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Carbonylation of Epoxides to Substituted 3-Hydroxy-δ-Lactones

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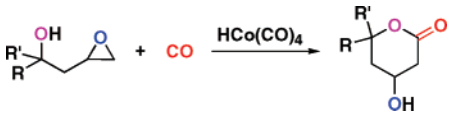
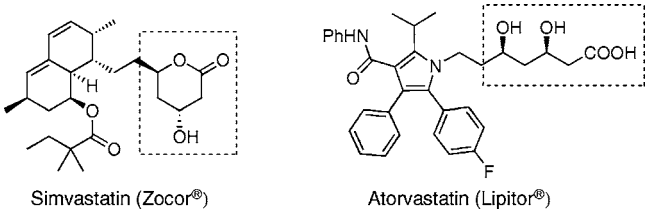
ABSTRACT



Substituted 3-hydroxy-δ-lactones (3HLs) are valuable intermediates in the synthesis of pharmaceuticals and other biologically active natural products. Herein we report the first example of the catalytic carbonylation of substituted homoglycidols to 3HLs using $HCo(CO)_4$. Upon optimization of the catalyst and reaction conditions, a functionally diverse set of 3HLs was prepared. Mechanistic insight was gained by observation of the carbonylation reaction using in situ IR spectroscopy, and we propose a mechanism that is consistent with previously studied epoxide carbonylation systems.

Substituted 3-hydroxy-δ-lactones (3HLs) are common structural motifs in natural products[1] and are valuable as intermediates in the synthesis of a variety of pharmaceutical compounds.[2−5] 3HLs are most prominent in the class of HMG-CoA reductase inhibitors known as statins, which are among the most potent cholesterol-lowering drugs available and constitute five of the top 100 selling drugs.[5] All approved statins have side chains comprising either a 3HL or the hydrolyzed 3,5-dihydroxycarboxylic acid analogue (Figure 1), which are essential for the bioactivity of statin drugs.[6] 3HLs have also been used in the synthesis of important drugs such as tetrahydrolipstatin,[2] a lipase inhibitor prescribed for the treatment of obesity, and the antiretroviral agent tipranavir.[3] Furthermore, dehydration of 3HLs produces a class of biologically active α,β-unsaturated lactone natural products.[4]



Simvastatin (Zocor®) Atorvastatin (Lipitor®)

Figure 1. Structures of two common statin drugs with 3HL portions highlighted.

As a result of their synthetic value, the synthesis of 3HLs has received a great deal of attention in recent years.[7−10] Biocatalytic routes have proven successful in the synthesis

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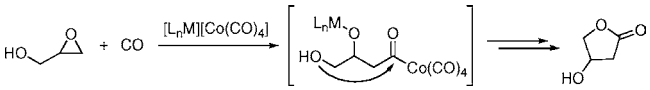
of statin side chains, although substrate scope is limited.[7] Synthetic routes to substituted 3HLs have employed a variety of methods, including aldol reactions using chiral auxiliaries,[8] reduction of diketoesters followed by cyclization,[1] allyl boration and ring-closing metathesis,[9] and rearrangement of β-lactones.[10] These methods, however, involve multiple steps and can suffer from low stereoselectivity.

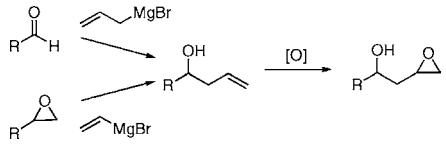
Our laboratory has recently reported a number of catalysts that are active for the carbonylation of a functionally diverse array of epoxides to β-lactones.[11] However, the expected β-lactone was not formed in the carbonylation of glycidol; instead, 3-hydroxy-γ-valerolactone was the sole product (Scheme 1).[12] While this method could be utilized in the

