Communication

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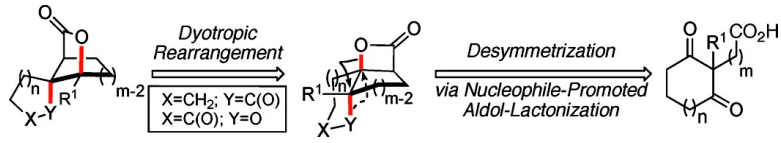

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Concise Synthesis of Spirocyclic, Bridged γ-Butyrolactones via Stereospecific, Dyotropic Rearrangements of β-Lactones Involving 1,2-Acyl and δ-Lactone Migrations

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The simultaneous or stepwise reorganization of functional groups on vicinal carbon atoms via a 1,2-shift constitutes a type I dyotropic rearrangement, a term first proposed by Reetz in 1972.[1] One of the earliest examples of this rearrangement was the mutarotation of vicinal dibromides in steroidal systems first studied by Winstein and Barton.[2] Seminal work by Mulzer employing Lewis acid mediated versions with β-lactone substrates provided insights into the relative migratory aptitude of electron-rich groups in these type I dyotropic rearrangements.[3] A requirement for such a molecular rearrangement is an antiperiplanar relationship between the migrating group and the β-C−O σ-bond of the β-lactone. Subsequent studies by Black[4] and Reetz[5] provided further information on the scope of this process for acyclic systems; however, debate remains regarding the degree of concertedness of the process.[6] We recently reported a biscyclization of ketoacids that provides access to bicyclic and tricyclic β-lactones.[7] Herein, we report the first examples of dyotropic rearrangements involving 1,2-migrations of electron-deficient groups leading to spirocyclic, bridged γ-lactones **3** from fused tricyclic β-lactones **2**, available from diketoacids **1** via biscyclizations (Figure 1). The first asymmetric variant of the latter process is also described.

We began our studies with tricyclic β-lactone **2a** (see Table 1),[8] available from biscyclization of a cyclohexanedione precursor by our previously described procedure.[7,9] We surmised that Lewis acid activation of the β-lactone would promote a dyotropic rearrangement via 1,2-acyl migration, leading to simultaneous, stereospecific[10] ring expansion of the β-lactone to a γ-lactone with concomitant ring contraction of the cyclohexanone. The sole diastereomer isolated from the biscyclization, β-lactone **2a**, possesses the required antiperiplanar relationship between the migrating C_4-O_1 bond of the β-lactone and the $C_5-C{=}O$ bond (relative stereochemistry confirmed by X-ray analysis[9]). Use of commonly employed conditions involving $MgBr_2 \cdot Et_2O$ in Et_2O gave only trace conversion; however, the use of CH_2Cl_2 improved conversion to the expected spiro-γ-lactone (±)-**3a** after 18 h (Table 1, entry 1). Other Lewis acids (e.g., $AlBr_3$, Et_2AlCl, $LaCl_3$, $PrCl_3$, YCl_3) resulted in either complex mixtures or no reaction. Employing $Yb(OTf)_3$ and $In(OTf)_3$ suggested the beneficial effects of triflate over halide ligands (entries 2 and 3). In addition, a major improvement in conversion was realized with Zn(II) salts (entries 4 and 5) and 1.1 equiv of $Zn(OTf)_2$ provided **3a** in 94% yield (entry 6). Substoichiometric amounts of $Zn(OTf)_2$ were ineffective in promoting catalytic turnover on practical time scales (entry 7). Surprisingly, $Mg(OTf)_2$ did not promote this process (entry 8). Inspired by recent studies of Fuchs,[6a] subjecting β-lactone **2a** to catalytic TMSOTf provided only ring-opened diacid **4** (73%, entry 9) suggestive of an intervening Grob-type fragmentation.[11]

Additonal tricyclic β-lactones **2b**−**d**, available in varying yields and diastereoselectivities via biscyclization of dione acids **1b**−**d**,[9] were also studied, and the major diastereomers gave excellent yields of bridged γ-lactones **3b**−**d** (Table 2, entries 2−4) with high stereospecificity (dr >19:1).

