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Switching between Concerted and Stepwise Mechanisms for Dyotropic Rearrangements of β-Lactones Leading to Spirocyclic, Bridged γ-Butyrolactones

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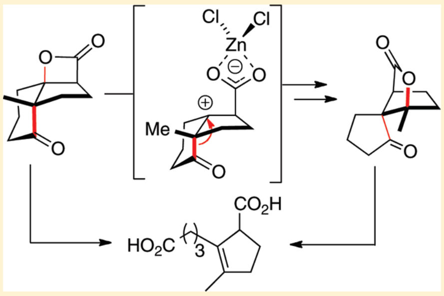
S Supporting Information

ABSTRACT: Quantum chemical computations (B3LYP/6-31+G(d,p)) were applied to examine the mechanisms of dyotropic rearrangements of spirolactones in order to assess whether these reactions are concerted. Mechanistic experiments, designed on the basis of the results of these calculations, support the conclusions derived from theory. In particular, Zn(II) salts or Brønsted acids induce stepwise dyotropic processes, whereas dyotropic rearrangements mediated by silyltriflates are concerted processes. Additional products isolated with Zn(II) salts support a stepwise process with a carbocationic intermediate. Furthermore, a facile Grob-type fragmentation emanating from both a tricyclic-β-lactone and a spiro-γ-lactone was identified.



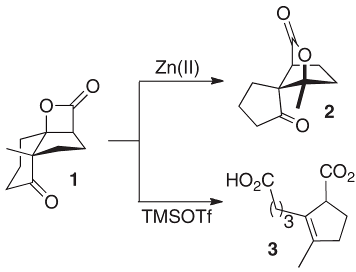
INTRODUCTION

Although dyotropic rearrangements were originally defined as reactions in which "two σ-bonds simultaneously migrate intramolecularly",[1] both concerted and stepwise examples of dyotropic rearrangements have been described.[2] Following seminal reports of a steroid-based dyotropic process by Winstein and Barton,[3] dyotropic reactions have become an important, synthetically useful tool in the field of organic synthesis.[2] For example, this type of reaction has been employed for conversion of silyl amides into *N-cis*-propenyl amides,[4] for the synthesis of stereodefined trisubstituted olefins,[5] and for generation of 1,4,5,8-tetraazanaphthalenes from tetraazafulvalenes.[6]

One of the most widely studied families of dyotropic reactions consists of reactions that generate various γ-butyrolactones from Lewis acid-mediated rearrangements of β-lactones, an area that commenced with seminal reports by Mulzer on the ring expansion of β-lactones through a type I[1] dyotropic process with electron-rich migrating groups.[7] Subsequent reports by Reetz demonstrated the migratory aptitude of acyclic amino groups in β-lactone dyotropic rearrangements to generate 3-amino-γ-lactones,[8] and Cossío reported a dyotropic rearrangement of propiolactones to γ-butyrolactones under similar conditions.[9] Black explored the migration of cyclic alkyl groups with β-lactones to provide a variety of fused γ-butyrolactone systems.[10]

Although β-lactone dyotropic reactions with electron-rich migrating groups are now well-known, we recently reported the first example of an acyl migration in a β-lactone dyotropic process.[11] In our preliminary communication, we reported that a number of Lewis acids, including $ZnCl_2$, $ZnBr_2$, and $Zn(OTf)_2$, could induce β-lactone **1** to undergo dyotropic rearrangement to spirolactone **2** in high yield (Scheme 1).[11,12] Interestingly and

Scheme 1. Spirolactone Rearrangements



unexpectedly, however, the major product of the trimethylsilyl (TMS) activated reaction (using TMSOTf) was diacid **3**, and it was proposed that this product arose via Grob-type fragmentation of TMS-bound **1**.[11] Herein we describe theoretical (B3LYP/6-31+G(d,p))[13] and experimental studies on the dyotropic rearrangements of tricyclic-β-lactones (e.g., **1** → **2**, Scheme 1)[11] that reveal that the concertedness of this intriguing rearrangement depends on the nature of the Lewis acid used to activate the substrate.[14] We also describe a Grob-like fragmentation process that proceeds from both a tricyclic-β-lactone and a spirocyclic-γ-lactone to form a monocyclic diacid.

In this report, we provide computational evidence that these dyotropic processes are stepwise when using Zn(II) Lewis acids, proceeding through a zwitterionic intermediate with carbocationic character; several isolated byproducts support this conclusion. For example, in some cases decarboxylation or simple

