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Synthesis and stereoselective aldol reaction of dihydroxyacetone derivatives

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Abstract

Efficient synthetic methods for 1,3-di-*O*-benzyldihydroxyacetone (**3**) and 1,3-*O*-cyclohexylidenedihydroxyacetone (**8**) were developed. $TiCl_4$-mediated aldol reaction of the silyl enol ether of **3** with aldehydes gave *syn* aldol products while the reaction of the silyl enol ether of **8** with aldehydes afforded *anti* aldol products.

Keywords: aldol reactions; diastereoselection; enol ethers; enolates.

Enzyme-catalyzed aldol reactions have become one of the most useful biotransformations in organic synthesis.[1] Four dihydroxyacetone phosphate (DHAP)-dependent aldolases are especially useful for the enantiopure synthesis of ketose sugars and possess an almost perfect ability to control the stereochemistry of the aldol products. Nevertheless, both enzymes and commercial DHAP are expensive and relatively unstable and the preparation and handling of DHAP are also not straightforward.[2] More importantly, although the enzymes accept quite a wide range of aldehyde acceptor substrates, they do not accept many useful aldehydes such as aromatic aldehydes, sterically hindered aliphatic aldehydes, and α,β-unsaturated aldehydes. Therefore, the chemical aldol reaction of dihydroxyacetone (DHA) derivatives with aldehydes, which could provide various intermediates for ketose sugars, would be a useful supplement or alternative to the enzymatic aldol reaction of DHAP. Surprisingly, however, only a few reactions of enolate of DHA derivatives are known[3] and the aldol reaction of DHA derivatives with aldehydes have not been investigated,[4] perhaps partly because of difficult accessibility to proper DHA derivatives. Di-*O*-acyl-DHA is readily available by the direct acylation[5] of the commercial DHA (exists as a dimer), whereas the direct alkylation and the acetalization of the two hydroxyl groups in DHA have not been realized so that syntheses of di-*O*-alkyl and acetal derivatives of DHA remain quite cumbersome procedures.[6] Herein, we report the new efficient method for the synthesis of DHA derivatives including DHA silyl enol ethers and their stereoselective aldol reactions with aldehydes.

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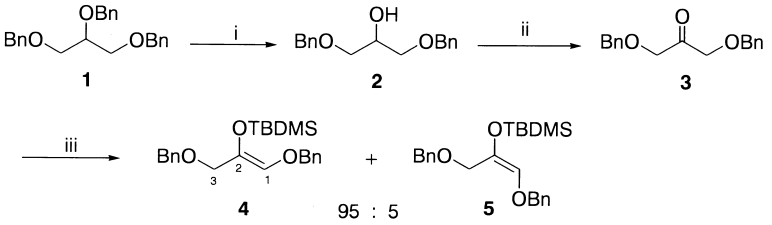
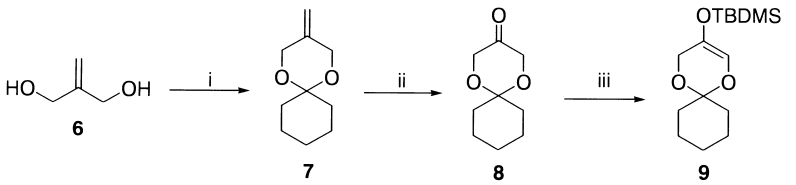
Selective deprotection of tri-*O*-benzylglycerol (**1**), which was readily obtained by perbenzylation of glycerol with benzyl bromide and NaH in DMF, was performed with $SnCl_4$ by the known procedure[7] and the subsequent oxidation of the resultant 1,3-di-*O*-benzylglycerol (**2**) with PCC gave desired 1,3-di-*O*-benzyl-DHA (**3**) (Scheme 1). Treatment of the ketone **3** with $KN(SiMe_3)_2$ and then addition of TBDMSCl at –78°C afforded a mixture of the *Z*-silyl enol ether **4** and the *E*-silyl enol ether **5**.[8] Flash column chromatography on SiO_2 provided pure **4** and **5** in the ratio of 95:5 in 80% yield.[9] The assignment of stereochemistry in **4** and **5** was made on the basis of NOE experiments. Thus, NOE was observed between the vinyl proton at C-1 and the methylene protons at C-3 in *Z*-isomer **4** but not in *E*-isomer **5**.



Scheme 1. Reagents and conditions: (i) $SnCl_4$ (1.5 equiv.), CH_2Cl_2, room temp., 2 h, 81%; (ii) PCC, room temp., 5 h, 72%; (iii) $KN(SiMe_3)_2$ (1.2 equiv.), –78°C, 20 min, then TBDMSCl (1.2 equiv.), –78°C, 4 h, 80%

Reaction of 2-methylene-1,3-propandiol (**6**) with cyclohexanone in the presence of TsOH and subsequent ozonolysis of the resulting cyclohexylidene **7** afforded 1,3-*O*-cyclohexylidene-DHA (**8**) (Scheme 2). Deprotonation of ketone **8** with $KN(SiMe_3)_2$ followed by treatment of the resulting enolate with TBDMSCl provided silyl enol ether **9** in 78% yield.

