Pergamon

*Tetrahedron Letters*, Vol. 37, No. 15, pp. 2541-2544, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00337-1

# A Selective Intramolecular Aldol Condensation Directed by a Bifunctional Enzyme Mimic

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*Abstract* The intramolecular aldol condensation of a dialdehyde carrying a t-butylphenyl group is almost random with simple imidazole buffer catalysis, but shows a 97% preference for a single regiochemistry of cyclization when the reaction is catalyzed by the imidazole groups of a cyclodextrin-bis-imidazole enzyme mimic. Copyright © 1996 Elsevier Science Ltd

We have described the enolization of ketones that bind in water solution into the cavity of a beta-cyclodextrin (cycloheptaamylose, betaCD) carrying imidazole groups. The enolization of a simple bound ketone, p-tert-butylacetophenone, was catalyzed by betaCD with a single imidazole group attached to the primary C-6 carbon (**1a**), and also by a set of betaCD bis-imidazoles in which the attachments were at the C-6 positions of neighboring glucose residues—the 6A,6B isomer (**1b**)—and at residues one apart (6A,6C--**1c**) and two apart (6A,6D--**1d**).[1] The 6A,6D isomer **1d** was the most effective catalyst, and a pH vs. rate profile indicated that the catalysis was bifunctional—one imidazole acted as a base while the other acted, in its protonated form, as an acid. The preference for the 6A,6D isomer was interpreted in terms of the preferred geometry of proton removal by the base group.

We also showed[2] that catalyst **1d** could catalyze the intramolecular condensation of ketoaldehyde **2** to aldol **3**. There was a considerable rate acceleration by **1d**, but the same product was also formed with simple buffer catalysts. However, it seemed likely that the bifunctional catalysis by **1d** or an isomer could be used to direct an aldol condensation so as to turn an otherwise random process into one with regioselectivity. We have now found such a case, and the selectivity is striking.

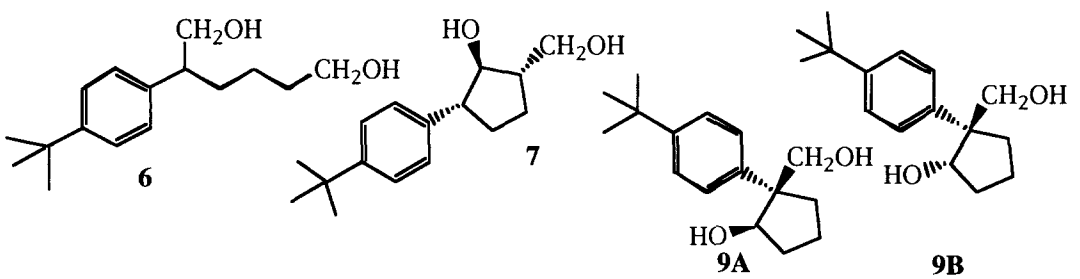
The cyclohexene derivative **4** was prepared by nickel-catalyzed coupling of 4-t-butylphenylmagnesium bromide with 3-phenoxycyclohexene, and converted to dialdehyde **5** by hydroxylation with catalytic $OsO_4$ and N-methylmorpholine-N-oxide, then cleavage of the resulting diol with sodium periodate. Dialdehyde **5** was characterized by MS and NMR; it was also quantitatively reduced with $NaBH_4$ in methanol at 0 °C to the corresponding diol **6**.

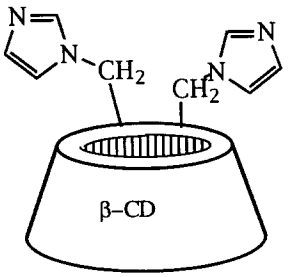
Intramolecular aldol condensations of **5** were carried out by adding 20 mL of a degassed aqueous solution of catalyst or buffer to a solution of **5** in 10 mL of degassed methanol. The concentrations involved are listed in the Table. The reaction mixture was maintained at 25 °C or 45 °C for the indicated time, and quenched with an excess of sodium borohydride at 0 °C,

converting all the products to stable diols. Methanol was evaporated and the residue was extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and analyzed by HPLC on a $C_{18}$ reverse phase column.

