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Enzymatic single aldol reactions of remote dialdehydes

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Abstract: Described here are the aldol reactions of unprotected, remote dialdehydes catalyzed by rabbit muscle aldolase (RAMA), leading to the synthesis of multifunctional monoaldehydes. © 1997 Elsevier Science Ltd

Enzymatic aldol reactions have been intensively exploited as a useful methodology for the synthesis of carbohydrates.[1] The aldol reactions based on rabbit muscle aldolase (RAMA, EC 4.1.2.13) provide useful routes to monosaccharides, azasugars, and related sugar analogs.[2] RAMA has been known to catalyze the stereoselective carbon–carbon coupling between a broad range of aldehydes and dihydroxyacetone phosphate (DHAP). In almost all the previous studies, RAMA has been used in the aldol reactions of monoaldehydes. Very recently, one group reported the tandem double aldol reaction of dihydroxydialdehydes based on RAMA.[3] To the best of our knowledge, no systematic study has been done to demonstrate the utility of RAMA in the aldol reaction of multialdehydes.[4] As a part of our research program directed toward the development of new aldolase reactions, we have explored RAMA-based aldol reactions of some remote dialdehydes. It was observed that RAMA transformed only one aldehyde group with the other one unreacted and showed no stereochemical preference toward the stereocenter slightly remote from the aldehyde functionality. We herein wish to report some of the preliminary results from these studies.

Dialdehydes **3a–e** used as potential substrates for RAMA were prepared in two steps from diols **1a–e**.[5] The diols were treated with NaH and reacted with bromoacetaldehyde dimethyl acetal (BDA) to give diacetals **2a–e**. The diacetals were then hydrolyzed under acidic conditions to give **3a–e**. The RAMA-catalyzed aldol reactions of **3a–e** (1 equiv) were carried out in the presence of DHAP (less than 1 equiv) at room temperature (Scheme 1). When most of DHAP was consumed, phosphatase (Pase) was added to dephosphorylate the aldol adducts **4a–d**. The resulting monoaldehydes **5a–d** were isolated by silica gel chromatography. The overall yield of the two sequential enzymatic reactions, aldol reaction and dephosphorylation, ranged from 37 to 44%.

The first important observation from these studies is that all the reactive dialdehydes **1a–d** underwent only single aldol reaction. Our observation is in contrast to the previous report that dihydroxydialdehydes underwent double aldol reactions in the presence of RAMA.[3] Since our substrates have no hydroxyl group, the dialdehydes seem to favor single aldol reactions over double aldol reactions. Second, all three stereoisomers of dialdehyde **3d** have been accepted by RAMA as substrates to give the corresponding stereoisomeric products **5d**, indicating that RAMA does not have a strong preference for the stereocenters slightly remote from the aldehyde groups. In addition, the aldol reaction of *meso*-stereoisomeric **3d** gave a roughly 1:1 mixture of two diastereomeric monoaldehydes **5d**-*RS* and **5d**-*SR*. Third, dialdehyde **3e** carrying a hydrophobic ring between the two aldehyde functionalities was unreactive, indicating that for better reactivity two aldehyde groups should be linked by an aliphatic chain.

In summary, this work has demonstrated that RAMA can catalyze a single aldol reaction of remote dialdehydes, leading to the synthesis of highly functionalized monoaldehydes. A potential

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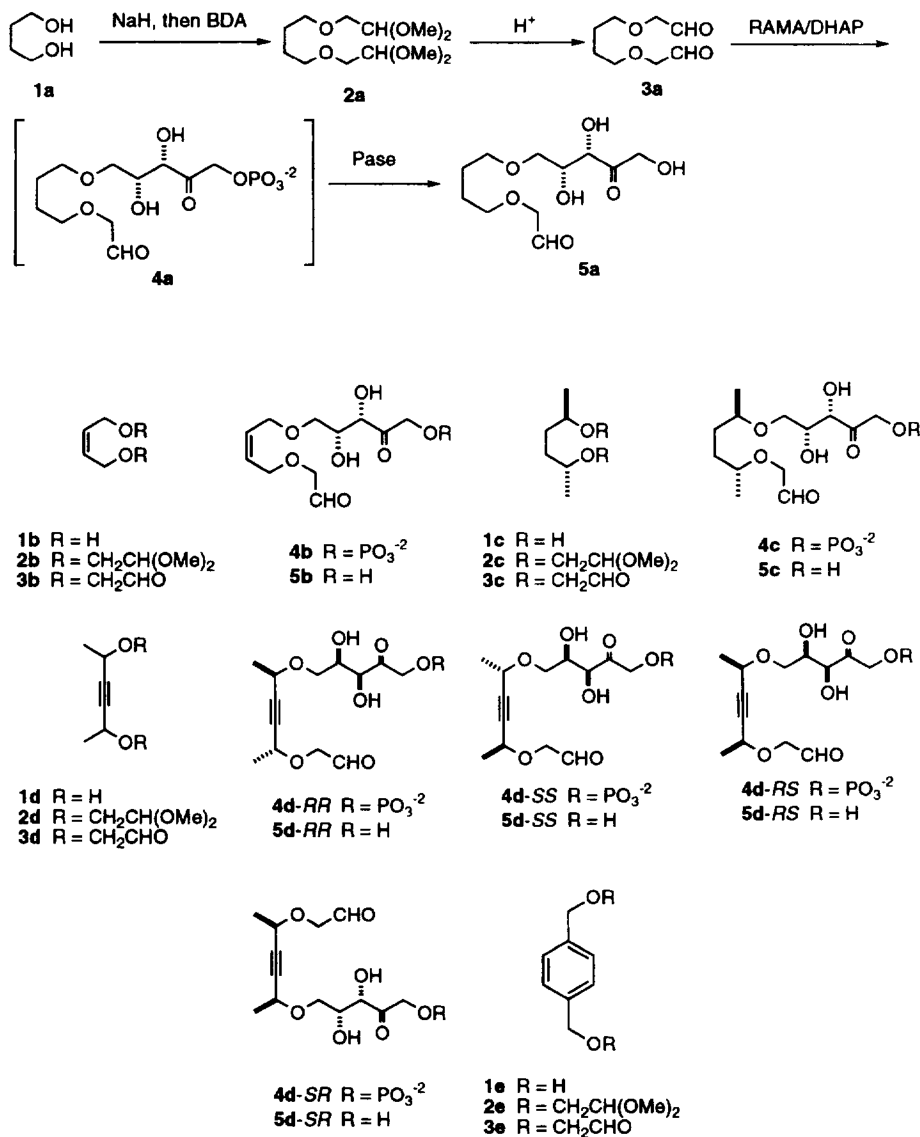

