

**DIRECT TRANSFORMATION OF 2,3-EPOXY ALCOHOLS INTO HYDROXY CARBONATES UNDER
MILDLY BASIC CONDITIONS**

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Summary: 2,3-Epoxy alcohols are transformed into the corresponding C2-inverted hydroxy carbonates upon treatment with cesium carbonate-powdered 3-Å molecular sieves in *N,N*-dimethylformamide under one atmosphere of carbon dioxide at 23-78 °C.

As part of a recent study we required a stereospecific method to transform the epoxy alcohols **1** and **2** into the hydroxy carbonates **3** and **4**.¹ Standard procedures, notably Lewis acid induced rearrangement of the corresponding phenyl urethane derivatives,² led to intractable product mixtures with these substrates, presumably a consequence of arene-facilitated epoxide opening at C1. McCombie and Metz recently described a similar outcome in attempts to transform the hydroxy epoxide **5** into the carbonate **6**. Though unsuccessful in this conversion, these authors found that treatment of **5** with cesium carbonate-paraformaldehyde in acetonitrile produced a 1,3-dioxolane derivative which upon acidic hydrolysis (HCl-H₂O-MeOH, 65 °C, 6 h) furnished the triol **7** in good yield.³ As a potential route to viable precursors to **3** and **4** (the corresponding triols), we applied this sequence to substrates **1** and **2**, but encountered only partial success; incomplete conversions in the initial transformation and poor yields in the subsequent acidic hydrolysis step led us to seek an alternative strategy. We describe below a simple and direct solution to the problem epoxy alcohol → hydroxy carbonate which holds considerable promise as a general method.

Scouting experiments quickly established the effectiveness of cesium carbonate-powdered 3-Å molecular sieves in catalyzing the direct incorporation of carbon dioxide into substrate epoxy alcohols to produce the corresponding C2-inverted hydroxy carbonates. Greatest reaction rate and selectivity were obtained in dimethylformamide as solvent, though reaction occurred in hydrocarbon (toluene) and protic (isopropanol) media as well. Proper preparation of the catalyst was critical; vigorous heating of a powdered mixture of cesium carbonate and 3-Å molecular sieves under vacuum with cooling under an atmosphere of dry carbon dioxide reproducibly provided a catalyst of high activity. Typically, 0.1 mole of cesium carbonate per mole of substrate was employed. While the role of molecular sieves in the reaction is unclear, their incorporation led to a definitive (ca. twofold) acceleration in rate (molecular sieves alone were ineffective as a catalyst).⁴ Increasing the pressure of carbon dioxide led to faster reaction, though the observed rate enhancement was less than one order of magnitude when the pressure was increased from one to four atmospheres. We encountered difficulty in quantitating the latter effect due to variations in stirring efficiency associated with different reaction vessels, parameters found to be important for uniform results. Reaction time and temperature varied with substrate. Thus,

1*S*,8*S*-**1**¹ reacted completely within 16 h at 40 °C under one atmosphere of carbon dioxide to produce 1*S*,8*R*-**3** (85%), whereas 1*S*,8*R*-**2**¹ was transformed into a mixture of 1*S*,8*S*-**4** (72%) and the product of internal transesterification, 1*S*,8*S*-**8** (9%, carbonate geometry verified by difference NOE), within 48 h at 23 °C.