Scheme 1. Carbonylation of Glycidol to 3-Hydroxy-γ-valerolactone



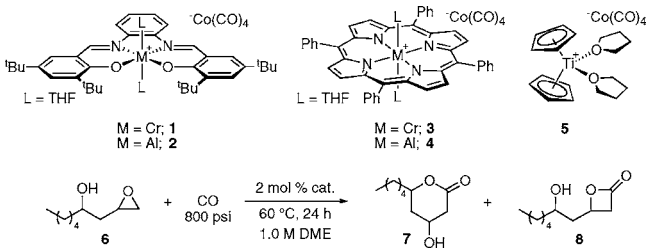
synthesis of γ-lactone natural products such as (−)-grandinolide,[13] this result led us to consider the carbonylation of substituted homoglycidols as a potential route to 3HLs. Such a process would provide simple access to δ-lactones with a variety of substitution starting from commercially available epoxides and aldehydes (Scheme 2).[14]

Scheme 2. Convergent Synthesis of Homoglycidols



Our initial efforts to carbonylate 4-hydroxy-1,2-epoxynonane (**6**)[15] to δ-lactone **7** using known epoxide carbonylation catalysts resulted in mixtures of β- and δ-lactones (Table 1, entries 1−6). In general, catalysts that are highly active for epoxide carbonylation to β-lactone (**1** and **3**) were more selective for β-lactone (**8**). This selectivity could be exploited in the synthesis of tetrahydrolipstatin and other β-lactone-containing lipase inhibitors.[2] Less active catalysts

Table 1. Catalyst Screening for 3HL Formation



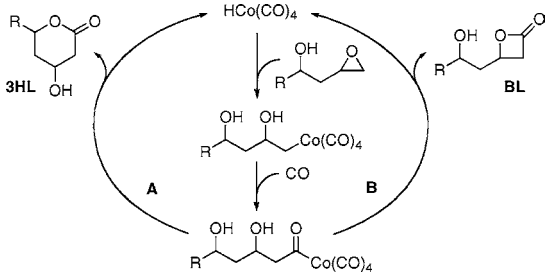
		conversion[a] (%)	
entry	catalyst	δ-lactone (**7**)	β-lactone (**8**)
1	**1**	16	84
2	**2**	73	27
3	**3**	33	67
4	**4**	58	42
5	**5**	83	17
6	$Co_2(CO)_8$	67	33
7	$HCo(CO)_4$[b]	>99	ND[c]

[a] Conversions determined by ^{1}H NMR spectroscopy; diastereomeric ratios of **6**, **7**, and **8** ca. 1:1. [b] Prepared in situ; see Supporting Information for details. [c] ND = Not Detected.

(**2** and **5**) produced more 3HL (**7**); thus, we reasoned that a catalyst that is active for epoxide ring opening but slow for β-lactone ring closing would give better selectivity for 3HL. When we used $HCo(CO)_4$ (entry 7) which is not known to produce β-lactones but is effective for the alkoxy carbonylation of epoxides to β-hydroxy esters,[16] 3HL was formed as the exclusive product.

Our proposed mechanism for the carbonylation of homoglycidols by $HCo(CO)_4$ (Scheme 3) is analogous to that of

Scheme 3. Proposed Mechanism for Competing δ-Lactone and β-Lactone Formation



other epoxide carbonylations by Lewis acid based catalysts.[17] The first step involves protonation and ring opening of the epoxide by $HCo(CO)_4$ to form a cobalt alkyl complex. After insertion of CO, the resulting cobalt acyl intermediate can cyclize to form either 3HL (Pathway A) or the more strained β-lactone (BL; Pathway B). Another potential mechanism for 3HL formation could involve a BL intermediate and its

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(14) See Supporting Information.

(15) Epoxides **6**, **6a**−**6d**, and **6g**−**6j** and their corresponding 3HLs were prepared as a ca. 1:1 mixture of diastereomers. Similar rates of carbonylation were observed for both epoxide diastereomers.[13]

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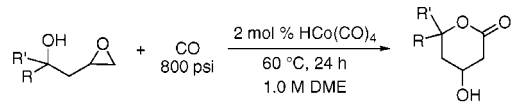
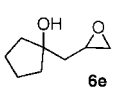
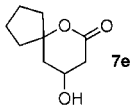
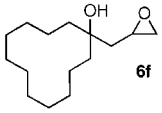
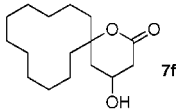
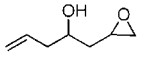
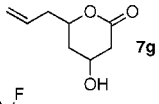
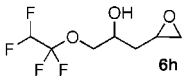
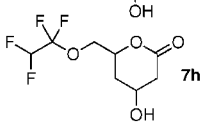
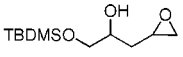
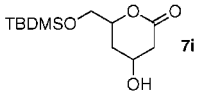
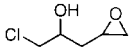
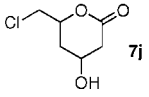
subsequent rearrangement to 3HL. However, using in situ IR spectroscopy, BL was not observed during the carbonylation of **6**.[14] Furthermore, rearrangement of BL **8** to 3HL **7** was negligible under the reaction conditions, eliminating this mechanistic possibility.