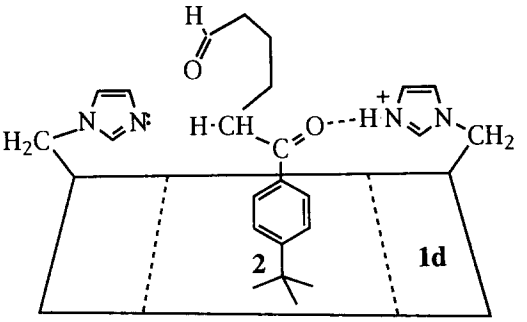
| catalyst | conc. of dialdehyde **5** | conc. of catalyst | Time and Temperature | Selectivity **10/8** [a] | ratio **10B/10A** [a] |
|---|---|---|---|---|---|
| A,B-Im2CD | 1.1 mM | | 12h@45° | 36.4 | 1.1 |
| **1b** | 1.1 mM | 1.3 mM | 3h@45° | 32.4 | 1.4 |
| w/ 1 eq HCl | 1.1 mM | | 5m@45° | 36.2 | 1.0 |
| | 1.2 mM | | 20m@25° | 32.9 | 2.8 |
| | 1.2 mM | | 15m@25° | 32.1 | 2.7 |
| A,D-Im2CD | 1.1 mM | | 12h@45° | 23.7 | 1.3 |
| **1d** | 1.1 mM | 1.3 mM | 1.25h@45° | 22.6 | 1.3 |
| w/ 1 eq HCl | 1.2 mM | | 40m@25° | 22.6 | 2.6 |
| Im-CD | 1.1 mM | 1.3 mM | 12h@45° | 12.5 | 1.0 |
| **1a** | 1.2 mM | 1.4 mM | 40m@ 25° | 14.6 | 2.6 |
| ß-CD | 1.1 mM | 2.4 mM | 12h@45° | 2.85 | 2.7 |
| in buffer | 1.1 mM | 2.8 mM | 40m@25° | 2.5 | 3.4 |
| Imidazole | 7.0 mM | 0.7 M | 12h@45° | 1.0 | 3.0 |
| buffer | 1.2 mM | 0.33 M | 40m@25° | 2.1 | 1.3 |
| 1/1 | 1.2 mM | 83 mM | 40m@25° | 1.9 | 1.5 |

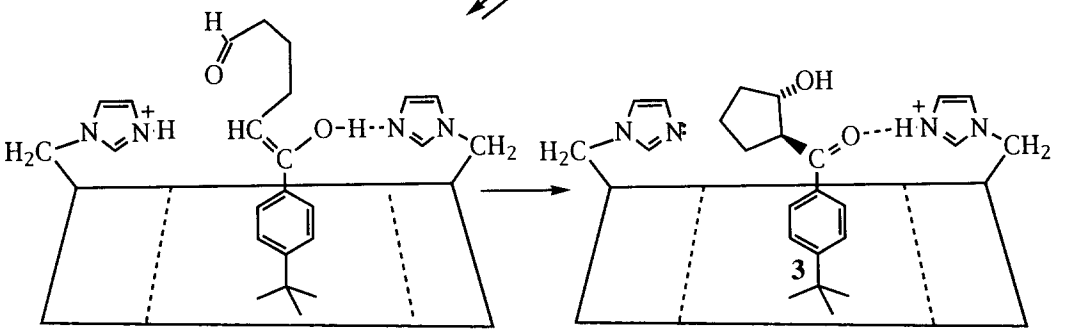
a. From the ratios of the corresponding diols **6**, **7**, and **9.** In all the runs at 25° there was some unreacted starting material, so the values reflect kinetic control. In the other cases some equilibration apparently occurred.

