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Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-β-Lactones Obtained by Epoxidation of 4-Alkylidene-2-Oxetanones

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Strained organic ring compounds are versatile intermediates for synthesis. Among them, epoxides have a very rich history and play a prominent role in synthetic endeavors. On the other hand, β-lactones (2-oxetanones, **1**) have only recently been tapped for their potential as intermediates to access an array of functional groups, including those found in natural products.[1] This increased interest in β-lactones as intermediates parallels activity in the area of catalytic, asymmetric synthesis of these strained systems.[2] In line with our group's interests in exploring new and potentially more concise strategies for natural product synthesis, we have studied the potential of β-lactones as synthetic intermediates.[1c] In one such endeavor, we were attracted to the possibility of utilizing a heretofore unknown spiroepoxy-β-lactone **2** as an intermediate that might undergo regioselective C−O cleavage. We envisioned that this system might be accessible by epoxidation of optically active ketene dimers available by the method of Calter (Scheme 1).[3] Herein we describe the synthesis and structure of a new class of unexpectedly stable, strained spiroketals, 1,4-dioxaspiro[2.3]-hexan-5-ones (**2**) that differ significantly in terms of stability and reactivity from the most analogous systems, spiroepoxy oxetanes,[4] spirobisepoxides,[5] and spiroepoxy-γ-lactones.[6]

Our epoxidation studies began with racemic ketene dimer **3a** prepared by in situ dimerization of hexylketene.[3] After brief exploration of oxidants and conditions, we found that exposure of ketene dimer **3a** to dimethyldioxirane (DMDO)[7] in CH_2Cl_2 at 23 °C provided a compound which exhibited spectral data (e.g., IR: 1859 cm^{-1}; ^{13}C NMR: δ 91.0 (ketal carbon)) consistent with spiroepoxy-β-lactone **2a**. Optimal yields were obtained only with purified ketene dimer since degradation of the dimer due to traces of amine hydrochloride salt from the dimerization step was competitive with epoxidation. In this manner, several spiroepoxides **2b**−**e** (Table 1) were prepared with good diastereoselectivity and proved to be surprisingly stable to silica gel chromatography, allowing separation of diastereomers. This stability contrasts significantly from dioxaspirohexanes and dioxaspiropentanes, which could not be chromatographed. However, spiro-β-lactones **2** did exhibit some thermal instability. When stored neat at −20 °C, these spiro-β-lactones were stable for ∼1 week; however, at 23 °C, decomposition was observed after 2 days. The presence of azido and silyl ether functionality was tolerated (entries 4 and 5, Table 1). Lower molecular weight and less hydrophobic spiroketals bearing alkoxy or siloxy groups less than three carbons removed from the spiroketal nucleus were also readily prepared. However, these proved to be difficult to isolate, and thus in situ transformation of these spirocycles may be required.

The ketene dimers **3a**−**e** used in these epoxidations possess *Z*-olefin geometry, as determined indirectly by Calter and based on the relative stereochemistry confirmed by single-crystal X-ray analysis of spiroepoxy-β-lactone **2b** (Figure 1).[8] As expected, the facial selectivity of epoxidation is governed by steric factors since the major diastereomeric spiro-β-lactone **2b** is derived from epoxidation on the least hindered face opposite the α-substituent.

Scheme 1. Structure of β-Lactones **1** and Proposed Synthesis of Spiroepoxy-β-lactones **2**

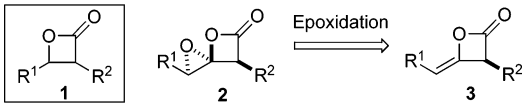
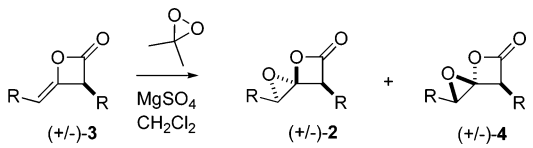