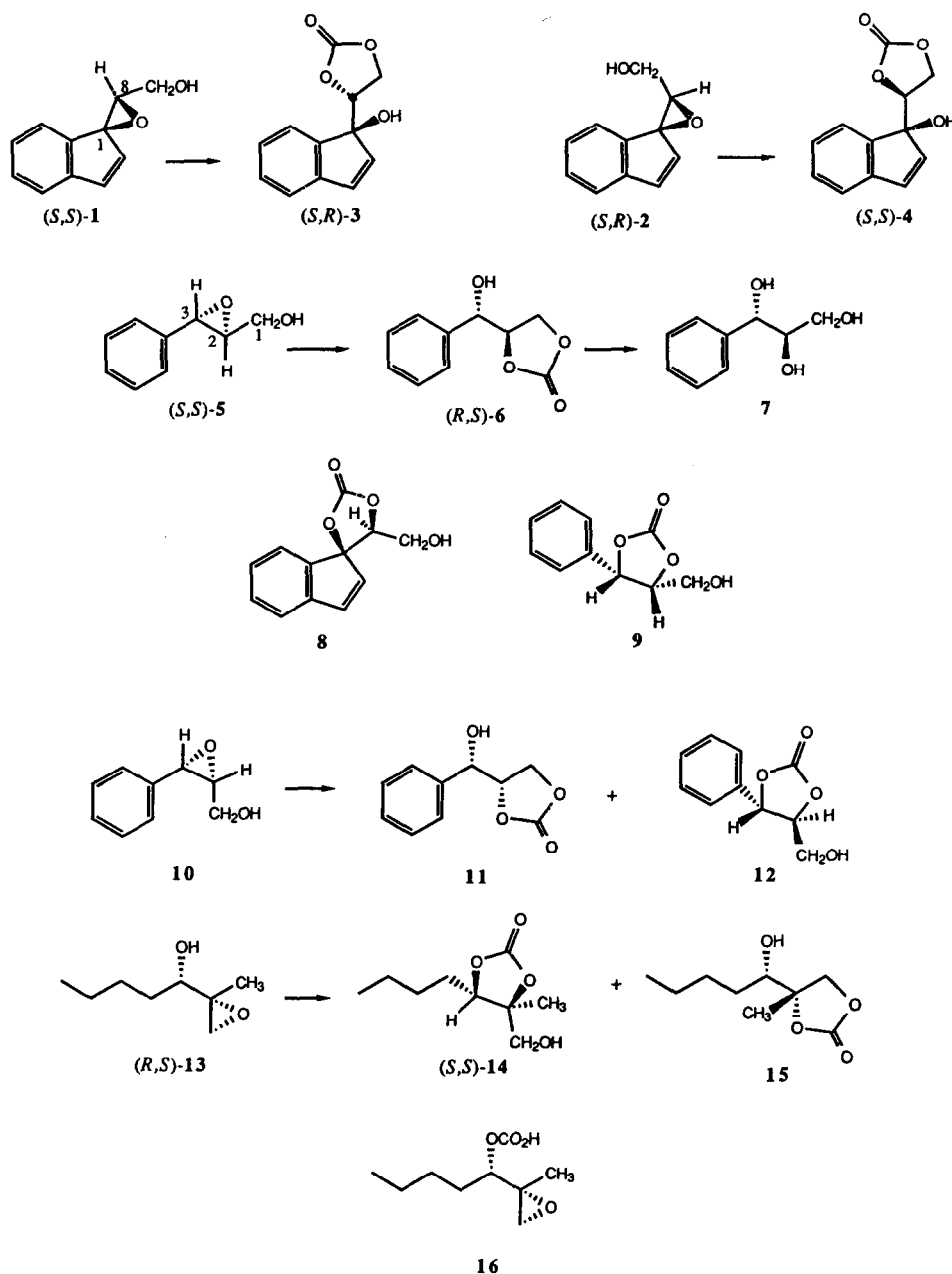
The stereochemistry of **3** was verified as follows. Saponification of **3** (K₂CO₃, 2:1 THF:H₂O, 23 °C, 3 h) produced a triol which was spectroscopically and chromatographically identical with the triol obtained from **1** and Cs₂CO₃-paraformaldehyde with subsequent acidic hydrolysis (1:1 6 N HCl:MeOH, 23 °C, 48 h),³ establishing net inversion in the transformation **1** → **3**. Separate conversion of each triol to the same *bis*-Mosher ester derivative upon limited treatment with (*S*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid chloride-4-dimethylaminopyridine confirmed the site of inversion as C8.⁵ Compounds **1** and **3** were shown to be of identical enantiomeric enrichment,⁵ demonstrating complete stereospecificity in formation of the latter.

The internal carbonate rearrangement exemplified by **4** → **8** was generally observed, producing a thermodynamic distribution of products. Control experiments showed that the rate of carbonate equilibration was comparable to the rate of initial transformation of epoxide to carbonate. These carbonate rearrangement isomers were readily separated by flash column chromatography, though this would be unnecessary in applications involving subsequent saponification to the parent triol.

