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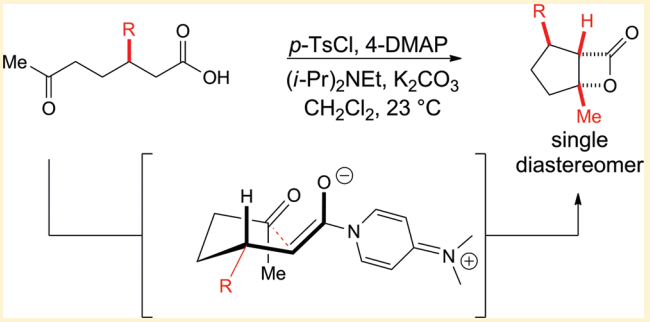
A Diastereoselective, Nucleophile-Promoted Aldol-Lactonization of Ketoacids Leading to Bicyclic-β-Lactones

Gang Liu, Morgan E. Shirley, and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012, United States

Supporting Information

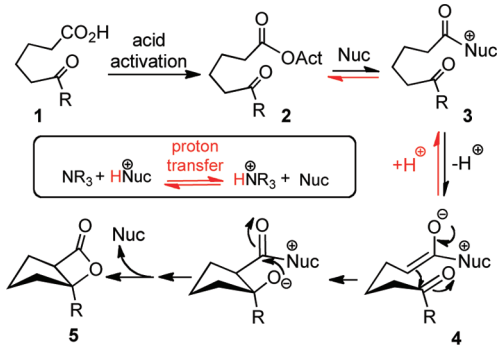
ABSTRACT: An improved, tandem acid activation/aldol-lactonization process is described. This more practical protocol shortens reaction times for the construction of bicyclic β-lactones from ketoacids and implements the use of commercially available reagents *p*-toluenesulfonyl chloride (*p*-TsCl) as activator and 4-dimethylaminopyridine (4-DMAP) as nucleophilic promoter (Lewis base). Substrates with β-substituents, with respect to the carboxylic acid, consistently showed excellent levels of diastereoselectivity during the bis-cyclization event.



As a class of structurally unique heterocycles, β-lactones continue to be the subject of intensive studies in organic synthesis with a focus on the development of concise strategies for their construction[1,2] and, more recently, the exploration of their utility as synthetic intermediates to more advanced structures.[3] The importance of β-lactones for biological chemistry is highlighted by the presence of this motif in numerous bioactive natural products[4,5] and a growing number of pharmaceutical agents. Our interest in β-lactone chemistry has focused on the construction of polycyclic fused β-lactones from ketoacids or aldehyde-acids via a nucleophile-catalyzed aldol lactonization (NCAL) process and the application of this C−C bond forming strategy in the assembly of complex natural products.[6] In the context of our recent total synthesis of (+)-omphadiol,[6f] we explored ways to add greater practicality to our established NCAL process, and these studies led to a highly improved, convenient synthetic process that is described herein.

As shown in Scheme 1, the aldol-lactonization process is proposed to involve an acyl ammonium species **3** and, following deprotonation, an ammonium enolate **4**. An aldol process followed by lactonization provides the β-lactone product **5**. While ketene intermediates can be invoked for this process, the high diastereoselectivity observed with β-substituted acid substrates is only rationalized via the intermediacy of an ammonium enolate leading to $A^{1,3}$-strain in transition states (vide infra).[7] Our previously reported procedure using linear ketoacid substrates produced fused bicyclic β-lactones with moderate to good yields after extended reaction times.[8] Analysis of our working mechanistic pathway for the NCAL process to rationalize the slow reaction rate revealed a possible deleterious equilibrium between the tertiary amine used as a Bronsted base and the amine employed as a Lewis base (inset, Scheme 1). This is related to observations made by Lectka[1f,9] in similar processes that render the Lewis

Scheme 1. Proposed Mechanistic Pathway for the Nucleophile Catalyzed Aldol-Lactonization



base non-nucleophilic due to its protonation state. Furthermore, the reversibility of the deprotonation step (**3** → **4**) and possibly to a lesser extent formation of the acyl ammonium species (**2** → **3**) could both significantly retard the reaction rate.

