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cis-Fused γ-lactones from simple precursors *via* β-lactone rearrangements

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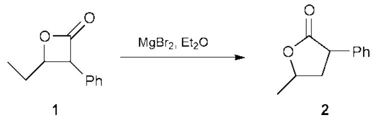
***cis*-Fused bicyclic γ-lactones were prepared in a three step sequence, featuring the stereospecific rearrangement of spiro bicyclic β-lactones; the dependence of the β- to γ-lactone ring expansion on the relative stabilities of the intermediate carbocations was also investigated.**

We have previously demonstrated that β-lactones, such as **1**, undergo ring expansion towards more highly or equally substituted carbon atoms, *via* carbocation rearrangements, to afford γ-lactones **2** (Scheme 1).[1] Moreover, it has also been determined that this ring expansion requires that both migrating bonds bear an antiperiplanar relationship with respect to one another to effect γ-lactone formation.



Scheme 1

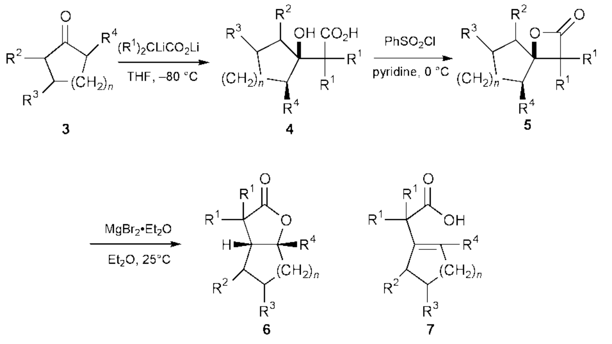
In an effort to further explore the scope and limitations of this very useful transformation, we examined the rearrangement of β-lactones derived from cyclic ketones, carefully selected in order to most accurately ascertain how structural variations within the spiro-bound carbocycle would affect β- to γ-lactone ring expansion reactions.

Scheme 2 depicts the method by which butyrolactones were prepared from simple carbonyl precursors.[2] In this study, the dianion of either isobutyric acid or acetic acid was condensed with cyclic ketones **3** to afford the corresponding β-hydroxy acids **4** in fair to good yields.[3] These acids were subsequently treated with $PhSO_2Cl$ in pyridine for 12 h at 0 °C to provide, in good to excellent yields, spiro bicyclic β-lactones **5**. Treatment of **5** with freshly prepared $MgBr_2$[4] in anhydrous diethyl ether initiated their rearrangement to the fused γ-lactones **6** or, in one case, the corresponding β,γ-unsaturated carboxylic acid **7**.[5] These results are summarized in Table 1.

Table 1 Structural and yield data for Scheme 2

						Isolated yield (%)			
Suffix	**3***n*	R¹	R²	R³	R⁴	**4**	**5**	**6**	**7**
a	1	CH_3	H	H	CH_3	67	85	88	0
b	2	CH_3	H	H	CH_3	63	93	73	0
c	2	H	H	H	CH_3	78	82	84	0
d	2	CH_3	H	H	OCH_3	89	73	85	0
e	2	CH_3	Benzo fused		H	79	67	0	57

The pivotal event in this transformation is the rearrangement of one intermediate tertiary carbocation to another tertiary carbocation; this is followed by annulation to form the γ-lactone ring. The *cis* fusion of these systems, although predicted on mechanistic grounds, could not be determined spectroscopically *a priori*; thus, stereochemical assignment of these compounds was made by analogy to compounds previously reported in the literature. Accordingly, the known[6] γ-lactone **6c** was prepared from the dianion of acetic acid and 2-methylcyclohexanone, **3c**, in 54% overall yield (three steps). This compound was found to have physical and spectral characteristics identical to those previously reported for the *cis* isomer.[4] Moreover, this analog permitted unequivocal stereochemical determination spectroscopically through the use of NOE techniques; these results are summarized in Fig. 1. Irradiation of the methyl group in Fig. 1 led to an NOE enhancement of 7.2% for the adjacent bridgehead proton, while reciprocal irradiation of the bridgehead proton led to an NOE enhancement of 3.7% for the adjacent methyl group. Therefore, compounds **6a,b,d** were also assigned a *cis* ring fusion by analogy.



