Tandem Wittig Rearrangement/Aldol Reactions for the Synthesis of Glycolate Aldols

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Supporting Information

Experimental procedures and characterization data for new compounds in Table 1 (27 pages).

General. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Dibutylboron triflate (1.0 M solution in methylene chloride) was purchased from Aldrich Chemical Co. and used without further purification. All aldehydes were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were purified by distillation from Ca_2SO_4 except acrolein, which was obtained from Fluka Chemical Co. and used without further purification. Triethylamine was obtained from Aldrich Chemical Co. and was purified by distillation from CaH. Phosphate buffer solution (pH 7) was obtained from Aldrich Chemical Co. Methylene chloride was purified using a GlassContour solvent purification system. Allyloxyacetic acid methyl ester (**11**)[1] was prepared from methyl 2-hydroxyacetate using a procedure analogous to that employed for the conversion of ethyl 2-hydroxyacetate to allyloxyacetic acid ethyl ester.[2] Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment, whereas

the yields reported in Table 1 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 1.

Methyl *O*-benzylglycolate (1).[3] A flame-dried flask was cooled under a stream of nitrogen and charged with benzyloxyacetyl chloride (3.67 g, 19.9 mmol), methylene chloride (60 mL) and methanol (1.6 mL, 39.8 mmol). The resulting solution was cooled to 0 °C, pyridine (3.4 mL, 41.7 mmol) was added slowly, and the mixture was warmed to rt and stirred for 15 h. The reaction mixture was then concentrated *in vacuo* and the crude material was partitioned between water (50 mL) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluent to afford 3.23 g (90%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H), 4.64 (s, 2 H), 4.11 (s, 2 H), 3.77 (s, 3 H).

General procedure for tandem Wittig rearrangement/aldol reactions (Table 1). An oven or flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in methylene chloride (4.0 equiv). The pale yellow solution was cooled to 0 °C and triethylamine (3.2 equiv) was added dropwise to afford a colorless solution. The ester substrate (1.0 equiv) was added dropwise and the mixture was warmed to rt and stirred for 15 min then cooled to 0 °C. The aldehyde was added dropwise (1.5 equiv) and the reaction mixture was warmed to rt and allowed to stir for 1-6 h. The reaction was then quenched by addition of pH 7 buffer (2 mL/mmol substrate). The heterogeneous mixture was transferred to a larger flask and diluted with MeOH (ca. 5–8 mL/mmol substrate) to afford a clear and homogeneous solution. The solution was cooled to 0 °C,

30% aqueous H_2O_2 (6 mL/mmol substrate) was added slowly, and the resulting mixture was warmed to rt and stirred for 1 h. The reaction mixture was then diluted with Et_2O (~15 mL/mmol substrate), water (~8 mL/mmol substrate) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ until the green color persisted in order to quench any peroxide remaining. *Caution! This procedure is highly exothermic. The $FeSO_4$ solution should be first added SLOWLY DROPWISE with a glass pipette*. The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 15–30% ethyl acetate/hexanes as the eluent.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxypent-4-enoate** (**3**). The reaction of methyl *O*-benzylglycolate (181 mg, 1.0 mmol) and acrolein (100 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 163 mg (69%) of the title compound as a white solid, m.p. 65–67 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3 H), 7.19–7.15 (m, 2 H), 6.10–6.02 (m, 1 H), 5.47–5.37 (m, 2 H), 4.38–4.33 (m, 1 H), 3.74 (s, 3 H), 3.32 (s, 1 H), 3.00–2.95 (m, 1 H), 2.91–2.86 (m, 1 H), 2.40 (d, J = 9.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 135.2, 135.1, 129.9, 128.2, 127.0, 119.1, 80.8, 77.1, 52.8, 41.6; IR (film) 3497, 1740 cm^{-1}. Anal calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.07; H, 6.97.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxy-3-phenylpropanoate** (**8**). The reaction of methyl *O*-benzylglycolate (181 mg, 1.0 mmol) and benzaldehyde (153 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the

desired product with >20:1 dr. Chromatographic purification afforded 216 mg (75%) of the title compound as a white solid, m.p. 134–135 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2 H), 7.40–7.31 (m, 3 H), 7.24–7.15 (m, 3 H), 7.11–7.04 (m, 2 H), 4.93 (d, *J* = 7.6 Hz, 1 H), 3.70 (s, 3 H), 3.43 (s, 1 H), 3.03–2.92 (m, 2 H), 2.46 (d, *J* = 13.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 138.9, 135.2, 129.8, 128.3, 128.2, 128.1, 128.0, 126.8, 81.3, 77.8, 52.8, 41.9; IR (film) 3476, 1734 cm^{-1}. Anal calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.10; H, 6.38.