Table 1. Spiroepoxy-β-lactones **2** and **4** Obtained via Epoxidation of Ketene Dimers **3**[a]



entry	R	compound	dr (**2**:**4**)[b]	% yield[c]
1	*n*-Bu	**2a**	14:1	80
2	$CyCH_2$	**2b**	10:1	76
3	$PhCH_2$	**2c**	24:1	57
4	$(i\text{-Pr})_3SiO(CH_2)_4$	**2d**	17:1	40
5	$N_3(CH_2)_4$	**2e**	16:1	61

[a] Epoxidations were performed at ∼0.1 M concentration using isolated, purified ketene dimers **3a**−**e**. [b] Ratios determined by analysis of crude reaction mixtures by ^1H NMR (500 MHz). [c] Refers to isolated, purified (SiO_2) yields.

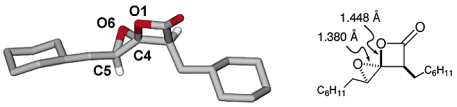


Figure 1. X-ray structure (POV Chem rendering) of epoxy-β-lactone **2b** and derived C−O bond lengths.

Table 2. Comparison of Calculated[a] and Experimentally Determined C−O Bond Lengths (Å) of β-Lactones, Epoxides, Oxetanes, and Spiro Systems

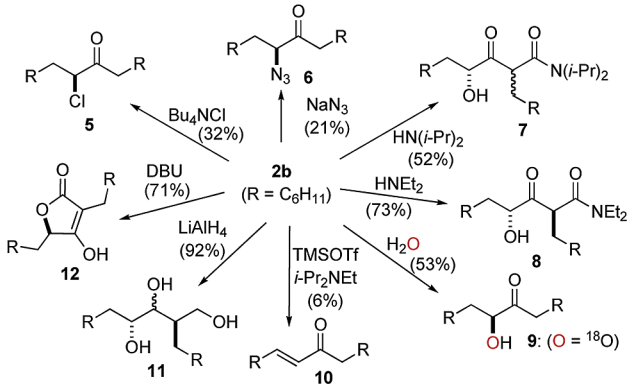
ring system bond[b]							
X1-C4	1.448[c]	1.492[d]	-	1.452[d]	1.415	1.458	1.531
C4-X6	1.380[c]	-	1.446[d]		1.399	1.487	1.423
C4-C5	1.437[c]	-	1.466[d]		1.461	1.487	1.467
C5-X6	1.486[c]	-	-		1.464	1.527	1.445

[a] All bond lengths were calculated (B3LYP/6−31+G**+zpe) unless noted otherwise. [b] X=O or C. [c] From X-ray structure reported herein. [d] Average X-ray derived C−O bond lengths for β-lactones[9] and epoxides.[10]

Analysis of the X-ray structure of spirolactone **2b** revealed that both the epoxide C4−O6 and the β-lactone C4−O1 bonds are significantly shorter compared to average values for the parent systems, Δ0.055[9]and Δ0.044 Å, respectively (Table 2).[10] This could be rationalized based on expected hybridization changes in small