Scheme 2

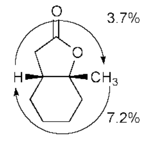


Fig. 1

In only one instance was a fused bicyclic butyrolactone not produced. The rearrangement of spiro bicyclic β-lactone **5e**, derived from α-tetralone, to such an entity, would have required the rearrangement of a tertiary benzylic carbocation to a secondary homobenzylic species. As this is obviously a thermodynamically unfavorable process, elimination occurred instead to provide exclusively β,γ-unsaturated carboxylic acid **7e**.[7]

An interesting observation noted during this investigation was the migration of a hydride, in place of an available methoxy group, in the **5d** to **6d** transformation. Reetz has demonstrated heteroatom migration preferentially to hydride in β-lactone ring expansions, when single bond rotation allows for ready alignment of either.[8] However, in β-lactone **5d**, only the hydrogen is situated in the required antiperiplanar alignment with the lactone ring oxygen; thus, exclusive migration of the hydride occurs in high yield. These reactions are illustrated in Scheme 3. The success of the transformation of **5d** to **6d** bodes very well for future applications as an alternative route for the preparation of γ-*exo*-enol lactones,[9] which are common structural units in natural products possessing a variety of applications.[10] Moreover, this strategy also allows for an alternative preparation[11] of 1,4-dicarbonyl compounds, which are useful

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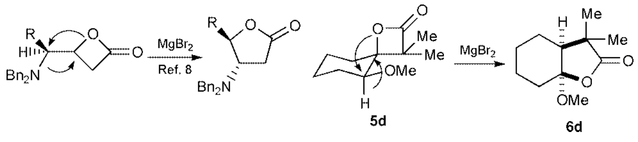

Scheme 3

synthons in natural products synthesis. Future studies of the generality of this procedure are planned, employing different heteroatom substituents in various conformations, to determine the scope and limitations of this potentially very useful new protocol.

In summary, the ability of β-lactones to rearrange to their corresponding butyrolactone derivatives depends upon both the relative stability of the two involved intermediate carbocations and the ability of the migrating bonds to achieve an antiperiplanar relationship. This method has also proved to be very efficient for the preparation of a variety of *cis* fused bicyclic lactones, and provides easy access to these important structural subunits.

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Notes and references

1 (*a*) T. H. Black and W. J. DuBay, *Tetrahedron Lett.*, 1987, **28**, 4787; (*b*) T. H. Black and J. D. Fields, *Synth. Commun.*, 1988, **18**, 125. See also ref. 2.

2 T. H. Black, W. J. DuBay III and P. S. Tully, *J. Org. Chem.*, 1988, **53**, 5922. All precursors were purchased from Aldrich Chemical Co., Inc.

3 These acids were routinely recrystallized (ethyl acetate) prior to lactonization, so that only the predominant (shown) stereoisomer was carried on. In early experiments, the *erythro*:*threo* isomer ratio was determined to be at least 95:5.

4 Note: it is important to use freshly prepared MgBr$_2$ to effect this rearrangement. This is most readily accomplished by treating 1,2-dibromoethane with magnesium metal in anhydrous ether for approximately 1 h prior to the addition of the β-lactone substrate. Employing either commercial MgBr$_2$ or its diethyl ether complex results in considerably lower yields of the γ-lactone.

5 Titanium tetrachloride is the only other Lewis acid found to mediate this transformation, although its much greater acidity occasionally causes undesired side reactions; see T. H. Black, J. A. Hall and R. G. Sheu, *J. Org. Chem.*, 1988, **53**, 2371.

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7 Similar behavior has been observed previously; see T. H. Black, S. A. Eisenbeis, T. S. McDermott and S. L. Maluleka, *Tetrahedron*, 1990, **46**, 2307.

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