Scheme 1.

application of the enzymatically produced monoaldehydes, we think, would be in the synthesis of novel macrocyclic molecules which are soluble in water. The research toward this end is under progress in this laboratory.

Experimental

The synthesis of dialdehyde acetals

A respresenative procedure is for the synthesis of **2c**: A solution of (*R*,*R*)-2,5-hexanediol **1c** (810 mg, 6.85 mmol), sodium hydride (800 mg, 33.3 mmol), tetrabutylammonium iodide (200 mg, 0.54 mmol) and bromoacetaldehyde dimethyl acetal (1.83 mL, 15.0 mmol) in anhydrous DMF (50 mL) was warmed to 40°C in a water bath. After 12 hours, sodium hydride (0.42 g, 17 mmol) and bromoacetaldehyde dimethyl acetal (1.83 mL, 15 mmol) was added and allowed to react at 70°C for additional 12 hours.

The reaction was quenched with methanol (0.20 mL, 50 mmol) at 0°C. Diethyl ether (100 mL) was added, and the resulting solution was washed with water (70 mL), cold 1N HCl (70 mL), saturated $NaHCO_3$ (70 mL), and brine (70 mL). The extracts were dried over Na_2SO_4, concentrated and the residue was purified by chromatography on silica gel (hexane:ethyl acetate=1:1) to give **2c**[6] (1.52 g, 75%): TLC R_f=0.35 (hexane:ethyl acetate=1:1).

The enzymatic aldol reaction of dialdehydes

A respresenative procedure is for the aldol reaction of **3c**: A solution of **2c** (883 mg, 3.00 mmol) in 0.1N H_2SO_4 (5 mL) was stirred overnight at 40°C in a water bath, and then neutralized with 1N NaOH, followed by the addition of DHAP (0.20 M, 10 mL, 2.0 mmol). The pH was again adjusted to 7.0 with 2N NaOH and the solution was degassed with argon for 30 min. RAMA (type X, 500 U) was added and stirring continued at room temperature for 24 hours. Another portion of the aldolase (500 U) was added and the solution was allowed to react for additional 24 hours. The pH of the solution was adjusted to pH 4.8 with 2N HCl followed by addition of acid phosphatase (from potato, type IV-S, 300 U) and incubated at 40°C for 36 hours. The reaction mixture was adjusted to pH 7.0 with 2N NaOH and lyophilized to give a crude solid products. Extraction with MeOH followed by concentration under reduced pressure afforded an oil which was chromatographyed on silica gel ($CHCl_3$:MeOH=8:1) to give **5c**[7] (232 mg, 40%): TLC R_f=0.42 ($CHCl_3$:MeOH=6:1).

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6. **2c**: $[\alpha]_D^{25}=-20.2$ (*c* 2.00, MeOH); ^1H NMR (300 MHz, D_2O, ppm) 4.47 (*t*, *J*=5.3 Hz, 2H), 3.53 (*dd*, *J*=10.6, 5.0 Hz, 2H), 3.48–3.38 (*m*, 4H), 3.39 (*s*, 12H), 1.66–1.59 (*m*, 2H), 1.49–1.42 (*m*, 2H), 1.15 (*d*, *J*=5.6 Hz, 6H); ^{13}C NMR (75.5 MHz, D_2O, ppm) 103.78, 76.77, 68.80, 54.44, 54.41, 32.74, 20.17; HRMS. Calcd for $C_{14}H_{31}O_6$ (M+H): 295.2121. Found: 295.2106.
7. **5c**: $[\alpha]_D^{25}=-23.9$ (*c* 2.00, MeOH); ^1H NMR (300 MHz, D_2O, ppm) 5.12 (*t*, *J*=5.0 Hz, 1H), 4.59 (*q*, *J*=19.3 Hz, 2H), 4.44 (*d*, *J*=2.5 Hz, 1H), 4.16 (*td*, *J*=6.2, 2.5 Hz, 1H), 3.70 (*dd*, *J*=10.6, 5.6 Hz, 1H), 3.63 (*m*, 2H), 3.56 (*dd*, *J*=10.6, 6.2 Hz, 1H), 3.52 (*dd*, *J*=10.6, 5.0 Hz, 1H), 3.45 (*dd*, *J*=10.6, 5.6 Hz, 1H), 1.64–1.49 (*m*, 4H), 1.18 (*d*, *J*=6.2 Hz, 6H); ^{13}C NMR (75.5 MHz, D_2O, ppm) 215.64, 91.51, 79.62, 78.36, 73.64, 73.30, 70.90, 68.91, 33.98, 33.92, 21.58; HRMS. Calcd for $C_{13}H_{25}O_7$ (M+H): 293.1601. Found: 293.1603.

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