After the reaction conditions were optimized for efficient δ-lactone formation,[14] a variety of substituted homoglycidols were carbonylated (Table 2).[15] Both alkyl- (entries 1 and 2) and aryl-substituted (entry 3) homoglycidols were carbonylated cleanly to 3HLs. Disubstituted homoglycidols (entries 4−6) produced **7d** and the spiro 3HLs **7e** and **7f**; however, a small amount of β-lactone was also formed in these carbonylations. We believe the more sterically hindered tertiary alcohols undergo slower ring closing, making β-lactone formation from a secondary alcohol (Scheme 3, Pathway B) competitive with 3HL formation. The alkene- and fluoroether-substituted epoxides (entries 7 and 8) required a higher catalyst loading to reach full conversion. Finally, the important synthetic intermediates **7i** and **7j** were synthesized under standard conditions. Both **7i** and **7j** have been used in the synthesis of more complex statin drugs.[18,6b]

Table 2. Synthesis of 3HLs Using $HCo(CO)_4$



entry	epoxide R	epoxide R'		δ-lactone	yield[a] (%)
1	Me	H	**6a**	**7a**	73
2	^{n}Bu	H	**6b**	**7b**	60
3	Ph	H	**6c**	**7c**	81
4	Me	Et	**6d**	**7d**	58[b]
5			**6e**	 **7e**	67[c]
6			**6f**	 **7f**	75[c]
7[d]			**6g**	 **7g**	76
8[d]			**6h**	 **7h**	92
9			**6i**	 **7i**	52
10			**6j**	 **7j**	81

[a] Yield of isolated product. [b] 6% β-lactone formed. [c] 4% β-lactone formed. [d] 5 mol % catalyst used.

The (3*R*,5*R*) absolute stereochemistry is essential to the efficacy of statin drugs,[6b] and the ability to control the stereochemical outcome of the carbonylation is of great importance for any synthetic application. Our proposed mechanism (Scheme 3) predicts retention of stereochemistry of these homoglycidols. To test this mechanistic hypothesis we carbonylated **(*R*,*R*)-6b** under standard conditions (Figure 2). Analysis by ^{1}H and ^{13}C NMR spectroscopy indicated the *trans* diastereomer was formed exclusively, and optical rotation established the product as the (3*R*,5*R*) isomer.[14] Thus, the carbonylation occurs with retention of both stereocenters.

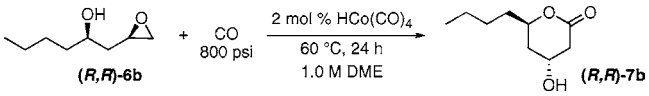


Figure 2. Carbonylation of enantiopure homoglycidol **(*R*,*R*)-6b** with retention of stereochemistry.

The synthesis of 3HLs by carbonylation of homoglycidols is an efficient method to access functionally diverse and optically pure lactones. We anticipate the substrate range and simple catalyst preparation will make this procedure useful in a variety of synthetic applications. We are currently applying this methodology to incorporate new functional groups for the synthesis of natural products.

Acknowledgment. We thank Dr. Christopher Byrne (Cornell University) for discussions and materials relating to catalyst preparation. This work was supported by the National Science Foundation (CHE-0243605) and the Department of Energy (DE-FG02-05ER15687) and by the National Institutes of Health through a Chemical/Biology Interface (CBI) Training Grant (to J.W.K.).

Supporting Information Available: Experimental procedures, in situ IR data, full characterization of all new compounds, and ^{1}H and ^{13}C NMR spectra for all δ-lactones. This material is available free of charge via the Internet at http://pubs.acs.org.

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