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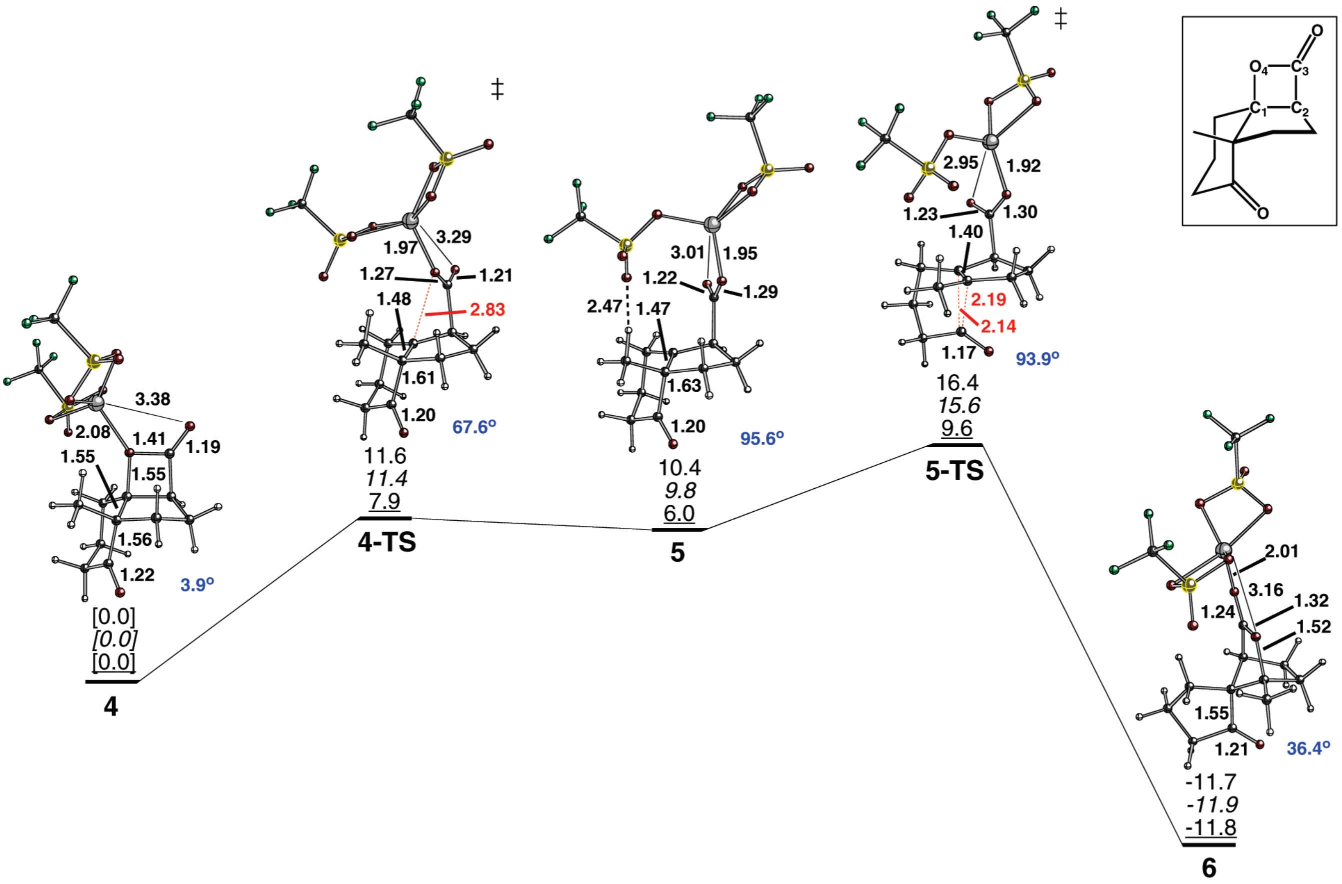


Figure 1. Species involved in the rearrangement of $Zn(OTf)_2$ activated spirolactone **1** (i.e., **4**). Energies shown are in kcal/mol and are relative to the energy of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics; ZPE-corrected solvent (dichloromethane) single point energies underlined).[13] Selected bond lengths are given in Å. C1−C2−C3−O4 dihedral angles (see structure in box) are shown in blue.

eliminative ring opening of the β-lactone was observed. In contrast, calculations indicate that the use of trimethylsilyl activation leads to a concerted dyotropic process. Furthermore, our results suggest that it was activation by trace Brønsted acid, specifically triflic acid, rather than TMSOTf, that led to diacid **3** via fragmentation of both **1** and **2**. Calculations on the acid-promoted fragmentation processes suggest that both **1** and **2** can form **3** with very low barriers.

■ RESULTS AND DISCUSSION

Calculations on the $Zn(OTf)_2$ promoted rearrangement of **1** to **2** reveal that the reaction occurs in a stepwise manner (Figure 1).[15] First, the complexed β-lactone (**4**) opens to form a zwitterionic intermediate (**5**). Zn coordination to both carboxylate oxygens keeps the carboxylate away from the carbocationic center. Note also that during this process a triflate oxygen dissociates from the Zn center, allowing for a weak interaction between Zn and the other carboxylate oxygen (3.01 Å apart) and for a weak interaction between a triflate oxygen and a slightly positively charged hydrogen on the methyl group near to the carbocationic center (2.47 Å apart, see structure **5**). The second step of the rearrangement (**5** → **6**) involves a concerted but asynchronous combination[16] of a 1,2-acyl shift and formation of the γ-lactone.[17] Therefore, three of the four σ-bond-making/breaking events involved in the dyotropic rearrangement (C−C cleavage, C−C formation, C−O formation) are concerted. The fourth (C−O bond cleavage) occurs first, but the energy barrier back from **5** to **4** is very low. Overall, the reaction is predicted to proceed with an activation energy of 16 kcal/mol in the gas phase and is product-favored by 12 kcal/mol. Since charge separation increases from the reactant complex to the intermediate and its flanking transition state structures (Figure 2), a polar solvent should lower the energies of the intermediate and transition state structures relative to that of the reactant complex. Calculations including dichloromethane solvent (which is much more polar than the gas phase; bottom energies in Figure 1) capture this effect, leading to a predicted overall rearrangement barrier of less than 10 kcal/mol. This is consistent with the observed occurrence of the rearrangement in dichloromethane at room temperature and below.[11,15]

$ZnCl_2$ promoted rearrangement of **1** was also examined.[18] To account for the possibility that $ZnCl_2$ might self-associate,[19] both $ZnCl_2$ and $(ZnCl_2)_2$ promoted rearrangements were investigated.[20] In the case of the (monomeric) $ZnCl_2$-promoted rearrangement, both transition state structures were found, and computed barriers were considerably higher (by approximately 10 kcal/mol) than those computed for the dimeric system. Optimization of the last points from intrinsic reaction coordinate calculations on the transition state structures led to species in which CO_2 dissociated, perhaps a result of a flat region on the potential energy surface with multiple low barrier exit channels near the "intermediate".

