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Synthesis of Acyclic Polyol Derivatives via Enzyme-Mediated Aldol Reaction

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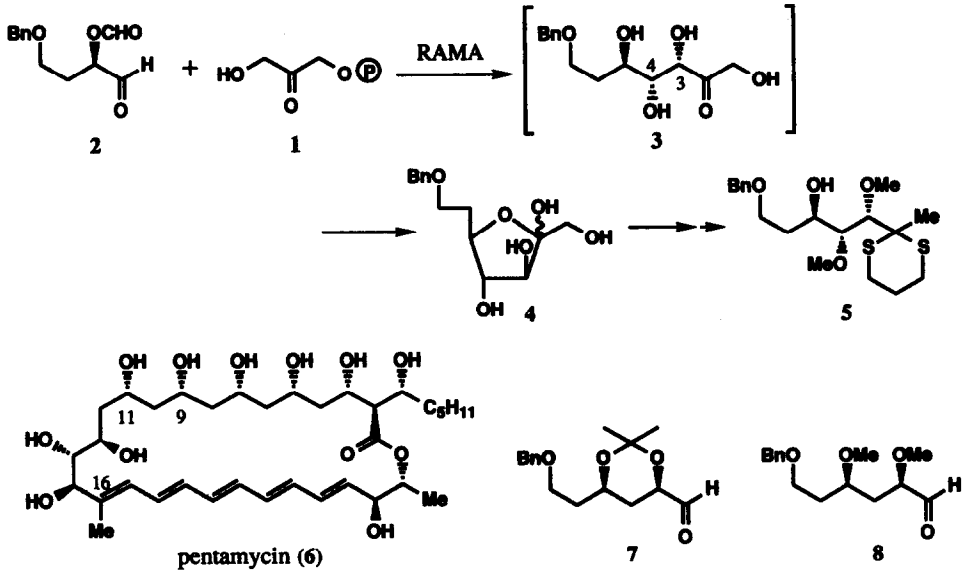
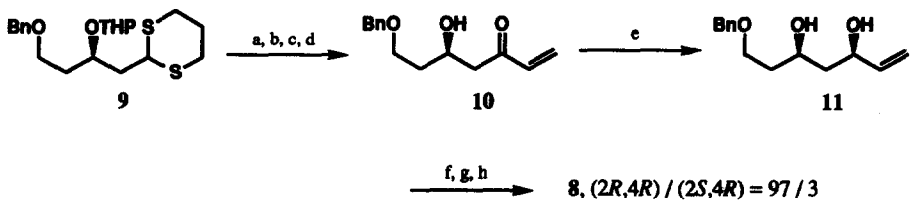
Abstract: Enzyme-mediated stereoselective aldol reaction between dihydroxyacetone phosphate (DHAP, **1**) and (2*R*,4*R*)-6-benzyloxy-2,4-dimethoxyhexanal (**8**) was catalyzed by rabbit muscle aldolase (RAMA) to generate (3*S*,4*R*,5*R*,7*R*)-trihydroxyketone **12**, which could be easily transformed to the masked polyhydroxylated compound **15** corresponding to the C-9~C-16 segment of pentamycin (**6**).

The importance of enzymes as biocatalysts for carbon-carbon bond forming reaction has become well recognized in recent years. For example, the reaction of dihydroxyacetone phosphate (DHAP, **1**) with aldehydes (aldol reaction) is known to be catalyzed by rabbit muscle aldolase (RAMA, E.C.4.1.2.13) producing (3*S*,4*R*)-diols stereoselectively.[1,2,3]

We already reported the use of the above enzymatic reaction for the synthesis of the polyhydroxylated building block **5** corresponding to the C-11~C-16 segment of pentamycin (**6**),[4] a polyene macrolide antibiotic.[5] The RAMA-catalyzed condensation of **1** and **2** proceeded expectedly, but the initially formed **3** cyclized readily to the five-membered hemiacetal **4**. The ring-opening and the subsequent derivatization of **4** leading to the synthetically useful building blocks were found to be much more difficult than was anticipated. In fact, several tedious steps were necessary for the conversion of **4** to **5**. The simplest way to avoide this unfavorable cyclic hemiacetal formation is to mask the C-2 hydroxyl group in aldehyde **2** by the protective group stable under the enzymatic reaction conditions.

