rotations were measured with a JASCO J-2000 digital polarimeter. Mass spectra were recorded on ESI-TOF Mariner (Perspective Biosystem; ESI ionization) and AMD-604 (AMD Intectra GmbH; EI ionization) spectrometers. Elementary analysis was recorded on a Perkin-Elmer 240 Elemental Analyzer.

Methyl (*S*)-2,3-*O*-Isopropylidenepropionate (6)

Step 1, (S)-2,3-Dihydroxypropionate:[20] To a solution of L-serine (50 g, 0.47 mol) in H_2O (100 mL) at 0 °C were added aq H_2SO_4 (5 M, 150 mL) and aq $NaNO_2$ (6 M, 85 mL). After stirring the reaction mixture for 5 h at r.t., an additional portion of aq $NaNO_2$ (6 M, 85 mL) was added at 0 °C. The reaction mixture was stirred for 3 d at r.t. and then aq H_2SO_4 (5 M, 150 mL) and aq $NaNO_2$ (6 M, 85 mL) were added at 0 °C. After stirring the reaction mixture for 2 d at r.t., H_2O (ca. 500 mL) was distilled out under reduced pressure. The resulting residue was treated with a solution of NaOH (20 g) in H_2O (50 mL) at 0 °C. Then, a mixture of MeOH–acetone (3:1, 200 mL) was added to the resulting mixture and it was filtered through a short pad of Celite. After removal of the solvent, a mixture of MeOH–acetone (3:1, 200 mL) was added again. The above operation was repeated 7 times. After partial evaporation of the solvent, toluene

(100 mL) was added to the residue, and the solvent was removed by distillation under reduced pressure. Additional portion of toluene (100 mL) was added to the residue and then the above operation was repeated twice. The residue was dissolved in MeOH (200 mL) and acidified with concd H_2SO_4, and then trimethyl orthoformate (50 mL) was added to the mixture. The mixture was stirred for 30 min at 60 °C and then neutralized with NaOMe at 0 °C. After filtration of the mixture and evaporation of the solvent, the crude product was distilled under diminished pressure (bp 65–70 °C/0.5 Torr) to afford methyl (*S*)-2,3-dihydroxypropionate (42 g, 75%) as a colorless oil; $[\alpha]_D^{20}$ –7.1 (*c* 0.94, CH_2Cl_2) {Lit.[20] $[\alpha]_D^{25}$ –6.11 (*c* 5, $CHCl_3$)}.

IR (neat): 3471, 1741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.16 (m, 1 H), 3.85–3.71 (m, 2 H), 3.70 (s, 3 H), 3.39 (br s, 1 H, OH), 2.55 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 72.2, 64.0, 53.5.

MS (EI) *m*/*z* = 120.0 [M].

Anal. Calcd for $C_4H_8O_4$: C, 40.00; H, 6.71. Found: C, 39.90; H, 6.67.

*Step 2, Methyl (S)-2,3-O-Isopropylidenepropionate (**6**)*:[22] To a solution of methyl (*S*)-2,3-dihydroxypropionate (30 g, 0.25 mol) in 2,2-dimethoxypropane (500 mL) was added *p*-TsOH (1.43 g, 7.5 mmol). After stirring at r.t. for 3 h, $NaHCO_3$ (3 g) was added, and the mixture was stirred for 1 h. Then solid was filtered off, washed with Et_2O (3 × 100 mL), and solvents were removed under diminished pressure. The residue was distilled under reduced pressure (bp 115–118 °C/20 Torr) to afford compound **6** (35.2 g, 88%) as a colorless oil; $[\alpha]_D^{20}$ –19.9 (*c* 1.5, $CHCl_3$) {Lit.[22] $[\alpha]_D^{20}$ –17.4 (*c* 3, $CHCl_3$)}.

IR (neat): 1760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.56 (dd, *J* = 7.2, 5.2 Hz, 1 H), 4.20 (dd, *J* = 8.7, 7.2 Hz, 1 H), 4.07 (dd, *J* = 8.7, 5.2 Hz, 1 H), 3.74 (s, 3 H), 1.45 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 111.3, 73.9, 52.2, 25.7, 25.4.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_7H_{12}O_4$ + Na: 183.0633; found: 183.0629.

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.33; H, 7.65.

2,3-*O*-Isopropylidene-L-glyceraldehyde (1)

To a solution of ester **6** (10 g, 62.4 mmol) in anhyd CH_2Cl_2 (250 mL) cooled to –78 °C was slowly added a 1 M solution of DIBAL-H in CH_2Cl_2 (75 mL) over 1 h. The reaction progress was monitored by GC. After disappearance of the substrate (ca. 5–6 h), the crude acetonide of L-glyceraldehyde **1** (7.3 g, yield 90%, calculated by GC with an internal standard) was ready for further transformations without isolation and purification. An analytical sample was obtained by extraction and distillation under diminished pressure; bp 68–75 °C/30 Torr [Lit.[15] bp 67–73 °C/30 Torr]; $[\alpha]_D^{20}$ −72 (*c* 6, CH_2Cl_2) {Lit.[15] $[\alpha]_D^{20}$ –75.4 (*c* 8, C_6H_6)}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 2.0 Hz, 1 H), 4.08–4.21 (m, 2 H), 4.38 (m, 1 H), 1.49 (s, 3 H), 1.44 (s, 3 H).