The pathway found for the $(ZnCl_2)_2$ promoted dyotropic rearrangement is analogous to that found with $Zn(OTf)_2$ (Figure 1).

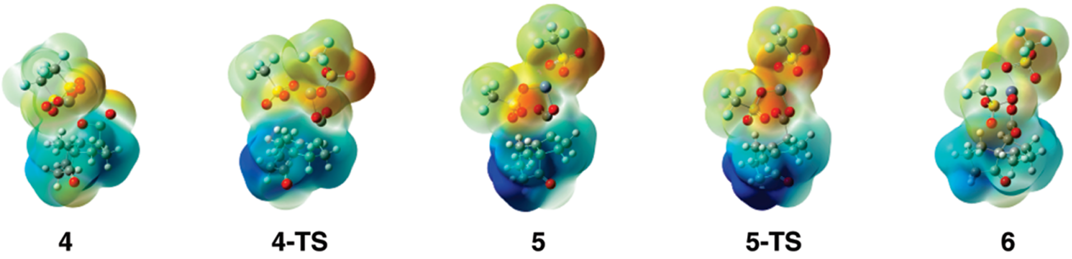
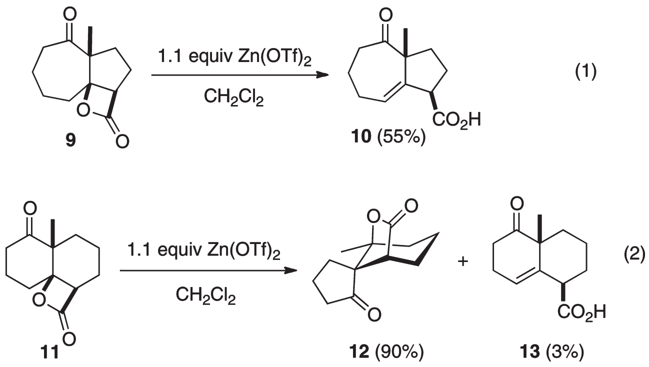
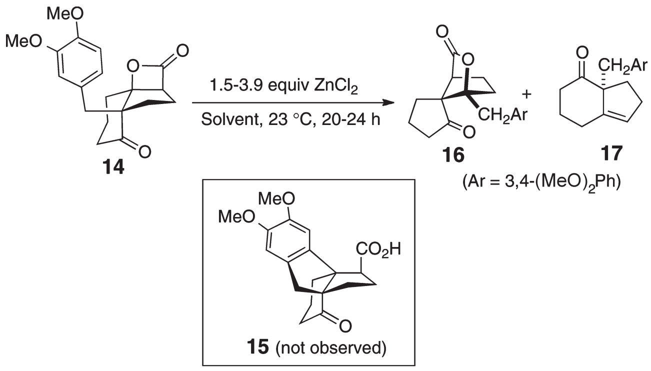


Figure 2. Electrostatic potential surfaces for the five stationary points shown in Figure 1 (blue is most positive and red is most negative; charge range: -5.5×10^{-2} to 5.5×10^{-2}; isovalue: 0.0200).

Scheme 2. Initial Evidence Consistent with Formation of Carbocationic Intermediates in the Dyotropic Process



Scheme 3. Intramolecular Trapping Attempts



entry	solvent	ratio **14** : **16** : **17**[a]
1	CH_2Cl_2	0 : 9 : 1[b]
2	THF	0 : 1 : 2
3	$CHCl_3$	1.3 : 0.6 : 1
4	DMF	1 : 0 : 0.3
5	CH_3CN	0 : 1 : 3[c]

[a] Ratios were determined by ^{1}H NMR (300 MHz). [b] 68% yield of **16** was obtained after column chromatography. [c] 62% yield of **17** was obtained after column chromatography.

Consistent with experimental observations,[11] this reaction is also predicted to be facile at room temperature in dichloromethane (relative energies of [0.0], 7.4, 7.9, 11.0, and −3.9 kcal/mol for the five structures analogous to those in Figure 1; see Supporting Information for additional details).

These computational results predict a stepwise dyotropic process involving a zwitterionic intermediate (a carbocation with a remote complexed carboxylate group) when employing Zn(II) salts as Lewis acids. Experimental evidence for the generation of carbocationic species from β-lactones with Zn(II) salts was described in our initial report.[11] The [7−5−0] tricyclic-β-lactone **9** (Scheme 2), which because of conformational constraints lacks the antiperiplanar relationship between the β-lactone C−O bond and the acyl carbon ideal for concerted dyotropic rearrangement, led to a 55% yield of olefin acid **10**, presumably generated from β-lactone opening to a zwitterionic intermediate and subsequent deprotonation (E1), which we believe is more likely than an E2 mechanism for this substrate. Although under these conditions the [6−6−4] tricyclic β-lactone **11** produced the expected dyotropic product **12** in high yield, trace amounts (3%) of β,γ-unsaturated acid **13** were also produced. Black and Mulzer previously observed similar eliminations with bicyclic-β-lactones.[21] Although these observations do not prove that discrete intermediates are formed in the Zn(II) promoted rearrangements of **1**, they are consistent with such intermediates being formed under the reaction conditions employed herein.