The readily accessed ketoacid **6a** derived from (*R*)-carvone in two steps, and a key intermediate in our recent synthesis of (+)-omphadiol,[6f] was used to screen conditions to improve reaction rates and improve practicality (Table 1). After a brief exploration of stoichiometric, insoluble bases, potassium carbonate emerged as the optimal base when compared to others tested (NaH, Na_2CO_3, and Li_2CO_3) as previously observed by Lectka.[1f,9] Under our previously described conditions,[8] the desired bicyclic product was obtained in only 42% yield after 24 h (Table 1, entry 3). The use of potassium carbonate in combination with $(i\text{-Pr})_2$NEt as a "shuttle" base[1f,9]

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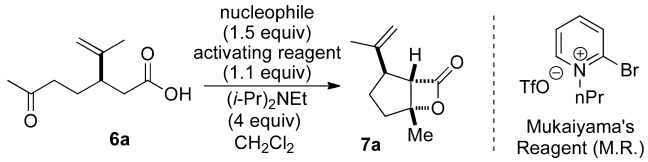
Table 1. Optimization of a Practical Nucleophile Promoted Aldol-Lactonization



entry	activating agent	nucleophile	additive	yield[a] (%)
1	M.R.	4-PPY	–	55
2	M.R.	4-PPY	K_2CO_3	69
3	*p*-TsCl	4-PPY	–	42
4	*p*-TsCl	4-PPY	K_2CO_3	73
5	*p*-TsCl	4-DMAP	K_2CO_3	76[b]
6	*p*-TsCl	NMI	K_2CO_3	<5

[a]Refers to isolated yields after column chromatography. [b]Performed on 8 g scale (of **6a**).

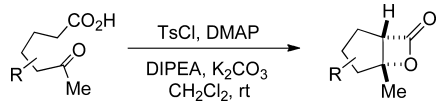
led to an increase in yield to 69% and dramatic reduction in reaction time to 2 h (Table 1, entry 2).

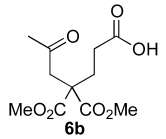
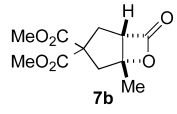
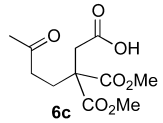
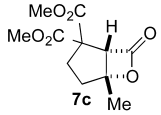
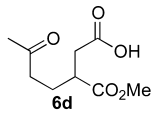
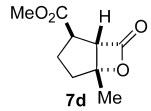
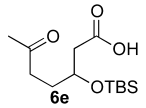
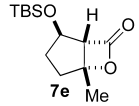
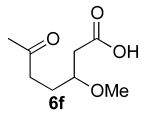
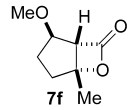
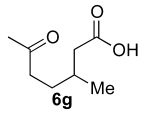
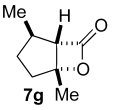
Having improved the rate of the bis-cyclization process, we also sought to explore the use of alternative carboxylic acid activating agents to avoid preparation of the modified Mukaiyama's reagent (M.R., Table 1) which we previously found to be optimal for the NCAL process.[6b] To address this issue, we explored alternative activating agents and found that *p*-tosyl chloride (*p*-TsCl) was a useful alternative to modified Mukaiyama's reagent (Table 1, entries 1 and 3). Use of *p*-TsCl without an additional insoluble base gave a 42% yield of *β*-lactone **7a**; however, once again, use of K_2CO_3 provided a clear advantage in terms of conversion providing a 73% yield (Table 1, entries 3 and 4).

Another salient reaction parameter is the nucleophilicity of the Lewis base, which plays a crucial role in the kinetics of the NCAL process. Previously, we noted that the NCAL process with aldehyde-acids could be mediated by cinchona alkaloids bearing a quiniculidine-type tertiary amine.[6a] In contrast, a stronger and more planar nucleophile, 4-pyrrolidinopyridine (4-PPY), was most effective for the bis-cyclization of ketoacids.[8] The cost of 4-PPY relative to other potential nucleophilic amines and the hygroscopic nature of this reagent led us to explore alternatives. Previously, we reported that while 4-*N*,*N*′-dimethylaminopyridine (4-DMAP) exhibited useful reactivity for the NCAL process with ketoacids, 4-PPY was superior in providing the highest yields of bicyclic *β*-lactones.[8] Utilizing the improved reaction conditions described above, we found that less expensive 4-DMAP promotes the bis-cyclization in yields comparable to those obtained with 4-PPY (Table 1, compare entries 4 and 5). *N*-Methylimidazole (NMI) was also explored but did not afford an appreciable amount of *β*-lactone **7a** (Table 1, entry 6). Deviation from these reaction conditions by altering the solvent from dichloromethane to diethyl ether, toluene, or acetonitrile did not improve conversion. This improved procedure renders a range of ketoacids suitable substrates for the bis-cyclization leading to a series of bicyclic *β*-lactones in useful yields (Table 2).