(±)-(2*R,3*S**)-Methyl-2-benzyl-3-cyclohexyl-2,3-dihydroxypropanoate** (**9**). The reaction of methyl *O*-benzylglycolate (181 mg, 1.0 mmol) and cyclohexane carboxaldehyde (182 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 14:1 dr. Chromatographic purification afforded 227 mg (78%) of the title compound as a white solid, m.p. 115–116 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 3 H), 7.19–7.15 (m, 2 H), 3.76–3.71 (m, 1 H), 3.69 (s, 3 H), 3.34 (s, 1 H), 3.05–2.94 (m, 2 H), 2.27 (d, *J* = 11.2 Hz, 1 H), 1.95–1.89 (m, 1 H), 1.84–1.73 (m, 3 H), 1.71–1.58 (m, 2 H), 1.54–1.44 (m, 1 H), 1.38–1.22 (m, 2 H), 1.20–1.09 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 135.4, 129.9, 128.2, 127.0, 81.5, 78.6, 52.8, 42.0, 38.9, 31.6, 26.7, 26.2, 25.8 (two aliphatic carbon signals are incidentally equivalent); IR (film) 3512, 1728 cm^{-1}. Anal calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.39.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxydodecanoate** (**10**). The reaction of methyl *O*-benzylglycolate (181 mg, 1.0 mmol) and decanal (282 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 259 mg (77%) of the title compound as a white

solid, m.p. 76–77 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 3 H), 7.20–7.16 (m, 2 H), 3.88–3.79 (m, 1 H), 3.73 (s, 3 H), 3.27 (s, 1 H), 3.02–2.92 (m, 2 H), 1.97–1.86 (m, 1 H), 1.78–1.70 (m, 1 H), 1.68–1.54 (m, 1 H), 1.52–1.22 (m, 14 H), 0.90 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 135.5, 129.9, 128.3, 127.0, 81.4, 75.4, 52.7, 41.3, 31.9, 31.0, 29.60, 29.57, 29.3, 25.9, 22.7, 14.1 (two pairs of aliphatic carbon signals are incidentally equivalent); IR (film) 3501, 1731 cm^{-1}. Anal calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.60.

(±)-(*E*)-(2*R,3*S**)-Methyl-2-allyl-2,3-dihydroxy-5-phenylpent-4-enoate** (**12**). The reaction of allyloxyacetic acid methyl ester (130 mg, 1.0 mmol) and cinnamaldehyde (189 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 17:1 dr. Chromatographic purification afforded 173 mg (66%) of the title compound as a white solid, m.p. 97–99 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.34–7.29 (m, 2 H), 7.28–7.23 (m, 1 H), 6.68–6.62 (m, 1 H), 6.34–6.27 (m, 1 H), 5.77–5.67 (m, 1 H), 5.13–5.06 (m, 2 H), 4.41 (t, J = 8.1 Hz, 1 H), 3.82 (s, 3 H), 3.60 (s, 1 H), 2.60–2.55 (m, 1 H), 2.45–2.34 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 136.1, 134.5, 131.5, 128.5, 128.1, 126.7, 125.8, 119.2, 80.4, 76.7, 53.0, 40.0; IR (film) 3482, 1738 cm^{-1}. Anal calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.90; H, 7.00.

(±)-(1'*S,2*R**)-Methyl-2-hydroxy-2-(1'-hydroxy-2'-methylpropyl)pent-4-enoate** (**13**). The reaction of allyloxyacetic acid methyl ester (130 mg, 1.0 mmol) and isobutyraldehyde (137 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 20:1 dr. Chromatographic purification afforded 131 mg (64%) of the title compound as a colorless oil. This material was judged to be of >20:1 dr by ^{1}H NMR

analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.67 (m, 1 H), 5.15–5.08 (m, 2 H), 3.79 (s, 3 H), 3.69 (dd, *J* = 2.4, 10.7 Hz, 1 H), 3.49 (s, 1 H), 2.45 (d, *J* = 7.3 Hz, 2 H), 2.22 (d, *J* = 10.7 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 131.8, 119.2, 80.7, 78.0, 53.0, 40.4, 28.5, 21.7, 15.4; IR (film) 3502, 2960 cm^{-1}. Anal calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.60; H, 9.22.

(±)-(1'*S,2*R**)-Methyl-2-hydroxy-2-(1'-hydroxybenzyl)pent-4-enoate** (**14**). The reaction of allyloxyacetic acid methyl ester (130 mg, 1.0 mmol) and benzaldehyde (153 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 174 mg (74%) of the title compound as a white solid, m.p. 104–105 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5 H), 5.71–5.59 (m, 1 H), 5.09–4.97 (m, 2 H), 4.84 (d, *J* = 7.6 Hz, 1 H), 3.83 (s, 3 H), 3.54 (s, 1 H), 2.83 (d, *J* = 7.6 Hz, 1 H), 2.44–2.36 (m, 1 H), 2.01–1.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 138.7, 131.6, 128.3, 128.1, 127.8, 119.0, 80.6, 77.5, 52.9, 40.1; IR (film) 3490, 1734 cm^{-1}. Anal calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.93.