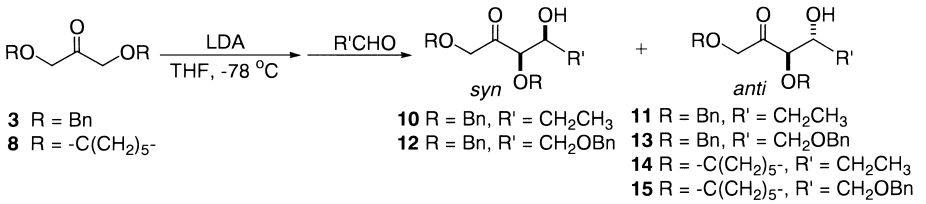


Scheme 2. Reagents and conditions: (i) cyclohexanone (1.3 equiv.), TsOH (cat.), benzene, 4 h, 91%; (ii) O_3, –78°C, then Me_2S, 90%; (iii) $KN(SiMe_3)_2$ (1.2 equiv.), –78°C, 20 min, then TBDMSCl (1.2 equiv.), –78°C, 4 h, 78%

Aldol reaction of the lithium enolate of dibenzyl-DHA **3** with propionaldehyde afforded an inseparable 58:42 mixture of *syn* product **10** and *anti* product **11** in 80% yield and a similar result was obtained with benzyloxyacetaldehyde as the electrophile, as shown in Table 1. On the other hand, the aldol reactions of the lithium enolate of the cyclohexylidene-DHA **8** with both aldehydes were completely stereoselective to provide only *anti* aldol products **14** and **15**, respectively. When the inseparable mixture of aldol products **10** and **11** (58:42) was treated with benzoyl chloride and pyridine in methylene chloride at room temperature, *anti* aldol **11** was preferentially benzoylated to give the benzoate **16** and the unreacted *syn* aldol **10**. Carefully repeated flash column chromatography provided pure **10** in 30% yield and a small amount of pure **16**.[10] Thus, the stereochemistry of the aldol products **10** and **11** was determined by the conversion of **10** and **16** into known compounds, 5,6-dideoxy-2-*threo*-hexulose and 5,6-dideoxy-2-*erythro*-hexulose, respectively.[11] The stereochemistry of **12** and **13** was also determined by a similar manner: again, *anti* isomer **13** was

more reactive under the benzoylation condition and each separated isomer was converted to known compounds *threo*-pentulose and *erythro*-pentulose, respectively.[12] The stereochemistry of aldol products **14** and **15** was also determined by their conversion to 5,6-dideoxy-2-*erythro*-hexulose and *erythro*-pentulose, respectively.

Table 1
Aldol reactions of the lithium enolates of DHA derivatives with aldehydes



3 R = Bn
8 R = -C(CH$_2$)$_5$-

10 R = Bn, R' = CH$_2$CH$_3$ **11** R = Bn, R' = CH$_2$CH$_3$
12 R = Bn, R' = CH$_2$OBn **13** R = Bn, R' = CH$_2$OBn
14 R = -C(CH$_2$)$_5$-, R' = CH$_2$CH$_3$
15 R = -C(CH$_2$)$_5$-, R' = CH$_2$OBn

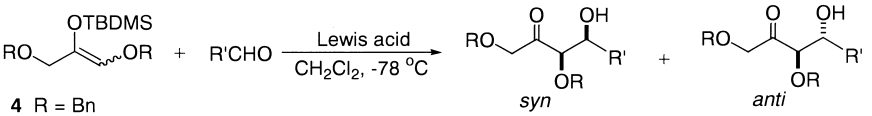
DHA derivatives	R'CHO	products *syn*/*anti*	ratio[a] *syn*/*anti*	yield[b] (%)
3	CH_3CH_2CHO	**10** / **11**	58 : 42	80
3	$BnOCH_2CHO$	**12** / **13**	58 : 42	82
8	CH_3CH_2CHO	**14**	*anti* only	73
8	$BnOCH_2CHO$	**15**	*anti* only	80

[a] Determined by HPLC using Chiracel OD column.
[b] Isolated yields.

Mukaiyama-type aldol reactions of silyl enol ethers **4** and **9** with aldehydes turned out to be more stereoselective than the direct aldol reactions of the lithium enolates of **3** and **8**. Reaction of **4** and **9** with aldehydes such as propionaldehyde and benzyloxyacetaldehyde mediated by Lewis acids afforded aldol products together with silylated aldol products. Without isolation of the products, treatment of the product mixture with *n*-Bu_4NF or with dilute hydrochloric acid afforded desilylated aldol products. The highest diastereoselection was achieved by employing $TiCl_4$ as the Lewis acid (Table 2). For example, a solution of propionaldehyde (0.54 mmol) and $TiCl_4$ (0.54 mmol) in CH_2Cl_2 (1 ml) was stirred at 0°C for 30 min. After the solution was cooled to –78°C, a CH_2Cl_2 solution (2 ml) of silyl enol ether **4** (0.45 mmol) was added slowly to this solution. After 5 h of stirring at –78°C, the reaction was quenched with 30 ml of 1 M $NaHCO_3$ and extracted with CH_2Cl_2. After evaporation of the dried CH_2Cl_2 solution, the residue was dissolved in 2 ml of THF. To this solution was added *n*-Bu_4NF (0.3 ml of 1 M solution in THF) at room temperature. After stirring for a further 4 h, the reaction mixture was diluted with 30 ml of Et_2O and washed with 1 M $NaHSO_4$ followed by chromatography to give a mixture of **10** and **11** in 85% yield (**10**:**11** = 95:5). $TiCl_4$-mediated reaction of **4** with benzyloxyacetaldehyde almost exclusively gave the *syn* product **12** (*syn* **12**/*anti* **13** = > 99.5: < 0.5).