With both computational-and experimental evidence consistent with the formation of carbocationic intermediates in these dyotropic processes, and with the desire to further expand the types of carbocycles available from tricyclic β-lactones, we considered the possibility of trapping the intermediate (Scheme 3). Our initial studies involved attempted intermolecular trapping with either a large excess of veratrole (1,2-dimethoxybenzene)[11] or allyltrimethylsilane (82 equiv, not shown). Both reactions gave only dyotropic rearrangement products with none of the trapped carbocation product detected by crude ^{1}H NMR (300 MHz). We next tried an intramolecular trap using a pendant nucleophilic dimethoxyaryl group, i.e., 3,4-dimethoxybenzyl β-lactone **14**, which would deliver an interesting propellane structure **15** (Scheme 3). Subjecting this substrate to typical dyotropic rearrangement conditions with $ZnCl_2$ in CH_2Cl_2 did not deliver propellane **15** but instead provided the dyotropic product **16** in good yield (Scheme 3, entry 1). These observations are consistent with the computational results, which suggested that the 1,2-acyl shift/carbocation capture process is extremely facile for the [6−5] bicyclic carbocations (e.g., Figure 1), making the intermediate difficult to intercept.

With no success in trapping the proposed intermediate using our standard $ZnCl_2/CH_2Cl_2$ conditions, we explored whether other solvents could increase the lifetime of this intermediate (Scheme 3). We screened a variety of solvents, including THF, $CHCl_3$, DMF, and CH_3CN. While none of the solvents screened provided the desired trapped product **15**, all solvents led to varying amounts of the CO_2 extrusion product **17**, a product that is likely formed from an intermediate with carbocation character.

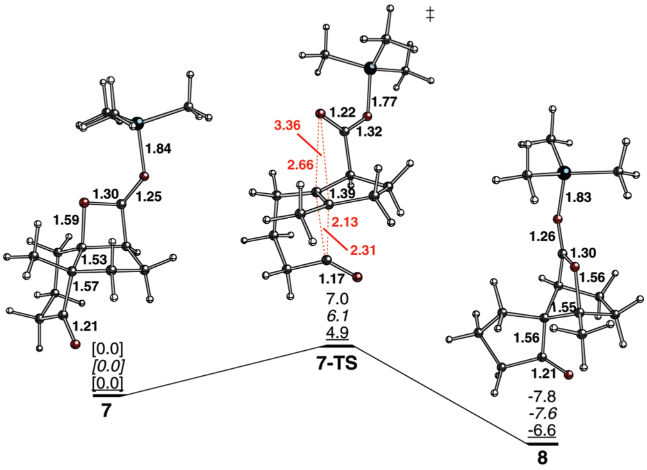
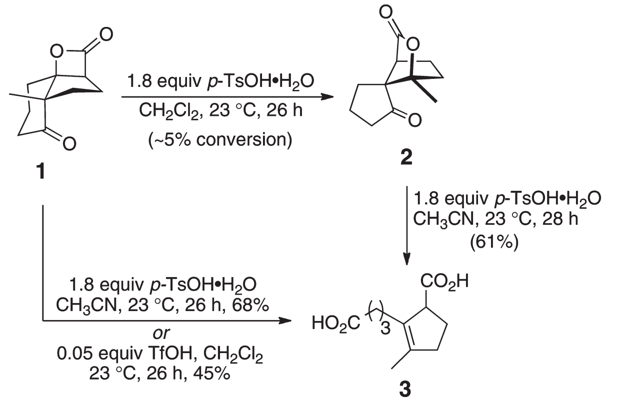


Figure 3. Species involved in the rearrangement of **1**-TMS (i.e., **7**). Energies shown are in kcal/mol and are relative to that of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics; ZPE-corrected solvent (dichloromethane) single point energies underlined).[13] Selected bond lengths are given in Å.

Scheme 4. Brønsted Acid Mediated Fragmentations of 1 and 2

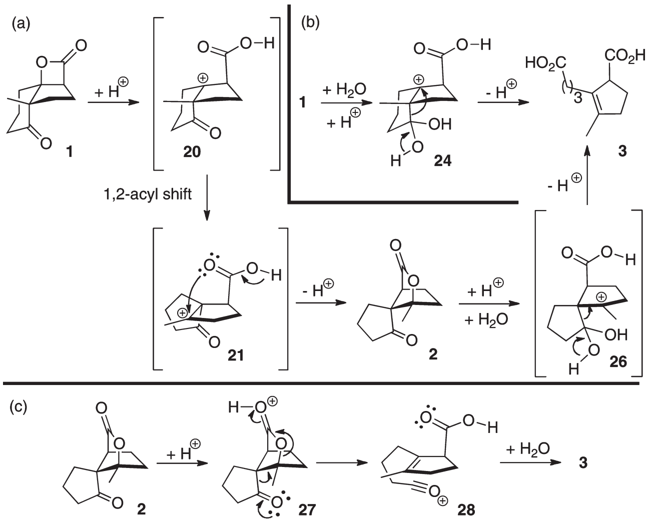


Interestingly, when using CH_3CN as a solvent instead of CH_2Cl_2, elimination product **17** was isolated in good yield with only a small amount of dyotropic product **16** formed (entry 5).

Theoretical examination of the rearrangement of TMS-bound **1** (**7** → **8**; Figure 3) indicated that, unlike the Zn-bound species, this species can undergo a low-barrier *concerted* dyotropic rearrangement.[22] This reaction is predicted to have a barrier of only 6−7 kcal/mol in the gas phase and only 5 kcal/mol in dichloromethane (Figure 3; note that the O−Si interaction is strongest, i.e., the O−Si distance is shortest, in the transition state structure, **7-TS**). These results indicate that the reaction can proceed readily at room temperature to produce the desired γ-lactone, despite the fact that only trace amounts of the γ-lactone product were observed experimentally.[11]

In light of these computational results, we reinvestigated the formation of diacid **3** in the presence of TMSOTf.[11] To our surprise, our previous result could not be reproduced (only recovered starting material was isolated) until *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) was employed. Use of CH_2Cl_2 led to slow conversion to the dyotropic product **2** (~5%, by ^1H NMR), likely as a result of solubility issues of *p*-TsOH·H_2O in this solvent (Scheme 4). However, use of acetonitrile led to smooth conversion to the diacid **3** (68%). Thus, we suggest that the formation of the diacid with TMSOTf observed previously was likely due to adventitious triflic acid and not TMSOTf. This was confirmed by use of 5 mol % TfOH with β-lactone **1** under the original reaction conditions leading to 45% yield of diacid **3** after 26 h (Scheme 4).