(±)-(2*R,3*S**)-Methyl-2-hydroxy-2-(1-hydroxy-3-phenylpropyl)pent-4-enoate** (**15**). The reaction of allyloxyacetic acid methyl ester (130 mg, 1.0 mmol) and 3-phenylpropionaldehyde (201 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 195 mg (74%) of the title compound as a white solid, m.p. 60–62 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.25 (m, 2 H), 7.23–7.15 (m, 3 H), 5.74–5.64 (m, 1 H), 5.12–5.05 (m, 2 H), 3.79–3.71 (m, 4 H), 3.57 (s, 1 H), 2.97–2.88 (m, 1 H), 2.71–2.62 (m, 1

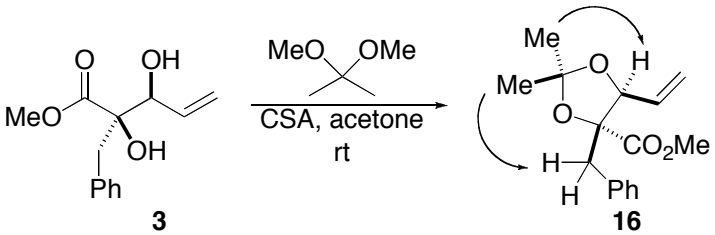
H), 2.42–2.34 (m, 3 H), 1.96–1.87 (m, 1 H), 1.81–1.71 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 141.7, 131.7, 128.4, 128.3, 125.8, 119.2, 80.6, 74.4, 52.8, 39.5, 32.3, 31.9; IR (film) 3493, 1732 cm^{-1}. Anal calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.15; H, 7.62.

(±)-Methyl-2-hydroxy-3-phenylpropanoate (7)[4] The reaction of methyl *O*-benzylglycolate (180 mg, 1.0 mmol) was conducted following the general procedure except that no aldehyde was added, and CH_2Cl_2 was used for extraction. This protocol afforded 148 mg (82%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2 H), 7.25–7.17 (m, 3 H), 4.46–4.40 (m, 1 H), 3.74 (s, 3 H), 3.14–3.07 (m, 1 H), 2.98–2.87 (m, 2 H).

(*E*)-7-benzyl-5,10-dibutyl-8-methoxy-6,9-dioxa-5,10-diboratetradec-7-ene (6). The reaction of methyl *O*-benzylglycolate (90 mg, 0.5 mmol) was conducted following the general procedure except that no aldehyde was added. After stirring for 15 min the crude reaction mixture was analyzed by mass spectrometry. A signal was observed with an isotopic distribution and exact mass in accord with the calculated value for **6**. MS (EI): 428.3650 (428.3633 calculated for $C_{26}H_{46}B_2O_3$, M +).

Assignment of stereochemistry

The stereochemistry of (2*R**,3*S**)-methyl-2-benzyl-2,3-dihydroxypent-4-enoate (**3**) was assigned by ^{1}H NMR nOe analysis of the corresponding acetonide derivative **16** as shown below. The stereochemistry of the other 1,2-diol products was assigned based on analogy to the (2*R**,3*S**)-methyl-2-benzyl-2,3-dihydroxypent-4-enoate product.



3 **16**

(±)-(4*R,5*S**)-Methyl-4-benzyl-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carboxylate (16)**. A flame-dried flask was cooled under a stream of nitrogen and charged with methyl-2-2-benzyl-2,3-

dihydroxypent-4-enoate (118 mg, 0.5 mmol), dry acetone (5 mL), 2,2-dimethoxypropane (0.7 mL, 5.7 mmol) and camphorsulfonic acid (14 mg, 0.06 mmol). The reaction mixture was stirred at rt for 25 h and then was concentrated *in vacuo* using a rotary evaporator. The residue obtained was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluant to afford 111 mg (80%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.13 (m, 5 H), 6.10–5.99 (m, 1 H), 5.59–5.52 (m, 1 H), 5.46–5.40 (m, 1 H), 4.69 (d, J = 5.9 Hz, 1 H), 3.64 (s, 3 H), 3.06–3.00 (m, 1 H), 2.82–2.76 (m, 1 H), 1.67 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.7, 131.4, 130.0, 128.1, 126.7, 119.1, 110.2, 86.3, 81.4, 52.1, 40.6, 28.0, 25.3; IR (film) 1732 cm^{-1}. MS (ESI): 299.1262 (299.1259 calculated for $C_{16}H_{20}O_4$, M + Na^+).

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