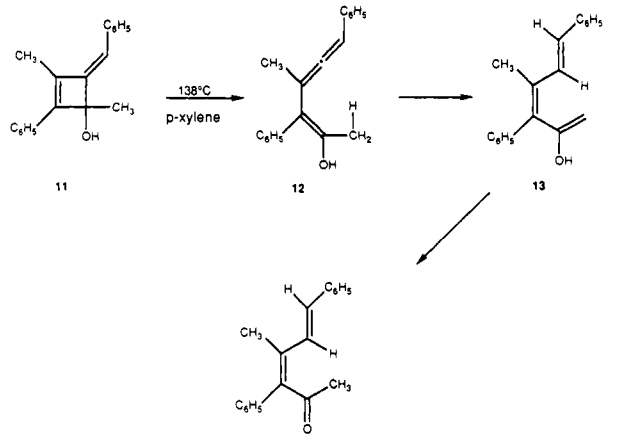
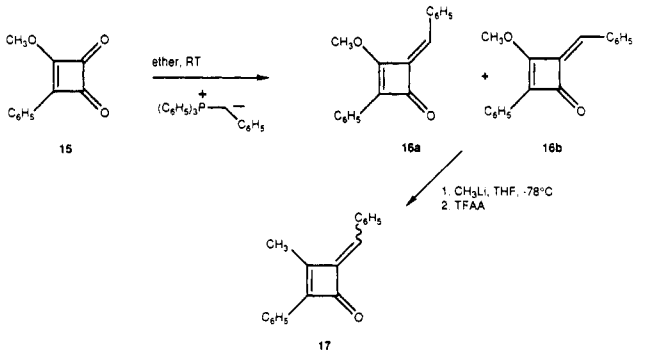
Scheme III



Scheme IV



alized by addition of methyllithium (THF, −78 °C) followed by hydrolysis (trifluoroacetic anhydride) to produce a diastereomeric mixture (1.5:1) of 17 (75–91%). This mixture served as the precursors to the isomeric mixtures of 1 (43%), 7 (61–66%), and 11 (70%) upon addition of hexynyllithium, vinyllithium, and methyllithium, respectively. It was noticed that the *Z* isomers of 1, 7, and 11 were much less thermally stable than their *E* counterparts, and thus the *E* isomers were employed for the thermolysis studies reported here.

In conclusion, the syntheses of 4-alkynyl-, 4-alkenyl- and 4-alkyl-4-hydroxybenzylidenecyclobutenes have been accomplished in an efficient manner starting from commercially available dimethyl squarate. These cyclobutenols undergo electrocyclic ring opening to conjugated allene intermediates which react further to give products arising from, respectively, biradical intermediates, electrocyclic ring closure and 1,5-hydrogen shifts. In view of the plethora of methods available for the synthesis of substituted cyclobutenediones, the ring expansions presented here represent potentially useful synthetic transformations.[6]

Acknowledgment. The authors thank the National Institutes of Health (GM-36312) for financial support of this work. We are also grateful to Catherine A. Moore for technical assistance in obtaining high resolution mass spectral data.

Supplementary Material Available: Experimental procedures and data for all compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) The stereochemical assignments of **16a**, **16b**, and **17** are based upon the deshielding anisotropic effects of the carbonyl group on the vinyl proton in the *E* isomer (**16a**). The resonance of the vinyl proton in this isomer appears at 6.48 ppm while that of the *Z* isomer **16b** came at 6.38 ppm. This downfield shift was also observed for the *E* isomer of 17. The assignments were confirmed by a 7% NOE enhancement of the vinyl proton of the *Z* isomer of 17 on irradiation of the methyl group. The stereochemistry of the respective isomers of 1, 7 and 11 was similarly established by NOE experiments.

A New Strategy for the Synthesis of Nucleoside Analogues Based on Enzyme-Catalyzed Aldol Reactions

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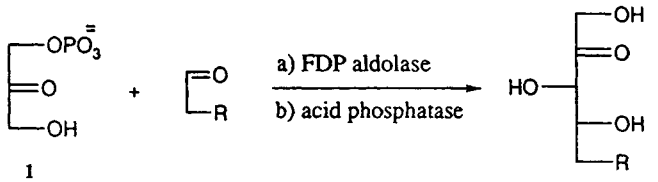
Received March 17, 1992

Summary: A new synthetic approach to nucleoside analogs based on enzyme-catalyzed aldol condensations has been demonstrated in the synthesis of 6-adenyl-6-deoxy-D-fructose and 6-adenyl-6-deoxy-L-sorbose.