Scheme 5. Proposed Mechanistic Pathways for Diacid 3 Formation under Brønsted Acid Conditions from Lactones 1 and 2



These results raise the question of whether diacid **3** is formed from degradation of the dyotropic product **2** or is instead simply generated directly by Grob-type fragmentation of the tricyclic β-lactone **1**.[23] One mechanism invokes initial dyotropic rearrangement (1,2-acyl shift) of fused tricyclic-β-lactone **1** to spiro-γ-lactone **2** and subsequent hydration and elimination via **26** to give the observed diacid **3** (Scheme 5a). Alternatively, direct formation of diacid **3** by acid-promoted β-lactone ring opening and hydration of the ketone leading to carbocation **24** is possible (Scheme 5b). Our initial mechanistic hypothesis invoked an acylium intermediate (Scheme 5c);[11] however, our quantum calculations indicate that this species is ~10 kcal/mol higher in energy than **1**-TMS, suggesting that dyotropic rearrangement is favored over fragmentation. Thus, this mechanistic pathway was not considered further.

To gain insight into these possible mechanistic pathways, we performed calculations on the Brønsted acid promoted rearrangement of **1** to **2**. These calculations revealed that the reaction occurs in a barrierless manner on a flat potential energy surface (**19** → **22**, Figure 4), suggesting that **1** is readily converted to **2** in the presence of a Brønsted acid. Starting from the hydrates of both **19** and **22**, we next explored fragmentation to form diacid **3**.[24] For the hydrate of **19**, structure **23**, fragmentation was found to occur in a stepwise manner (via a carbocation intermediate) with essentially no barrier (Figure 5). Fragmentation of the hydrate of ketone **22**, structure **25**, was also found to proceed in a stepwise manner, with a small barrier (Figure 6). On the basis of these results, it appears that diacid **3** can be formed from fragmentation of both **1** and **2**, although hydration of **1** is likely to be slower than its conversion to **2** (Scheme 5). Spiro-γ-lactone **2** was also submitted to the same reaction conditions over the

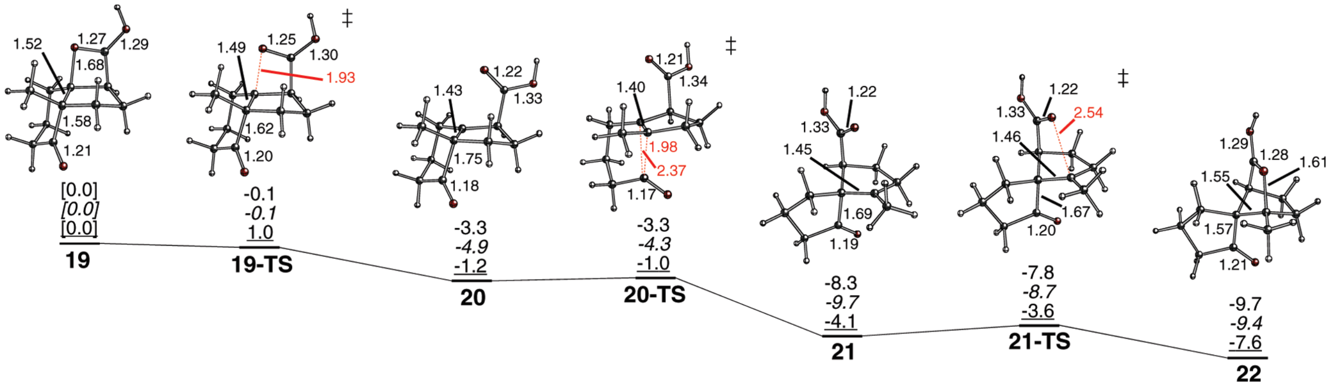


Figure 4. Species involved in the rearrangement of protonated **2** (i.e., **19**). Energies shown are in kcal/mol and are relative to the energy of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics; ZPE-corrected solvent (acetonitrile) single point energies underlined). Selected bond lengths are given in Å.

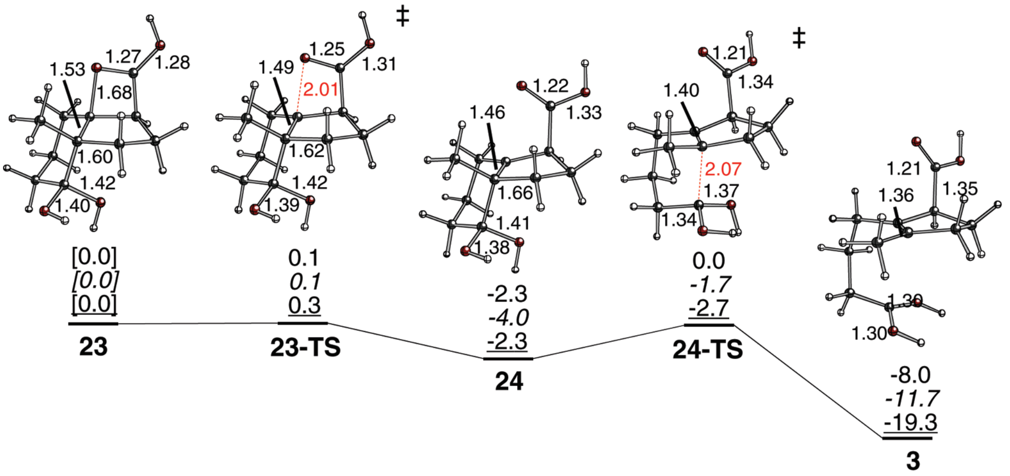


Figure 5. Species involved in the proton activated fragmentation of **23**, the hydrate of **19**. Energies shown are in kcal/mol and are relative to the energy of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics; ZPE-corrected solvent (acetonitrile) single point energies underlined). Selected bond lengths are given in Å.

