A New Approach to Cyclitols Based on Rabbit Muscle Aldolase (RAMA)[1]

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The synthesis of cyclitols having well-defined stereochemistry starting with nonchiral precursors is a current challenge in organic synthesis. Most synthetic strategies either start from chiral precursors (e.g., carbohydrates),[3-5] or resolve the racemic adduct formed in a Diels–Alder reaction.[6,7] Here we report the application of rabbit muscle aldolase (RAMA; EC 4.1.2.13) to the preparation of cyclitols and *C*-glycosides (Scheme I).

RAMA catalyzes the aldol condensation of dihydroxyacetone phosphate (DHAP) and aldehydes and forms products with the

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(7) Micobial oxidation of benzene with *Pseudomonas putida* followed by appropriate transformations of the products also yields cyclitols: (a) Ley, S.; Sternfeld, F. *Tetrahedron* **1989**, *45*, 3463–3476. (b) Ley, S.; Sternfeld, F. *Tetrahedron Lett.* **1988**, *29*, 5305–5308. (c) Ley, S.; Sternfeld, F.; Tylor, S. *Tetrahedron Lett.* **1987**, *28*, 225–226.

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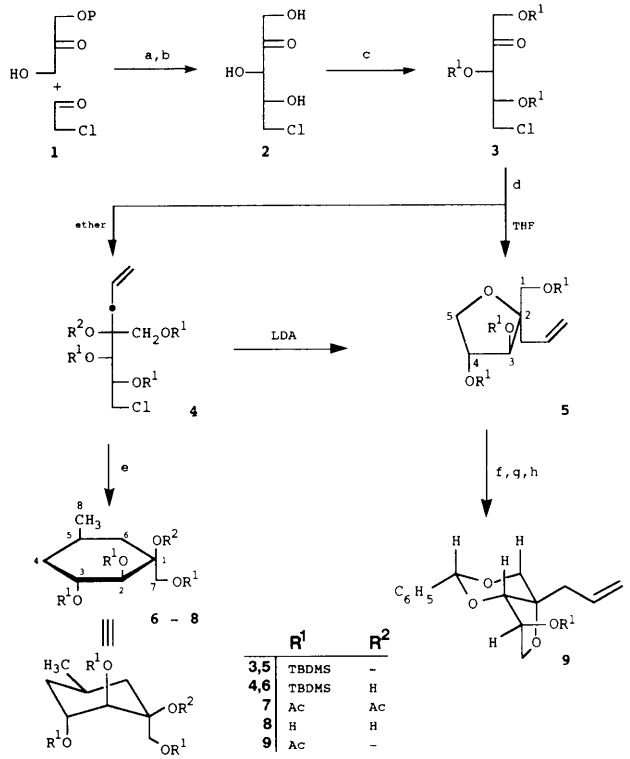
Scheme I[a]



[a] Reagents and conditions: (a) RAMA; (b) acid phosphatase, 50%; (c) TBDMSiOTf/Et_3N, 67%; (d) allylmagnesium bromide, 79%; (e) Bu_3SnH/AIBN, 75%, Δ; (f) TBAF, 96%; (g) $C_6H_5CH(OCH_3)_2$/TsOH; (h) Ac_2O/Pyr/DMAP.

D-threo (3*S*,4*R*) stereochemistry.[8-10] The aldol condensation between DHAP and chloroacetaldehyde **1** catalyzed by RAMA proceeds rapidly[9] and conveniently generates 5-deoxy-5-chloro-*threo*-pentulose (**2**) on a gram scale. Enzymatic dephosphorylation of **2** in situ with acid phosphatase (AP; EC 3.1.3.2) and protection of the hydroxyl groups as *tert*-butyldimethylsilyl ethers leads to **3**. Reaction of **3** with allylmagnesium bromide shows an interesting solvent dependence: in dry tetrahydrofuran (THF), the Grignard addition leads to an easily separable 2.7:1 mixture of *threo*-pentulose-*C*-allylglycoside **5** and the branched chain alditol **4**; in dry diethyl ether, this reaction gives **4** exclusively in 79% yield. Radical ring closure[11] starting from **4** forms the cyclitol **6**.[12]

We assigned the stereocenters in **4** and **6** in several ways. First, we transformed the alditol **4** into the *C*-glycoside **5** by treatment with LDA; this transformation establishes that the stereochemistry generated by the Grignard reaction is the same in **4** and **5**. Since the branched-chain alditol **4** can be converted to the cyclitol derivative **6**, the stereochemistry at the quaternary center in **6** must be the same as that of the anomeric center in **5**. This assignment was supported by NOE studies on **9**,[13] which showed a syn relationship between the hydrogen at C-3 and the allyl moiety at the "anomeric" center. The conformation shown in Scheme I is consistent with $J_{3,4} \sim 0$ Hz for **9**. ^1H NMR and NOE experiments on **6** showed $J_{2,3} = 3.3$ Hz and indicated a trans diaxial arrangement of the silyloxy groups at C-2 and C-3. The axial attachment of the hydrogen at C-5 was assigned on the basis of the large coupling constant of this proton to the proton H-6ax ($J = 12.5$ Hz), and because there was a significant NOE effect (4.2%) between H-5 and the CH_2 protons at C-7. These observations define the conformation of **6** unambiguously.[14] Since RAMA-catalyzed aldol condensations produce vicinal diols having only the 3*S*,4*R* stereochemistry, we were thus able to assign all the stereocenters.

The synthetic route outlined in Scheme I demonstrates an efficient approach to both cyclitols and *C*-glycosides based on catalysis by RAMA. Other aldolases generate other stereochemistries in the original aldol adduct.[15] Investigations directed toward expansion of these strategies are under way.

Supplementary Material Available: Experimental procedures for all compounds, ^1H and ^{13}C NMR data for **2**–**7**, **8** (^1H), and **9**, high-resolution mass spectra for **3**, **5**, and **6**, and elementary analysis for **3**–**6** (7 pages). Ordering information is given on any current masthead page.

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(14) Compound **6** has an unusual conformation; it contains three (rather than two) axial substituents. This assignment agrees with an analogous one by Paulsen and co-workers.[3] The same conformation is observed for **7** and **8**.
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