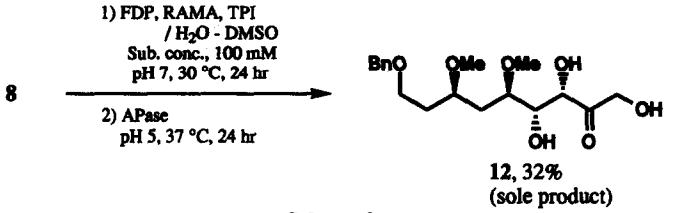


Scheme 1.



a) MeI, $NaHCO_3$ / CH_3CN - H_2O, r.t.; b) CH_2=CHMgBr / THF, 0 °C (2 steps, 62%); c) Swern oxidn. (95%); d) AcOH - H_2O, r.t. (99%); e) Et_2BOMe, $NaBH_4$ / THF, –78 °C (91%); f) MeI, KH / THF, r.t. (80%); g) OsO_4, NMO, *t*-BuOH / Acetone - H_2O, r.t. (84%); h) $NaIO_4$ / THF - H_2O, r.t. (96%).

Scheme 2.

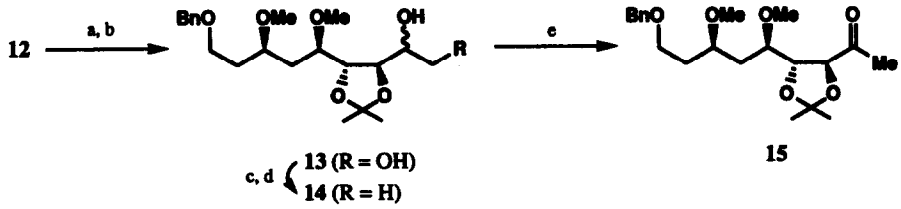


Scheme 3.

Initially, aldehyde **7** whose C-2 and C-4 dihydroxyl groups were protected as an acetonide was used as the substrate. However, significant hydrolysis of the acetonide group was observed during the reaction. Then, (2*R*,4*R*)-6-benzyloxy-2,4-dimethoxyhexanal (**8**) was chosen as an aldehyde. The reasons for selecting the O-methyl derivative are that i) it is necessary to test whether the C-2 alkoxy aldehydes can be a substrate for enzymatic reaction, ii) the syntheses of the stereochemically well defined **8** and its diastereoisomers are possible and thus the stereochemistry of the condensation products with **1** can be determined unequivocally.

The optically active aldehyde **8** was prepared as shown in Scheme 2. Dithioacetal **9** [6] derived from L-malic acid was converted to hydroxyketone **10** in four steps. The keto group in **10** was then reduced stereoselectively with Et_2BOMe and $NaBH_4$ in THF at -78°C [7] to furnish *syn*-diol **11** which was converted to aldehyde **8** [8,9] in three steps. Although the chemical synthesis of DHAP (**1**) has been reported,[10] we chose the *in situ* generation method from D-fructose-1,6-diphosphate (FDP) using RAMA and triosephosphate isomerase (TPI, E.C.5.3.1.1) because the reaction procedure was simple and the handling of the reagents was easy.