(*S*)-4-Ethynyl-2,2-dimethyl-1,3-dioxolane (7)

Anhyd MeOH (150 mL) was added to a solution of crude **1** (7.3 g, 325 mL) and the mixture was cooled to –10 °C. Subsequently, anhyd K_2CO_3 (112 mmol, 15.6 g), and Bestmann–Ohira reagent (84 mmol, 16.1 g) were added. After 12 h, the mixture was treated with sat. aq NH_4Cl (200 mL) and stirred for additional 1 h. Subsequently, the mixture was extracted with pentane (2 × 100 mL) and the combined extracts were dried ($MgSO_4$). The solvent was evaporated under diminished pressure (40° C/650 mbar) and the residue distilled at 110–112 °C/250 Torr to afford 6.3 g (80%, 2 steps from **6**) of acetylene **7** as a colorless syrup; $[\alpha]_D^{20}$ –40 (*c* 1.0, CH_2Cl_2) {Lit.[30] for the D-enantiomer $[\alpha]_D^{20}$ +40.6 (*c* 1.1, $CHCl_3$)}.

IR (film): 2120, 1068 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.67 (ddd, *J* = 6.4, 6.2, 2.3 Hz, 1 H, H-3), 4.14 (dd, *J* = 8.1, 6.4 Hz, 1 H, H-4a), 3.92 (dd, *J* = 8.1, 6.2 Hz, 1 H, H-4b), 2.47 (d, *J* = 2.3 Hz, 1 H, H-1), 1.47 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 110.7, 81.6, 74.3, 70.0, 65.5, 26.4, 26.3.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.59; H, 8.02.

(*R*,*Z*)-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylene]-*N*-benzylamine *N*-Oxide (8)

A solution containing crude **1** (7.3 g, 325 mL) at r.t. was diluted with CH_2Cl_2 (200 mL) and treated with anhyd $MgSO_4$ (14 g, 112 mmol) and BnNHOH (7.4 g, 60 mmol) in CH_2Cl_2 (40 mL). After 5 h, the suspension was filtered and the solvent was evaporated. To the oily residue was added cold Et_2O (75 mL) and the crude nitrone was separated by filtration to afford 10 g of **8** (72%, 2 steps from **6**) as a colorless solid; mp 90–91 °C (Lit.[26] mp 90 °C); $[\alpha]_D^{20}$ –96 (*c* 0.50, CH_2Cl_2) {Lit.[26] for the D-enantiomer $[\alpha]_D^{25}$ +96.8 (*c* 0.5, $CHCl_3$)}.

IR (film): 1599 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 6.78 (d, *J* = 4.6 Hz, 1 H), 5.08 (ddd, *J* = 7.1, 5.9, 4.6 Hz, 1 H), 4.80 (br s, 2 H), 4.35 (dd, *J* = 8.7, 7.1 Hz, 1 H), 3.82 (dd, *J* = 8.7, 5.9 Hz, 1 H), 1.37 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 132.1, 129.4, 129.2, 109.8, 72.0, 67.0, 67.8, 26.2, 24.9.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.96. Found: C, 66.40; H, 7.25; N, 5.99.

(*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethylene-1,1-diphenylmethylamine (9)

A solution containing crude **1** (7.3 g, 325 mL) at r.t. was diluted with CH_2Cl_2 (150 mL) and treated with Ph_2CHNH_2 (62 mmol, 11.3 g) and anhyd $MgSO_4$ (112 mmol, 13.4 g). After 2 h, the mixture was filtered and the solid was washed with anhyd CH_2Cl_2 (3 × 50 mL). The solvent was evaporated from the combined organic layers under diminished pressure to afford 16.6 g (90%, 2 steps from **6**) of imine **9** as a colorless syrup; $[\alpha]_D^{20}$ –35 (*c* 1, CH_2Cl_2).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 4.8 Hz, 1 H, CH=N), 7.10–7.23 (m, 10 H, ArH), 5.34 (s, 1 H, C*H*Ph), 4.62 (td, *J* = 6.8, 6.0, 4.8 Hz, 1 H, C*H*CH_2O), 4.12 (dd, *J* = 8.4, 6.8 Hz, 1 H, OCH_2), 3.91 (dd, *J* = 8.4, 6.0 Hz, 1 H, OCH_2), 1.33 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 143.0, 142.9, 128.5, 127.6, 127.5, 127.14, 127.11, 110.2, 67.4, 26.5, 25.4.

MS (EI): *m*/*z* = 295.4 [M].

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.25; H, 7.15; N, 4.75.

***E*/*Z*-Mixture of Ethyl (*R*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylate (10)**

Ethyl triphenylphosphorylideneacetate (84 mmol, 29.3 g) was added to a solution containing crude aldehyde **1** (7.3 g, 325 mL) and the mixture was stirred for 16 h at r.t. Subsequently, the mixture was filtered and the solid was washed with CH_2Cl_2 (3 × 100 mL). The solvent from the combined washings was evaporated under diminished pressure. The residue was purified on a silica gel column using hexane–EtOAc (9:1) as an eluent to afford 10.1 g of the *E*-isomer **10** (81%, 2 steps from **6**) as a colorless syrup and 0.9 g of the *Z*-isomer.

***E*-Isomer 10**

$[\alpha]_D^{20}$ –40.1 (*c* 1, CH_2Cl_2) {Lit.[29] $[\alpha]_D^{20}$ –40 (*c* 1.1, $CHCl_3$)}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.79 (dd, *J* = 16.0, 5.3 Hz, 1 H), 6.01 (dd, *J* = 16.0, 0.9 Hz, 1 H), 4.58 (q, *J* = 6.0 Hz, 1 H), 4.16–4.06

(m, 3 H), 3.58 (t, J = 7.6 Hz, 1 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.20 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 144.7, 122.4, 110.2, 75.0, 68.8, 60.6, 26.5, 25.8, 14.2.

HRMS (ESI): m/z calcd for $C_{10}H_{17}O_4$ [M + H$^+$]: 201.1127; found: 201.1127.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.96; H, 8.03.

Acknowledgment

Financial support for this work was provided through the Polish Ministry of Science and Higher Education Grant N 204 156036.

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