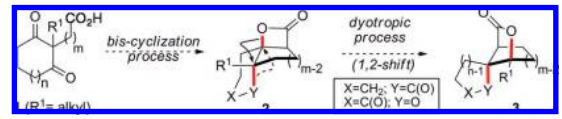
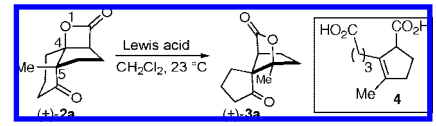


Figure 1. Sequential biscyclization/dyotropic rearrangement route to tricyclic spiro-γ-lactones.

Table 1. Survey of Lewis Acids for Dyotropic Rearrangement of Tricyclic β-Lactone **2a**



entry	Lewis acid[a]	equiv	*T* (°C)	time (h)	% yield (±)-**3a**[b]
1	$MgBr_2 \cdot Et_2O$	1.5	0→23	18	ND[c] (2:1)[d]
2	$Yb(OTf)_3$	1.1	23	12	ND (3:2)[d]
3	$In(OTf)_3$	1.1	23	12	ND (1:9)[d]
4	$ZnCl_2$[e]	1.1	23	1.5	87
5	$ZnBr_2$	1.1	23	1.5	90
6	$Zn(OTf)_2$	1.1	0→23	1.5	94
7	$Zn(OTf)_2$	0.5	0→23	12	ND (1:1)[d]
8	$Mg(OTf)_2$	1.1	23	12	NR[f]
9	TMSOTf	0.2	23	12	(73)[g]

[a] All reactions were conducted at 0.05 M. [b] Refers to isolated yields. [c] ND = not determined. [d] Ratios in parentheses are for **3a**/**2a** as determined by ^1H NMR (500 MHz) analysis of crude reaction mixtures. [e] 1.0 M solution in CH_2Cl_2. [f] NR = no reaction. [g] Yield for diacid **4** accompanied by trace amounts of **3a**.

A plausible synchronous mechanism invokes a two-electron three-centered acylium intermediate **6**,[3] reminiscent of transition states proposed for Friedel−Crafts acylation,[12] or a carboxylate-stabilized, four-membered transition state **7**, both benefiting from a homoconjugated, carbonyl-assisted migration (frangomeric effect) (Figure 2).[13] To the best of our knowledge, 1,2-acyl migrations are unprecedented in type I dyotropic processes. Formation of diacid **4** with TMSOTf (Table 1, entry 9) points to a mechanistic extreme (i.e. **9**) involving a stepwise dyotropic rearrangement leading to Grob-type fragmentation[11] that currently cannot be excluded as a pathway to **3a** when employing Zn(II) Lewis acids.[14]

Toward optically active tricyclic γ-lactones, we prepared β-lactone (−)-**2a** (53%, 97% ee, chiral GC[9]) via nucleophile-promoted desymmetrization of diketone **1a** with stoichiometric tetramisole hydrochloride (Scheme 1), recently employed by Birman for enantioselective acylations.[15] This provides the first direct evidence for nucleophile involvement in the stereochemical setting step of biscyclizations with ketoacid substrates.[7,16] Dyotropic rearrangement then gave γ-lactone (−)-**3a** in excellent yield with high stereochemical fidelity (99% ee, chiral GC).

Finally, we envisioned a 1,2-δ-lactone dyotropic rearrangement with application toward natural product synthesis (Scheme 2). Despite the

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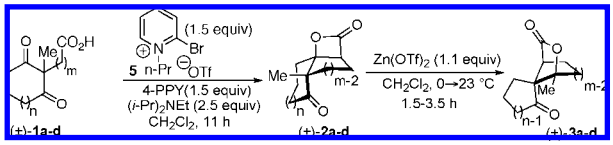
Table 2. Additional Examples of Dyotropic 1,2 Acyl Migration



entry	β-lactone **2**[a]	%yield **2**[b] (dr)[c]	γ-lactone **3**[d]	% yield **3**[b] (dr)[c]
1	(±)-**2a**	93 (>19:1)	(±)-**3a**	94 (>19:1)
2	(±)-**2b**	38 (>19:1)	(±)-**3b**	90[d] (>19:1)
3	(±)-**2c** + (±)-**2c′**	91 (2.5:1)	(±)-**3c**	85[e] (>19:1)
4	(±)-**2d** + (±)-**2d′**	44 (3.7:1)	(±)-**3d**	63[e] (>19:1)