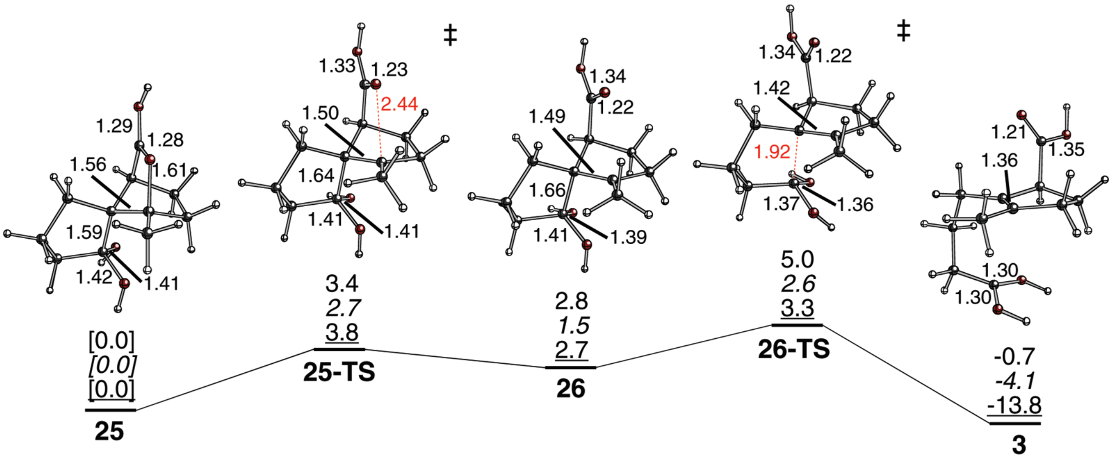


Figure 6. Species involved in the proton activated fragmentation of **25**, the hydrate of **22**. Energies shown are in kcal/mol and are relative to the energy of the reactant complex (ZPE-corrected energies in normal text; free energies at 25 °C in italics; ZPE-corrected solvent (acetonitrile) single point energies underlined). Selected bond lengths are given in Å.

same time frame as fused β-lactone **1** (Scheme 4, right), and the diacid **3** was indeed obtained (61%).

Based on the observed and calculated data suggesting that both β-lactone **1** and γ-lactone **2** can independently be

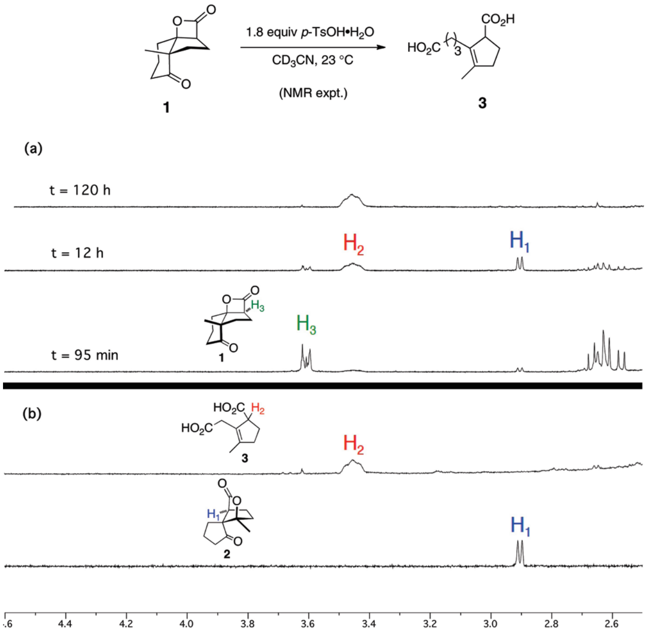


Figure 7. ^{1}H NMR monitoring of Brønsted acid mediated generation of diacid **3** from tricyclic-β-lactone **1**: (a) ^{1}H NMR expansion (δ 2.5−4.5) of Brønsted acid mediated conversion of lactone **1** to diacid **3** after 95 min, 12 h, and 120 h. Signal (H_1) from dyotropic rearrangement product **2** at δ 2.9 appears after 95 min and 12 h and then is absent after 120 h, replaced by H_2 signal of diacid **3**. (b) ^{1}H NMR expansion (δ 2.4−4.5) of authentic samples of diacid **3** and lactone **2** for comparison.

converted to diacid **3** with p-TsOH·H_2O in CH_3CN, we were interested in following the conversion of β-lactone **1** by ^{1}H NMR to determine whether dyotropic product **2** is an intermediate in the conversion of **1** to diacid **3** (Scheme 5, **20**→**21**→**2**→**26**→**3**). NMR studies clearly show initial formation of dyotropic product **2** at multiple time points (Figure 7, t = 95 min and t = 12 h, monitoring H_1, H_2, and H_3) with slower conversion to the diacid **3** after several days (t = 120 h).