Ketoacids bearing *γ*- and *β*-diester substituents, with respect to the carboxylic acid functionality, gave moderate to good yields in short reaction times (Table 2, entries 1 and 2), presumably assisted by the *gem*-disubstituent effect. Among the monosubstituted substrates, *β*-substituted acids were found to be unique in providing high diastereoselectivity as previously observed.[8] Ketoacid substrates with various substituents at this position ranging from methyl ester (entry 3), silyloxy (entry 4),

Table 2. Practical Nucleophile Promoted Aldol-Lactonization of Ketoacids Mediated by 4-DMAP



entry[a]	ketoacid	β-lactone	time (h)	yield (%)[b]
1	 **6b**	 **7b**	0.5	81
2	 **6c**	 **7c**	0.5	67
3	 **6d**	 **7d**	1	75
4	 **6e**	 **7e**	2	68
5	 **6f**	 **7f**	2	64
6	 **6g**	 **7g**	6	57

[a]General reaction conditions: 4-DMAP (1.5 equiv), *p*-TsCl (1.1 equiv), DIPEA (4.0 equiv), K_2CO_3 (3.0 equiv), CH_2Cl_2, 23 °C (= rt). Diastereoselectivity of entries 3–6 is >19:1 as judged by 500 MHz H^1NMR. [b]Values refer to isolated yields after column chromatography (DIPEA = *N*,*N*-diisopropylethylamine).

methoxy (entry 5), and alkyl groups (entry 6) all gave the corresponding bicyclic *β*-lactones **7d–g** with high diastereoselectivity (>19:1 dr, judged by 500 MHz ^{1}H NMR) delivering the *anti* diastereomers **12** (Scheme 2).

The high diastereoselectivity observed with *β*-substituted acid substrates can be rationalized on the basis of the proposed transition-state arrangements for the aldol-lactonization process

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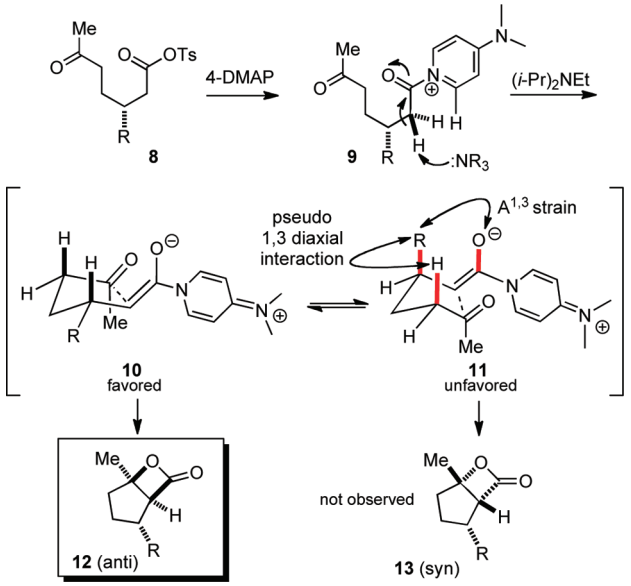
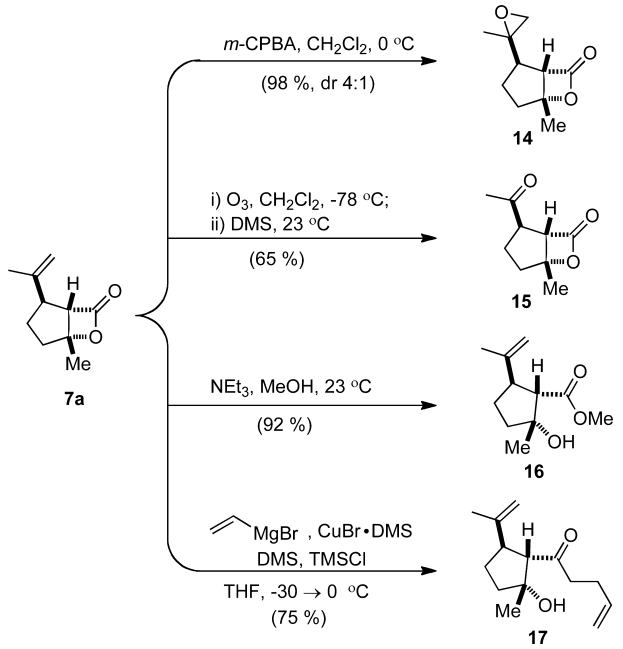
Scheme 2. Rationale for High Diastereoselectivity with β-Substituted Ketoacids in the Aldol-Lactonization Process



Scheme 3. Transformations of β-Lactone 7a



(Scheme 2). Following formation of the acylammonium species **9**, generated by nucleophilic addition to the activated acid by the Lewis base promoter, deprotonation leads to an ammonium enolate, which can exist in two reactive conformations, **10** and **11**. Note that the olefin geometry of the enolate has not been assigned but expected to the *Z*(O)-ammonium enolate which minimizes developing torsional strain with the *ortho*-hydrogens of the pyridine ring during the deprotonation step (see structure **9**). This leads to two possible transition-state arrangements **10**/**11**, and in the higher energy arrangement **11**, the β-substituent (R) is pseudoaxial and a further unfavorable1,3-allylic interaction is present in this conformation. The absence of these unfavorable steric interactions in transition-state arrangement **10** leads to this conformation being the lower energy pathway and the formation of the *anti*-substituted cyclopentane.