Nucleoside analogues with modifications at the carbohydrate or base portion have been used extensively as antibiotics and as biological probes.[1-7] Nucleosides are traditionally synthesized by chemical methods.[3] Enzymatic synthesis of nucleosides based on nucleoside phos-

Scheme I



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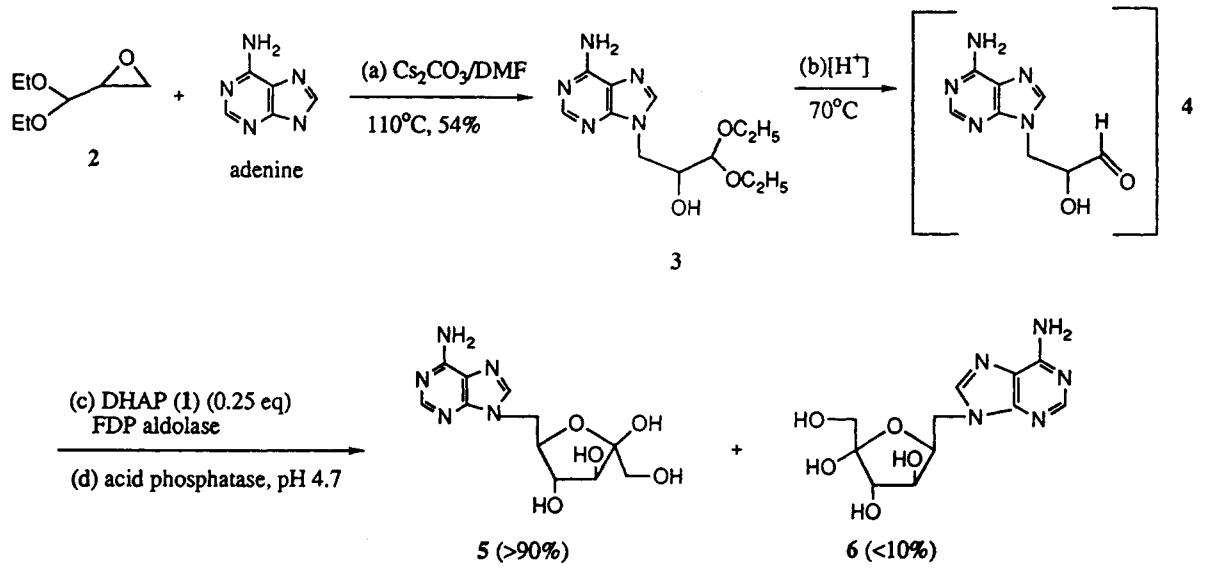
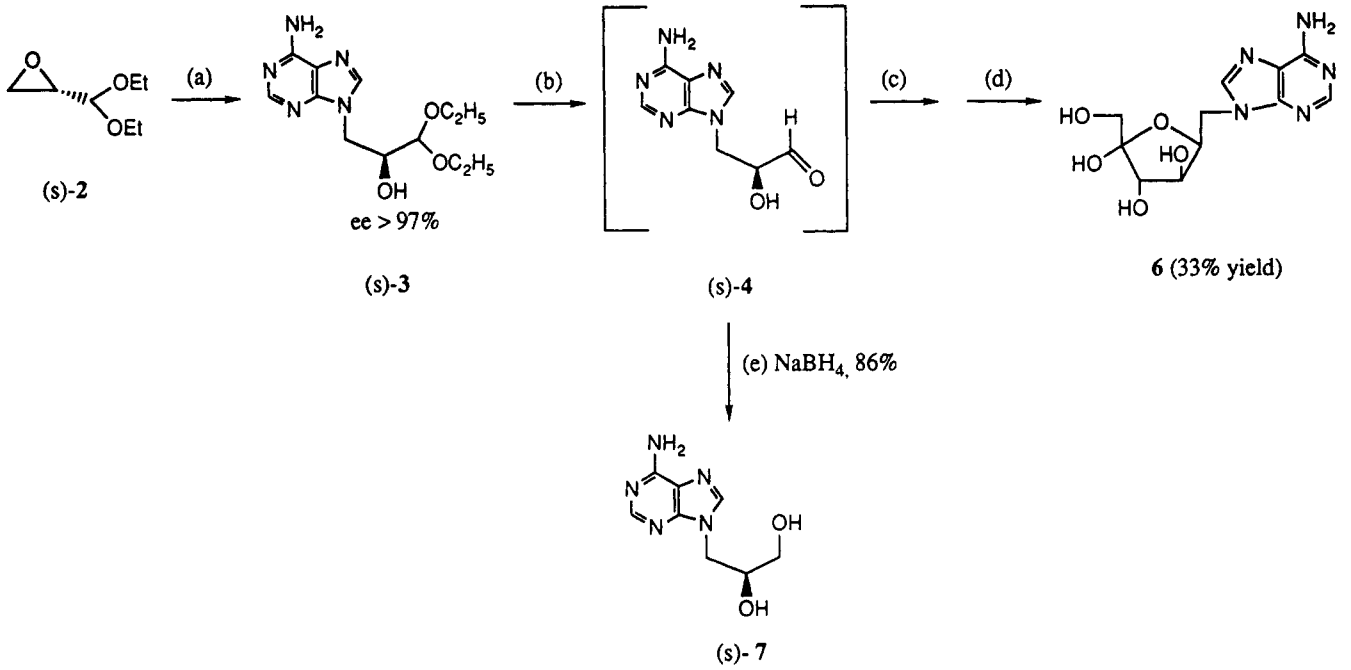
(5) Shimada, N.; Saito, S.; Hasegawa, S.; Takahashi, K.; Fuji, A.; Takita, T.; Seki, J.; Hoshino, H.; Nishiyama, Y.; Nagahata, T.; Matsubara, K. 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, CA 1988; Abstract 1008.
(6) Norbeck, D.; Sparton, S.; Broder, S.; Mitsuya, H. *Tetrahedron Lett.* **1989**, 6263.