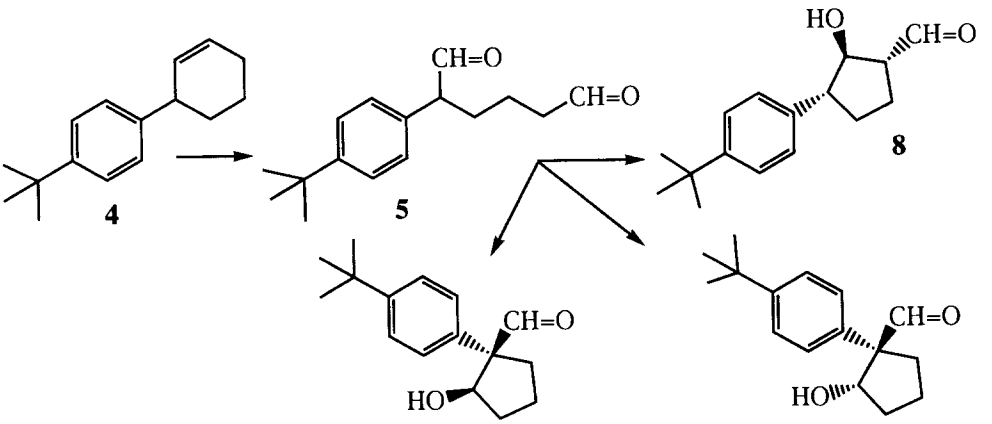





**1a:** only one imidazole
**1b:** on neighboring glucoses
**1c:** one glucose apart
**1d:** two glucoses apart



At 45° most of the reactions went to completion, and equilibration may have occurred. The reactions at 25° left from 14 to 54% unreacted starting material, so the ratios observed are more likely kinetic. Thus the 25° data will be discussed.

A single stereoisomer of diol **7** was isolated, corresponding to aldol product **8**.[3] However, diol **9** was formed as two stereoisomers, **9A** and **9B**, derived from aldols **10A** and **10B**.[4] From NMR studies using a chiral shift reagent, the products are essentially racemic. The relative amounts of these three isomeric products depended on the catalyst used, as the Table summarizes. With a simple 1/1 imidazole buffer the cyclization occurred almost randomly with the two possible regiochemistries, forming a 1/2 mixture of **8** and **10**. The ratio of **10B** to **10A** was 1.4. However, with the betaCD 6A,6B-bisimidazole **1b**—half protonated, so there is one basic imidazole and one acidic imidazolium ion—there is a 97% preference for formation of aldol **10** rather than **8**. This indicates that the substrate **5** binds into the cyclodextrin cavity and that the two catalytic groups then catalyze enolization of the benzylic aldehyde group, and addition of this enol to either face of the remote aldehyde group.

There is a difference in selectivity among the catalysts. The **10** to **8** ratio is only 23/1 with the AD isomer **1d**, and only 15/1 with the cyclodextrin monoimidazole **1a** that had no HCl added and acted as a simple base catalyst. When simple betaCD is used along with the imidazole buffer the ratio of **10** to **8** is only ca. 2.5/1, almost the same as with buffer alone.

The reaction within the complex of substrate with the catalysts is probably completely selective for **10**, with the formation of **8** occurring outside the complex. In any case, the very high selectivity of the cyclization with the AB catalyst isomer **1b** is striking, and in contrast with our previous findings that the enolization of t-butylacetophenone or the aldol condensation of the ketoaldehyde **2** was preferentially catalyzed by the AD isomer **1d**. The geometric preferences among these catalysts are obviously subtle, as is the selectivity between the isomers of **10**.

Acknowledgment. This work has been supported by the NIH, including an NIH postdoctoral fellowship to J.D., and by the NSF and ONR.

## References

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2. Desper, J.M.; Breslow, R. *J. Am. Chem. Soc.* **1994**, *116*, 12081.
3. HNMR: 7.36 (d, 2H), 7.22 (d, 2H), 3.90 (t, 1H), 3.82 (dd, 1H), 3.69 (dd, 1H), 2.94 (q, 1H), 1.4-2.2 (m, 5H), 1.32 (s, 9H) ppm. The stereochemistry is assigned from the finding of an NOE at 3.90 ppm and 1.75 ppm when 7.22 is irradiated, indicating that the phenyl ring is trans to the OH, and the fact that the proton at 3.90 is coupled to two protons with J=9.1 Hz for each, suggesting that both protons next to the CHOH group are trans to its proton.
4. Isomer 9A HNMR: 7.41 (d, 2H), 7.28 (d, 2H), 4.34 (t, 1H), 3.59 (d, 1H), 3.40 (d, 1H), 1.7-2.2 (m, 6H), 1.32 (s, 9H) ppm. NOE between 7.28 and 4.34. Isomer 9B HNMR: 7.41 (d, 2H), 7.38 (d, 2H), 4.61 (t, 1H), 4.00 (d, 1H), 3.73 (d, 1H), 1.5-2.2 (m, 6H), 1.33 (s, 9H) ppm. No NOE between 7.38 and 4.61.

(*Received in USA* 8 *February* 1995; *accepted* 15 *February* 1996)