Treatment of 2*S*,3*S*-**5**⁶ (98 ± 2% ee, 13 h, 36 °C), as above, produced the direct insertion product 2*R*,3*S*-**6** (85%, 98 ± 2% ee⁵) and its carbonate rearrangement product **9** (8%). Saponification of **6** (NaOH, THF-H₂O, 23 °C) produced the known triol (1*S*,2*R*)-**7** ([α]₂₅^D = 20.2°, C = 6.34 in water, literature: [α]₂₃^D = 19.6°, C = 6.34 in water⁷) confirming the stereochemical formulation of **6**. Traces (≤ 5%) of the diastereomeric products **11** and **12** were also isolated. These products presumably arise from a Payne rearrangement⁸-carbon dioxide insertion sequence (control experiments showed that conversion of **6** to **11** and **12** was a very slow process) and were less prevalent at higher pressures of carbon dioxide and at lower reaction temperatures. Among those we examined, substrate **5** alone showed propensity towards competitive Payne rearrangement. When the diastereomeric epoxide, **10**, was submitted to now standard conditions (6 h, 45 °C), the direct insertion product **11** and its carbonate rearrangement isomer **12** were obtained as a 1:3 mixture in 85% combined yield.

Substrate (2*R*,3*S*)-**13**⁶ was examined to test the effects of increased substitution at the hydroxyl-bearing carbon atom and the adjacent epoxide center, both anticipated to slow the reaction. While a higher temperature was required (78 °C, 16 h), reaction was nevertheless clean producing the direct insertion product (2*S*,3*S*)-**14** (geometry verified by difference NOE) in 78% yield along with 13% of the carbonate rearrangement product **15**. This reaction was the subject of a brief mechanistic study. When the course of reaction was monitored by ¹³C NMR spectroscopy (DMF, 70 °C, ⁷Li external lock), signals due to **13** were gradually and exclusively (at low conversion) displaced by those of **14**. We therefore conclude that if the hydrogen carbonate **16** is an intermediate, its concentration in solution must be low. From our general observations we believe this process to be subject to heterogeneous catalysis.

Our results suggest that cesium carbonate-3Å molecular sieves is a generally effective catalyst for the one-step conversion of 2,3-epoxy alcohols to the corresponding hydroxy carbonates. The propensity for certain products to undergo thermodynamically-controlled internal transesterification remains a detractor.⁹ Nevertheless, synthetically useful yields of stereospecific carbon dioxide insertion products are obtained with many substrates. We anticipate that this direct procedure will be the method of choice for some epoxy alcohols, certainly those which are acid-sensitive. The procedure which follows provides experimental detail.



Experimental

A 25-mL flask with a side-arm connection to vacuum/carbon dioxide was charged with anhydrous cesium carbonate (0.21 g, 0.09 equiv), powdered 3-Å molecular sieves (0.50 g) and a teflon-coated stir bar. A rubber septum was affixed and the flask was evacuated (0.01 mm). The catalyst mixture was stirred over a good flame

for 3 min, then blanketed with an atmosphere of anhydrous carbon dioxide and allowed to cool to 23 °C. A solution of (2*S*, 3*S*)-2,3-epoxy-3-phenyl-1-propanol (**5**, 1.106 g, 1 equiv, 98 ± 2% ee, azeotropically dried with two 2-mL portions of toluene) in anhydrous DMF (0.5 mL) was transferred via cannula to the catalyst flask; the transfer was quantitated with additional DMF (4 x 0.5 mL). The resulting suspension was brought to 36 °C and held at that temperature for 13 h under one atmosphere of carbon dioxide with good magnetic stirring throughout. The progress of the reaction can be conveniently monitored by thin-layer chromatography (ether, R_f = 0.49, 0.53 and 0.31 for **5**, **7**, and **9**, respectively). The reaction mixture was allowed to cool to 23 °C and the basic mixture was neutralized by the addition of saturated aqueous ammonium chloride solution (3 mL). The resulting suspension was partitioned between half-saturated brine (100 mL)-saturated ammonium chloride (20 mL) and ethyl acetate (50 mL). The phases were separated and the aqueous layer was further extracted with two 50-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate-toluene) afforded separately pure (2*R*,3*S*)-**7** (1.217 g, 85%) and **9** (0.112 g, 8%). Through 400 MHz ¹H NMR analysis of the derived (*S*)-Mosher ester, **7** was found to be of 98 ± 2% ee.⁵

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References and Notes

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