The RAMA-catalyzed condensation of **8** with the enzymatically derived **1** gave the desired (3*S*,4*R*,5*R*,7*R*)-9-benzyloxy-5,7-dimethoxy-1,3,4-trihydroxynonan-2-one (**12**) in 32% yield (Scheme 3). The experimental procedure is as follows. To a solution of **8** (73.4 mg, 0.276 mmol) in 2.8 ml of H_2O containing 20% DMSO (v/v) was added FDP (trisodium salt, 71.8 mg, 0.140 mmol)[11] and the mixture was adjusted to pH 7, and then 100 units of RAMA[11] and 200 units of TPI [11] were added. After incubation for 24 hr at 30 °C under Ar atmosphere, the remaining **8** was recovered by extraction with AcOEt in 51% yield. The aqueous layer (ca. 20 ml) was adjusted to pH 5, and then 26 units of acid phosphatase (APase, E.C.3.1.3.2)[11] was added to remove the phosphate group in the condensation product under mild condition. The solution was incubated for 24 hr at 37 °C. The products were extracted with AcOEt and purified by column chromatography on silica gel (eluent, AcOEt) to afford **12** (31.2 mg).[12] It is noteworthy that the product was obtained as a single isomer despite the starting **8** included a small amount of its diastereomer.[8] The diastereomeric ratio of recovered **8** was much lower [(2*R*,4*R*) / (2*S*,4*R*) = 65 / 35] than that of the starting **8**.[13] These results indicate that epimerization[14] of **8** occurred slowly during the reaction and the reactivity of the epimer with **1** is much lower than that of **8**.



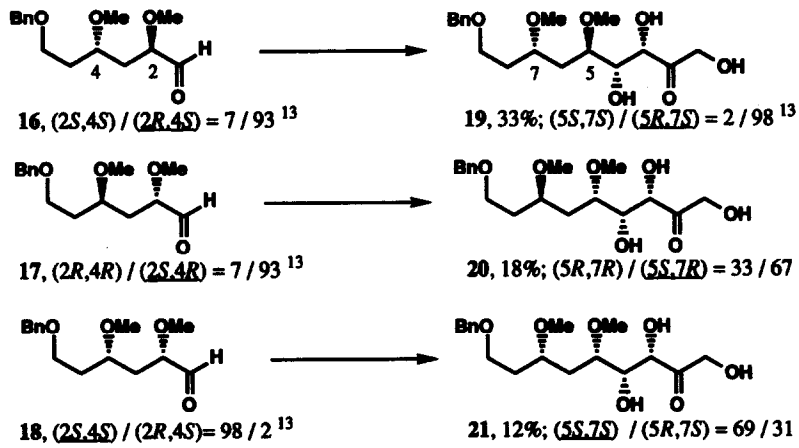
a) TsOH / Acetone, r.t. (79%); b) $LiAlH_4$ / THF, 0°C (82%); c) TsCl / Py, r.t.; d) $LiAlH_4$ / THF, 0 °C (2 steps, 70%); e) PDC, MS3A / CH_2Cl_2, r.t. (81%).

Scheme 4.

The keto-triol **12** was converted to the acetonide, reduced with $LiAlH_4$ to give diol **13**. The primary hydroxyl group in **13** was removed selectively by tosylation, followed by reduction producing **14**. PDC oxidation of **14** gave the desired ketone **15**.[15] The spectral data (^1H and ^{13}C NMR, IR, HRMS, and $[\alpha]_D$) of **15** are identical with those of an authentic sample [16,17] prepared from D-mannitol.

Then, we carried out RAMA-catalyzed reaction of DHAP (**1**) with diastereomers **16**, **17** and **18** of known stereochemistry to examine the effect of configurations of the C-2 methoxy group on the selectivity of the products, because the above results suggest that the reactivity of (2*S*)-derivative is much lower than that of the corresponding (2*R*)-derivative.

In fact, (2*R*,4*S*)-isomer **16** having the same configuration at C-2 position with **8** gave (5*R*,7*S*)-**19** in 33% yield with excellent selectivity. Contamination of (5*S*)-isomer in **19** was less than (2*S*)-isomer in **16**. These results were the same with those obtained by the reaction of **1** with **8**. Then, the aldol reaction was carried out using (2*S*)-isomers, **17** and **18**. The yields of the products mixture were very low in each case and the ratio of the (5*R*)-isomer in the products **20** and **21** increased significantly, which can be explained by considering that epimerization of (2*S*)-methoxyl group took place slowly during the reaction and the produced (2*R*)-isomers react with **1** much faster than (2*S*)-isomers, (5*R*)-isomers being eventually accumulated in the products. These findings show clearly that (2*S*)-2-methoxy aldehydes are the mismatched substrates for the RAMA-catalyzed aldol reaction, while the stereochemistry at the C-4 positions in the starting aldehydes had no detrimental effect on the reactivity.



Scheme 5.