Taken together, our calculations and experiments using Zn(II) Lewis acids, a silyl triflate, and Brønsted acids to promote dyotropic rearrangements of tricyclic-β-lactone **1** indicate that the rearrangement mechanism depends on the nature of the activating agent. When Zn(II) Lewis acids are used, a two-step pathway is predicted, perhaps because interactions with both oxygens of the carboxylate group and these Lewis acids can occur, providing some stabilization to the zwitterionic intermediate. This intermediate is very short-lived, however, and is not easily trapped, but it can be deprotonated. A TMS group, however, does not participate in such bridging interactions, and a concerted rearrangement is predicted. Brønsted acids also lead to a facile dyotropic rearrangement that is essentially barrierless and that occurs on a flat potential energy surface, but which may continue further to hydration and a Grob-type fragmentation to provide a diacid. The results described herein provide further information on the mechanistic features of dyotropic rearrangements, which have been a fascinating subject for theoretical studies for many years, and which provide useful synthetic routes to complex polycycles.[2,11,25]

EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane and acetonitrile were purified by passing through activated molecular sieves or alumina, tetrahydrofuran was distilled over sodium and benzophenone, p-TsOH·H_2O was azeotroped from xylenes, and $ZnCl_2$ was fused under vacuum prior to use. Other solvents and reagents were used as received from commercially available sources. ^{1}H NMR and ^{13}C NMR spectra were taken in $CDCl_3$ and recorded at 300 or 500 MHz. ^{1}H NMR chemical shifts were measured at 300 MHz, referenced relative to trace amounts of chloroform (7.26 ppm) or CD_3CN (1.96 ppm), and are reported in parts per million. Coupling constants (J) are reported in Hertz (Hz), with multiplicity following convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; m, multiplet; bs, broad singlet. ^{13}C NMR spectra were measured at 75 MHz and referenced relative to residual chloroform (77.23 ppm) and are reported in parts per million (ppm). Flash column chromatography was performed with 60 Å silica gel (230−400 mesh) as a stationary phase using a gradient solvent system (EtOAc/hexanes as eluant unless indicated otherwise). Thin layer chromatography (TLC) was performed using glass-backed silica gel F254 (250 μm thickness). Visualization of developed plates was performed by fluorescence quenching or by staining with potassium permanganate ($KMnO_4$) or Hanessian's (CAM) stain. Infrared spectra were obtained as thin film on NaCl plates on a FTIR spectrometer.

Representative Procedure for Dyotropic Rearrangement of (±)-14 to (±)-16 as Described Using $ZnCl_2$/CH_2Cl_2. To a stirred suspension of $ZnCl_2$ (23.0 mg, 0.17 mmol, 1.48 equiv) in CH_2Cl_2 (1.25 mL) at 0 °C under a N_2 atmosphere was added a solution of β-lactone (±)-**14**[25] (22.3 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) dropwise by syringe. The heterogeneous reaction was stirred at 0 °C for 10 min then warmed to 23 °C and stirred for 24 h. The reaction mixture was filtered through a short plug of Celite and SiO_2 and eluted with additional CH_2Cl_2 (∼1 mL). The combined filtrates were concentrated under reduced pressure to provide 15.1 mg (68%) of (±)-**16** as a white solid containing a trace amount of (±)-**17**. (±)-**16**: R_f = 0.41 (50% EtOAc/hexanes); IR (thin film) 2956, 1782, 1730, 1516, 1457, 1258, 1239, 1144, 1027, and 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55−1.65 (m, 1H), 1.81−2.53 (m, 9H), 2.60 (d, J = 14.4 Hz, 1H), 2.82−2.95 (m, 1H), 3.18 (d, J = 14.4 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), and 6.75−6.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.6, 176.1, 148.9, 148.4, 127.8, 122.4, 113.4, 111.2, 94.7, 64.9, 56.18, 56.10, 52.0, 40.1, 36.4, 31.2, 28.4, 21.0, and 19.1; HRMS (ESI+) calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545, found 331.1560.

Conversion of (±)-14 to (±)-16 and (±)-17 Using $ZnCl_2$/CH_3CN. Compounds (±)-**16** and (±)-**17** were generated following the representative procedure described above from (±)-**14** (10 mg, 0.030 mmol, 1.0 equiv) using $ZnCl_2$ (15.5 mg, 0.114 mmol, 3.8 equiv) and anhydrous CH_3CN (1.4 mL). The homogeneous reaction was stirred for 20 h at 23 °C and then filtered over Celite/SiO_2 as described above. Crude ^{1}H NMR ($CDCl_3$, 300 MHz) showed a 1:3 ratio of **16** to **17**. The mixture was submitted to flash column chromatography (40% EtOAc/hexanes) yielding 1.8 mg (18%) of (±)-**16** as a white solid and 5.3 mg (62%) of (±)-**17** as a clear oil. (±)-**17**: R_f = 0.59 (40% EtOAc/hexanes); IR (thin film) 2935, 2850, 1709, 1522, 1456, 1263, 1238, 1142, and 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52−1.68 (m, 2H) 1.86−1.92 (m, 2H), 2.04−2.13 (m, 1H), 2.16−2.26 (m, 1H), 2.39−2.61 (m, 3H), 2.63−2.74 (m, 1H), 2.80 (d, J = 13.5 Hz, 1H), 2.92 (d, J = 13.5 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 5.37−5.39 (m, 1H), and 6.63−6.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.9, 148.4, 148.0, 144.7, 129.7, 125.9, 122.3, 113.5, 111.0, 66.6, 56.0 (2); 41.9, 39.3, 29.8, 29.2, 26.1, and 25.9; HRMS (ESI+) calcd for $C_{18}H_{23}O_3$ $[M + H]^+$ 287.1647, found 287.1660.