10.1021/ja053478h CCC: $30.25

Scheme 2. Reactions of Spiroepoxy-β-lactones

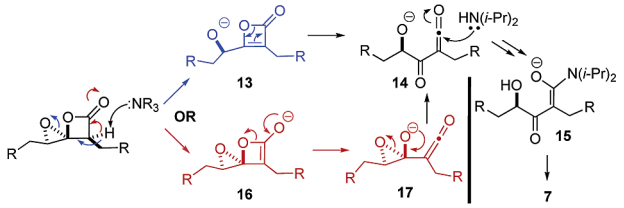


rings leading to increased p-orbital character, which occurs to relieve ring strain and results in concomitant increased s-orbital character in exocyclic bonds leading to shorter bonds. Alternatively, bond shortening could be rationalized by $n\rightarrow\sigma^*$ overlap of an epoxide (O6) and a β-lactone (O1) lone pair with the σ^* orbitals of the C4−O1 and C4−O6 bond of the epoxide and β-lactone, respectively, indicative of a double anomeric effect. Calculations performed on related systems suggest that, while hybridization effects play a role in bond shortening (Table 1), this is insufficient to explain the degree of bond shortening observed, thus pointing to a greater role of anomeric effects. The observed anomeric effects may be more pronounced in these systems due to the rigidity of the spirocycle and may contribute to the unexpected stability of these systems. The C5−O6 bond of the epoxide is also lengthened predictive of the greater reactivity of this bond (vide infra). Further bond length comparisons between these systems and those of spiroepoxycyclobutanes, spirocyclopropyl-β-lactones, and spiroepoxyoxetanes indicate the greatest degree of C4−O6 bond shortening for the present systems also pointing to a double anomeric effect (Table 2).

Initial studies of these spiro systems with nucleophiles reveal some unique reactivity that differs significantly from spiroepoxyoxetanes and spirobisepoxides, including increased stability. Initial reactions to effect regioselective C−O cleavage were unfruitful as several conditions (e.g., TESOTf, Et_3SiH, −78 → 23 °C; KHB(O*i*-Pr)$_3$, THF, −78 °C) only returned starting material. Subsequently, it was found that TMSOTf in conjunction with Hünig's base led to low conversion to enone **10**.[11] Reaction with tetrabutylammonium chloride and sodium azide led to the α-chloroketone **5** and α-azidoketone **6**, respectively, likely resulting from invertive opening of the longer epoxide C5−O6 bond and β-lactone cleavage followed by decarboxylation. Addition of neutral water led to epoxide cleavage, as determined by incorporation of ^{18}O in the hydroxy group of ketone **9** when $H_2{}^{18}O$ was employed. Reduction with $LiAlH_4$ gave triol **11** as expected. In attempts to generate a tertiary amide that would be immune to epimerization at the α-carbon,[12] addition of diisopropylamine provided a 1:1 mixture of *syn:anti* diastereomeric amides **7**. On the other hand, addition of diethylamine led to a single diastereomeric amide **8**. Addition of the non-nucleophilic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), led to butenolide **12** (Scheme 2).

These disparate results taken together suggest a base-induced process proceeding through an intermediate that results in loss of stereochemistry at the α-position. One possibility is α-ketoketene **14** (Scheme 3).[13] Two base-initiated reaction pathways (red and blue arrows) could ultimately lead to this intermediate by stepwise or concerted processes. In the presence of *i*-Pr_2NH, addition to ketoketene **14** could occur leading to a mixture of diastereomeric

Scheme 3. Proposed Mechanistic Pathways for Base-Initiated Transformations of Spiroepoxy-β-lactones Leading to Amide **7**



amides **7** following protonation of the intermediate enolate. With the less sterically demanding diethylamine, classical addition−elimination at the β-lactone carbonyl carbon presumably occurs to provide diethylamide **8** with retention of stereochemistry at the α-carbon. In the presence of DBU, ketene **14** could ultimately provide butenolide **12**; however, other mechanistic scenarios can be envisioned.

In summary, we have synthesized the first examples of spiroepoxy-β-lactones and found them to be surprisingly stable. This may be due to a double anomeric effect garnered from analysis of bond lengths by X-ray crystallography. Initial studies of their reactivity demonstrate interesting potential for these intermediates, and their reactivity contrasts significantly from related systems previously described by Howell[4] and Crandall.[5] At the present time, a limitation is the symmetry of the ketene dimer substrates. We are continuing to explore the unique reactivity of these new spiro systems and their potential as synthetic intermediates and enzyme inhibitors.

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Supporting Information Available: General procedures for epoxidation and subsequent transformations with characterization data (including ^1H and ^{13}C NMR spectra) for ketene dimers **1d**−**e**, spiroepoxy-β-lactones **2a**−**e**, and products **5**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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