Scheme II



Scheme III



phorylase or deoxyribosyl transferase has recently been developed.[8] We report here a new method for the synthesis of nucleoside analogous based on enzyme-catalyzed aldol condensations. This enzymatic approach provides a new route to nucleosides with a novel structure at the sugar and/or the base moiety.

Aldolases are a class of enzymes with flexible acceptor specificity. Fructose-1,6-diphosphate (FDP) aldolase, for example, catalyzes the stereospecific condensation of dihydroxyacetone phosphate (DHAP, 1) and D-glyceraldehyde-3-phosphate (G-3P) to give fructose-1,6-diphosphate.[9] The enzyme accepts a wide variety of aldehydes to form products stereospecifically with the D-threo (3*S*,4*R*) stereochemistry (Scheme I).[10] When α-hydroxy aldehydes were used as acceptors, the D-isomer with configuration related to the natural substrate G-3P generally reacted faster than the L-isomer to form preferentially a kinetic product of the D-fructofuranose type of structure. The L-sorbose type of product was obtained as a minor product; however, it can be synthesized in high yield with the use of enantiomerically pure L-aldehyde as substrate.[10,11]

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The racemic aldehyde component used in our kinetically controlled enzymatic synthesis was obtained as shown in Scheme II. Glycidaldehyde diethyl acetal (2)[12] was treated with adenine in the presence of cesium carbonate as a base to generate 3-adenyl-2-hydroxypropanal diethyl acetal (3) in 54% yield. The protected aldehyde was hydrolyzed to form the free aldehyde 4 in situ. DHAP[13] was added, and the solution was neutralized to pH 7. The FDP aldolase from rabbit muscle was then added, and the solution was stirred slowly at room temperature. After the reaction was complete, the phosphate moiety was cleaved with acid phosphatase in situ to afford 6-adenyl-6-deoxy-D-fructose (5) in 20% yield.[14] In this representative reaction, 4 equiv of aldehyde were used to obtain the kinetically preferred product 5. The minor product 6-adenyl-6-deoxy-L-sorbose (6) was obtained in <10% of the reaction mixture. In a separate synthesis of 6, enantiomerically pure (S)-3 (97% ee)[15] was prepared from (S)-2[16] and used as a substrate for the enzymatic reaction (Scheme III, 33% yield). Compound (S)-4 was further reduced with sodium borohydride to (S)-3-adenyl-2-hydroxy-propanol (7),[17] an analog of the biologically active compound 9-(3,4-dihydroxybutyl)-guanine.[18]

In summary, this paper illustrates that nucleoside analogs can be prepared effectively based on enzymatic aldol reactions. With the increasing availability of different aldolases, this enzymatic stragegy should provide a new entry to a variety of novel nucleosides.