Conversion of (±)-14 to (±)-16 and (±)-17 Using $ZnCl_2$/THF. Compounds (±)-**16** and (±)-**17** were generated following the representative procedure described above from (±)-**14** (10 mg, 0.030 mmol, 1.0 equiv) using $ZnCl_2$ (15.4 mg, 0.110 mmol, 3.7 equiv) and anhydrous THF (1.4 mL). The homogeneous reaction was stirred for 20 h at 23 °C then filtered over Celite/SiO_2 as described above. Crude ^1H NMR ($CDCl_3$, 300 MHz) showed a 1:2 ratio of (±)-**16** to (±)-**17**.

Conversion of (±)-14 to (±)-16 and (±)-17 Using $ZnCl_2$/$CHCl_3$. Compounds (±)-**16** and (±)-**17** were generated following the representative procedure described above from (±)-**14** (10 mg, 0.030 mmol, 1.0 equiv) using $ZnCl_2$ (16.1 mg, 0.118 mmol, 3.9 equiv) and anhydrous $CHCl_3$ (1.4 mL). The heterogeneous reaction was stirred for 20 h at 23 °C then filtered over Celite/SiO_2 as described above. Crude ^1H NMR ($CDCl_3$, 300 MHz) showed a 1.3:0.6:1 ratio of products **14**:**16**:**17**, respectively.

Conversion of (±)-14 to (±)-16 and (±)-17 Using $ZnCl_2$/DMF. Compounds (±)-**16** and (±)-**17** were generated following the representative procedure described above from (±)-**14** (10 mg, 0.030 mmol, 1.0 equiv) using $ZnCl_2$ (15.9 mg, 0.117 mmol, 3.9 equiv) and anhydrous DMF (1.4 mL). The homogeneous reaction was stirred for 20 h at 23 °C then filtered over Celite/SiO_2 as described above. Crude ^1H NMR ($CDCl_3$, 300 MHz) showed a 1:0.3 ratio of unreacted starting material **14** to **17**.

Procedure for Formation of (±)-2 with *p*-TsOH·H_2O/CH_2Cl_2. To a 1-dram vial containing a magnetic stir bar were added β-lactone (±)-**1** (15.0 mg, 0.077 mmol, 1.0 equiv) and *p*-TsOH·H_2O (27.0 mg, 0.142 mmol, 1.8 equiv). CH_2Cl_2 (1.5 mL) was added, and the heterogeneous reaction mixture was vigorously stirred in the sealed vial at 23 °C under a N_2 atmosphere for 26 h. The reaction mixture was diluted with brine (~1 mL) and H_2O (~1 mL), the organic layer was removed by pipet, and the aqueous layer was washed with additional CH_2Cl_2 (~1 mL). The combined organic layers were dried over Na_2SO_4, removed by pipet, filtered through a short pipet containing a plug of cotton and Celite, and eluted with additional CH_2Cl_2 (0.5 mL). Concentration under reduced pressure provided 14.0 mg of a 20:1 ratio of starting material (±)-**1** and spirolactone (±)-**2** as determined by ^1H NMR ($CDCl_3$, 300 MHz). ^1H NMR spectral data of the components in the crude mixture matched that previously reported.[11]

Procedure for Formation of Diacid (±)-3 from Tricyclic β-Lactone (±)-1. To a 1-dram vial containing a magnetic stir bar were added β-lactone (±)-**1** (15.0 mg, 0.077 mmol, 1.0 equiv) and *p*-TsOH·H_2O (27.0 mg, 0.142 mmol, 1.8 equiv). The mixture was dissolved in CH_3CN (1.5 mL,) and the homogeneous reaction mixture was stirred in the sealed vial at 23 °C under a N_2 atmosphere for 26 h. After concentration en vacuo, the residue was redissolved in CH_2Cl_2 (~1 mL). To the resulting suspension were added brine (~1 mL) and H_2O (~1 mL). The organic layer was removed by pipet, and the aqueous layer was washed with additional CH_2Cl_2 (~1 mL). The combined organic layers were dried over Na_2SO_4, removed by pipet, filtered through a short pipet containing a plug of cotton and Celite, and eluted with additional CH_2Cl_2 (0.5 mL). Concentration under reduced pressure provided 11.1 mg (68% yield) of diacid (±)-**3** as a slightly brown oil, requiring no further purification. Characterization data matched that previously reported for this compound.[11]

Procedure for Formation of Diacid (±)-3 from Spirolactone (±)-2. To a 1-dram vial containing a magnetic stir bar were added spirolactone (±)-**2** (11.0 mg, 0.057 mmol, 1.0 equiv) and *p*-TsOH·H_2O (19.8 mg, 0.104 mmol, 1.8 equiv). The mixture was dissolved in CH_3CN (1.1 mL), and the homogeneous reaction mixture was stirred in the sealed vial at 23 °C under a N_2 atmosphere for 26 h. After concentration en vacuo, the residue was redissolved in CH_2Cl_2 (~1 mL). To the resulting suspension was added brine (~0.75 mL) followed by H_2O (~ 0.5 mL). The organic layer was removed by pipet, and the aqueous layer was washed with additional CH_2Cl_2 (~1 mL). The combined organic layers were dried over Na_2SO_4, removed by pipet, filtered through a short pipet containing a plug of cotton and Celite, and eluted with additional CH_2Cl_2 (0.5 mL). Concentration under reduced pressure provided 7.4 mg (61% yield) of diacid (±)-**3** as a slightly brown oil, requiring no further purification. Characterization data matched that previously reported for this compound.[11]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Additional details on experiments and computations, including energies and coordinates for all minima and transition state structures, IRC plots, full *GAUSSIAN03* reference, spectral data (^1H and ^{13}C NMR) for compounds **16** and **17**, and full spectra (NMR monitoring) of the conversion of **1** and **2** to **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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