Acknowledgements

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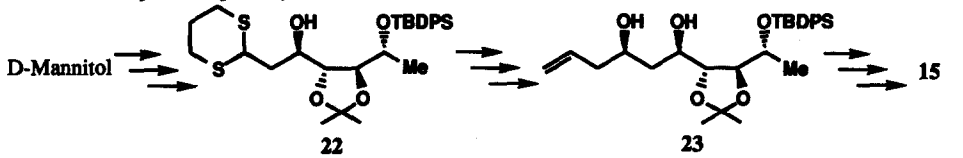
8. The obtained (2*R*,4*R*)-**8** included a small amount of (2*S*,4*R*)-isomer [(2*R*,4*R*) / (2*S*,4*R*) = 97 / 3]. The diastereomeric ratio was determined by ^{1}H NMR analysis.
9. **8**: $[\alpha]_D^{23}$ +16.8° (c 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 - 1.88 (m, 2H), 1.88 - 2.02 (m, 2H), 3.25 (s, 3H), 3.43 (s, 3H), 3.50 - 3.59 (m, 1H), 3.55 (t, J = 6.2 Hz, 2H), 3.68 (t, J = 5.1 Hz, 1H), 4.49 (s, 2H), 7.23 - 7.39 (m, 5H), 9.59 (s, 1H).
10. a) F. Effenberger and A. Straub, *Tetrahedron Lett.*, **28**, 1641 (1987); b) R. L. Pederson, J. Esker, and C. -H. Wong, *Tetrahedron*, **47**, 2643 (1991).
11. These enzymes and reagent were purchased from Sigma.
12. **12**: $[\alpha]_D^{24}$ -24.2° (c 1.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 - 1.88 (m, 2H), 1.88 - 2.00 (m, 2H), 3.03 (br.s, 1H), 3.31 (s, 3H), 3.31 - 3.36 (m, 1H), 3.35 (s, 3H), 3.51 - 3.60 (m, 1H), 3.55 (t, J = 4.7 Hz, 2H), 3.60 - 3.66 (m, 1H), 3.77 (dd, J_1 = 1.8 Hz, J_2 = 7.9 Hz, 1H), 3.92 (br.s, 1H), 4.50 (s, 2H), 4.54 (dd, J_1 = 9.8 Hz, J_2 = 9.8 Hz, 1H), 4.56 (d, J = 19.5 Hz, 1H), 7.25 - 7.39 (m, 5H).
13. Isomeric ratios were determined by ^{1}H NMR analysis.
14. After blank test by using **8** [(2*R*,4*R*) / (2*S*,4*R*) = 97 / 3] [in H_2O (pH 7) for 48 hr at 30 °C], the diastereomeric ratio of recovered **8** was reduced to 92 / 8.
15. **15**: $[\alpha]_D^{25}$ +6.26° (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.48 (s, 3H), 1.60 - 1.66 (m, 1H), 1.75 - 1.83 (m, 1H), 1.79 - 1.90 (m, 2H), 2.27 (s, 3H), 3.31 (s, 3H), 3.43 (s, 3H), 3.48 - 3.565 (m, 2H), 3.59 (dt, J_1 = 2.0 Hz, J_2 = 6.4 Hz, 2H), 4.24 (d, J = 6.6 Hz, 1H), 4.26 (dd, J_1 = 6.6 Hz, J_2 = 3.2 Hz, 1H), 4.51 (dd, J_1 = 11.9 Hz, J_2 = 16.2 Hz, 2H), 7.23 - 7.40 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.9, 26.7, 34.0, 34.6, 56.6, 58.4, 66.9, 73.0, 75.4, 78.0, 79.4, 81.8, 110.7, 127.5, 127.6, 128.3, 138.5, 208.9; IR (neat) 1710 cm^{-1}; HRMS m/z 365.1942 (365.1962 calcd for $C_{20}H_{29}O_6$, M^+)
16. An authentic sample of **15** was synthesized from D-mannitol through **22** and **23** as key intermediates. The detail will be reported separately.



17. $[\alpha]_D^{24}$ +6.77° (c 0.93, $CHCl_3$).

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