Supplementary Material Available: Experimental procedures (3, 5, 6, and 7) and ^{1}H NMR spectra (5, 6, and 7) (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Compounds 5 and 6 were purified with Bio-gel P-2 column. Compound 5: $[\alpha]^{23}_D$ = +24.50 (c = 1, H_2O); ^{1}H-NMR (D_2O) δ 3.31–3.38 (2 H, m), 3.84–3.96 (3 H, m), 4.27 (1 H, dd, J = 15, 6 Hz), 4.31 (1 H, dd, J = 15, 4 Hz), 7.94 (1 H, s), 7.99 (1 H, s) ppm; ^{13}C-NMR (D_2O) δ 46.47, 63.17, 75.73, 76.20, 78.90, 102.72, 119.5, 143.89, 149.72, 153.1, 156.148 ppm; HRMS (M+Na$^+$) calcd 320.0971, found 320.0971. Compound 6: $[\alpha]^{23}_D$ = −28 (c = 1, H_2O); ^{1}H-NMR (D_2O) δ 3.45 (1 H, d, J = 12 Hz), 3.50 (1 H, d, J = 12 Hz), 4.05 (1 H, dd, J = 14.5, 9 Hz), 4.13 (1 H, d, J = 6 Hz), 4.28 (1 H, dd, J = 14.5, 3 Hz), 4.38–4.44 (2 H, m), 7.91 (1 H, s), 7.94 (1 H, s) ppm; ^{13}C-NMR (D_2O) δ 45.37, 63.17, 75.37 (2×C), 76.87, 103.02, 118.61, 143.27, 149.35, 152.67, 155.75 ppm; HRMS (M + H$^+$) calcd 298.1151, found 298.1157.

(15) The enantiomeric excess of (S)-3 was determined to be greater than 97% ee after converted to the corresponding acetate by ^{1}H-NMR in the presence of Eu (hfc)$_3$. The relative intensities of the acetoxy group at 3.04 and 2.85 were used for ee determination.

(16) Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.

(17) Compound 7: $[\alpha]^{23}_D$ = −24 (c = 0.8, H_2O); ^{1}H-NMR (D_2O) δ 3.48 (1 H, dd, J = 12, 6 Hz), 3.59 (1 H, dd, J = 12, 4.5 Hz), 3.96–3.98 (1 H, m), 4.00 (1 H, dd, J = 14, 8.5 Hz), 4.14 (1 H, dd J = 14, 3 Hz), 7.83 (1 H, s), 7.87 (1 H, s); ^{13}C-NMR (D_2O) δ 47.0, 49.6, 63.6, 70.4, 118.5, 143.3, 149.1, 152.7, 155.6 ppm; HRMS (M + H$^+$) calcd 210.0991, found 210.0993.

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Kinetic Evidence for the Solvent Intervention in the Solvolysis of 2-Aryl-2-propyl *p*-Nitrobenzoates. Electronic and Steric Effects

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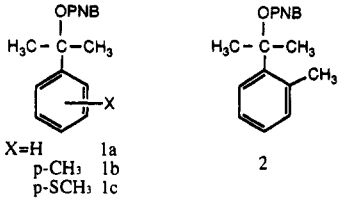
Summary: Kinetic observation indicates significant nucleophilic solvent intervention at the cationic transition state in the solvolysis of 2-phenyl-2-propyl *p*-nitrobenzoate (1a).

The solvolysis of 2-aryl-2-propyl (*tert*-cumyl) derivatives has long been considered to proceed via a limiting S_N1 mechanism, and from which σ^+ constants are defined.[1] Recently, the absence of nucleophilic assistance by solvent or by azide ion to the reaction of some *tert*-cumyl derivatives was reaffirmed.[2] On the other hand, in our recent solvolytic studies for establishing new Y_{BnX} scales[3-5] and for correlating reactivities with the Grunwald–Winstein equation (1),[6] we observed the depression of log *k*s measured in ethanol-trifluoroethanol solvent systems for several *tert*-cumyl substrates, such as 2-phenyl-2-propyl *p*-nitrobenzoate (1a).[5] Certain kinds of solvent assistance were considered to be involved.[4,5] Now we would like to report kinetic evidence for significant accelerations by nucleophilic solvents in the solvolysis of 2-aryl-2-propyl *p*-nitrobenzoates (1) based on the influence of electronic and steric effects of solvolytic reactivities.

$$\log (k/k_0) = mY \qquad (1)$$



2-Phenyl-, 2-(4′-methylphenyl)-, 2-[4′-(methylthio)-phenyl]-, and 2-(2′-methylphenyl)-2-propyl *p*-nitrobenzoate (1a–1c and 2, respectively) were solvolyzed in a variety of solvents, and their reactivities were monitored conductimetrically. The pertinent rate constants are listed in Table I. Since it is generally accepted that different Y_X scales should be used in the correlation analysis for substrates containing the specific leaving group X,[7] and we have

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