[a] Relative stereochemistry of **2a**, **2b**, **2c**, **2c′**, **3a**, and **3c** was verified by X-ray analysis (ref 9). [b] Refers to isolated yields. [c] Ratios determined by ^{1}H NMR (500 MHz) of crude reaction mixtures. [d] Accompanied by 3% elimination byproduct (see ref 17). [e] Using major diasteromers **2c** and **2d** as substrates.

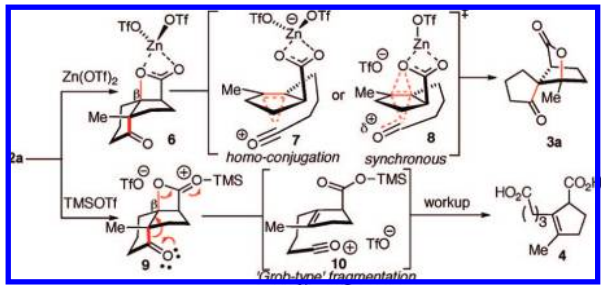
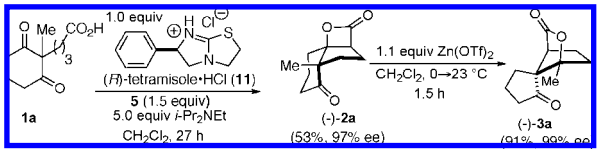


Figure 2. Proposed mechanistic pathways for dyotropic 1,2-acyl shift and Grob-type fragmentation of β-lactone **2a**.

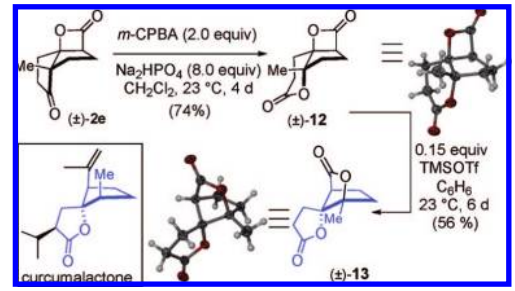
Scheme 1. Enantioselective Biscyclization Process with Diketoacid **1a** and Subsequent Dyotropic Rearrangement



potential reactivity of the β-lactone nucleus, we attempted a Baeyer−Villiger oxidation of β-lactone **2e** using buffered conditions.[6a] Although requiring long reaction times, oxidation proceeded smoothly to give the desired bislactone **12** in 74% yield (X-ray analysis, inset Scheme 2). While conditions described above gave only recovered **12**, a brief survey of Lewis acids led to use of substoichiometric TMSOTf, which slowly produced the desired spiro-γ-lactone **13** constituting the core of curcumalactone (X-ray analysis, inset Scheme 2).

In summary, the repertoire of dyotropic rearrangements with β-lactone substrates has been expanded to include stereospecific 1,2-shifts of both acyl and δ-lactone groups. This process, in conjunction with the enantioselective biscyclization of ketoacids, enables rapid

Scheme 2. Synthesis and Dyotropic Rearrangement of Bislactone **12** (X-ray Structures of **12** and **13** Are Shown) Providing Spiro[5.5]lactone **13**



construction of molecular complexity from simple ketoacid substrates in the form of novel spirocyclic, bridged keto-γ-lactones bearing a quaternary carbon adjacent to a tertiary alcohol center.

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Supporting Information Available: Experimental procedures and characterization data for tricyclic β-lactones **2a**−**d**, spiro-γ-lactones **3a**−**d**, bislactones **12**, **13**, including ^{1}H and ^{13}C NMR spectra, chiral GC traces of (−)-**2a** and (−)-**3a**, and single-crystal X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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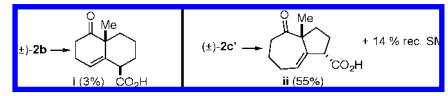

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