Other Lewis acids such as $BF_3{\cdot}OEt_2$ and $SnCl_4$ showed much reduced stereoselectivity. The Lewis acid-promoted aldol reaction of the cyclohexylidene silyl enol ether **9** with both aldehydes gave exclusively *anti* aldol products **14** and **15** regardless of which Lewis acid was used. Other aldehydes such as benzaldehyde and phenylacetaldehyde also showed the similar stereoselectivity in the aldol reaction with both silyl enolate and lithium enolate.[13] The stereochemical outcome of $TiCl_4$-mediated aldol reactions of silyl enol ethers **4** and **9** with aldehydes could be explained by

Table 2
Lewis acid-mediated aldol reactions of silyl enol ethers of DHA derivatives



4 R = Bn
9 R = -C(CH_2)$_5$-

10 and **12** | **11**, **13**, **14**, and **15**

silyl enol ethers	R'CHO	Lewis acids	products *syn*/*anti*	ratio[a] *syn*/*anti*	yield[b] (%)
4	CH_3CH_2CHO	$TiCl_4$	**10** / **11**	95 : 5	85
4	CH_3CH_2CHO	$SnCl_4$	**10** / **11**	84 : 16	83
4	CH_3CH_2CHO	$BF_3 \cdot OEt_2$	**10** / **11**	50 : 50	73
4	$BnOCH_2CHO$	$TiCl_4$	**12** / **13**	>99.5 : <0.5	90
4	$BnOCH_2CHO$	$SnCl_4$	**12** / **13**	62 : 38	82
4	$BnOCH_2CHO$	$BF_3 \cdot OEt_2$	**12** / **13**	60 : 40	82
9	CH_3CH_2CHO	$TiCl_4$	**14**	*anti* only	73
9	CH_3CH_2CHO	$SnCl_4$	**14**	*anti* only	70
9	CH_3CH_2CHO	$BF_3 \cdot OEt_2$	**14**	*anti* only	71
9	$BnOCH_2CHO$	$TiCl_4$	**15**	*anti* only	82
9	$BnOCH_2CHO$	$SnCl_4$	**15**	*anti* only	72
9	$BnOCH_2CHO$	$BF_3 \cdot OEt_2$	**15**	*anti* only	78

[a] Determined by HPLC using Chiracel OD column.
[b] Isolated yields.

assuming a transition state of the Zimmermann–Traxler type[14] rather than the usual acyclic extended transition state or the silatropic ene reaction mechanism.[15] Similar stereochemical results in the aldol reactions of *O*-silyl ketene acetals with aldehydes have been reported.[14,16] We are currently searching for a chiral catalyst for the enantioselective aldol reaction of DHA derivatives with high ee.

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9. Compound **4**: $R_f = 0.67$ (silica gel, hexane:ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.14 (s, 6H), 0.94 (s, 9H), 3.78 (s, 2H), 4.47 (s, 2H), 4.76 (s, 2H), 5.75 (s, 1H), 7.25–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ –4.3, 18.1, 25.9, 70.1, 71.3, 74.0, 127.5, 127.8, 127.9, 128.1, 128.4, 128.6, 131.6, 132.9, 137.4, 138.5. Compound **5**: $R_f = 0.72$ (silica gel, hexane:ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.07 (s, 6H), 0.86 (s, 9H), 4.09 (s, 2H), 4.45 (s, 2H), 4.68 (s, 2H), 6.09 (s, 1H), 7.23–7.34 (m, 10H). All new compounds gave satisfactory spectroscopic and microanalytical data.
10. Compound **10**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.51–1.59 (m, 2H), 2.16 (brs, 1H), 3.77–3.88 (m, 1H), 3.94 (d, $J = 9.8$ Hz, 1H), 4.37 (s, 2H), 4.47–4.64 (m, 4H), 7.25–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 10.1, 25.7, 73.5, 73.7, 73.8, 74.1, 86.0, 127.9, 128.2, 128.5, 128.6, 128.7, 136.8, 137.1, 208.1. Compound **16**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.77–1.86 (m, 2H), 4.26 (d, $J = 3.6$ Hz, 1H), 4.30 (d, $J = 2.9$ Hz, 2H), 4.41–4.70 (m, 4H), 5.37–5.40 (m, 1H), 7.28–7.57 (m, 13H), 8.00 (d, $J = 7.5$ Hz, 2H).
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