To further demonstrate the utility of this practical, diastereoselective β-lactone synthesis, β-lactone **7a** was subjected to further manipulations to increase functionality and probe the stability of these bicyclic β-lactones (Scheme 3). Oxidative conditions were found to be compatible with the β-lactone moiety since epoxidation of the pendant olefin with *m*-CPBA (*m*-chloroperoxybenzoic acid) afforded the corresponding epoxide **14** with excellent yields (98%) with moderate diastereoselectivity (dr 4:1). In addition, ozonolysis of the olefin under standard conditions delivered the methyl ketone **15** in 65% yield. The utility of the β-lactone as a masked aldol adduct was revealed upon mild alcoholysis to give β-hydroxyl methyl ester **16** in high yield (92%). The electrophilicity of the β-lactone carbonyl was further exploited by a tandem double addition of a vinyl copper species to deliver the γ,δ-enone **17** via a four-carbon homologation.[10,11] This useful homologation demonstrates the synthetic utility of β-lactones beyond their use as simple surrogates of ester aldol products. Importantly, these transformations do not lead to α-epimerization of the ester or ketone, respectively.

In summary, a practical nucleophile-promoted, aldol lactonization of ketoacids is described that renders this process much more amenable to scale-up as demonstrated by the ∼5 g synthesis of β-lactone **7a**. The improved procedure utilizes potassium carbonate as a stoichiometric, insoluble base to accelerate the reaction and further improvements using commercially available, inexpensive reagents provided rapid access to a series of bicyclic β-lactones. The high diastereoselectivity observed for β-substituted ketoacid substrates renders this procedure a very reliable method for the rapid construction of complex, substituted five-membered carbocycles. As a complement to a fully catalyst-controlled enantioselective cyclization of nonchiral ketoacid substrates recently reported[6c] using homobenzotetramisole,[12] this highly substrate-controlled, bis-cyclization process of ketoacids allows a stereochemical relay of a single substituent to two new stereogenic centers. Further exploration of this chemistry and applications to complex molecule synthesis is underway.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Dichloromethane, methanol, and diethyl ether were purified by passage through activated molecular sieves or alumina (solvent system). Tetrahydrofuran was freshly distilled over sodium and benzophenone. All commercial reagents were used as received. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.26 ppm,), coupling constants (*J*) are reported in hertz (Hz), and multiplicity follows convention. Deuterated chloroform ($CDCl_3$) served as an internal standard (77.16 ppm) for all ^{13}C spectra. Flash column chromatography was performed using 60 Å silica gel (Baker, 230−400 mesh or Silacycle, 230−400 mesh) as a stationary phase. Thin-layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (Merck, 250 μm thickness).

Hazard Warning. Ozonides produced from the oxidative cleavage were reduced using excess dimethyl sulfide. Stirring for at least 9 h at 23 °C prior to workup ensured complete ozonide reduction however an ozonide test is recommended.[13]

3-(Methoxycarbonyl)-6-oxoheptanoic Acid (6d). A mixture of **6c** (461 mg, 1.77 mmol) and NaCl (200 mg) in DMSO (5 mL) and H_2O (0.5 mL) was heated to 160 °C for 30 min. The reaction was then cooled to 23 °C, diluted with H_2O, washed with EtOAc, and purified by flash column chromatography (SiO_2, eluting with 30 →

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70% EtOAc/hexanes) to afford **6d** as a colorless liquid (121 mg, 34%): IR (thin film) 2988, 2947, 1734, 1723, 1651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 1H), 3.68 (s, 3H), 2.74 (m, 2H), 2.51(m, 3H), 2.13 (s, 3H), 1.84 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 174.6, 170.4, 52.0, 40.5, 40.0, 35.8, 29.9, 25.3; HRMS (ESI+) calcd for $C_9H_{15}O_5$ (M + H) 203.0919, found 203.0994.

3-Methoxy-6-oxoheptanoic Acid (6f). Ethyl 3-hydroxy-6-methylhept-6-enoate[14] (0.90 g, 4.8 mmol) was dissolved in 8 mL of CH_2Cl_2 along with 0.1 g of 4 Å powdered molecular sieves and Proton Sponge (0.37 g, 1.7 mmol). The flask was then wrapped in foil, trimethyloxonium tetrafluoroborate (0.25 g, 1.7 mmol) was added, the resulting mixture was stirred overnight (~8 h). After completion of the reaction, 1 mL of 2-propanol was added, and the reaction mixture was extracted with $NaHCO_3$ (3 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was of sufficient purity to carry on. It was redissolved in 5 mL of methanol and 1 mL of 2 M NaOH and heated to 65 °C for 3 h. After 3 h, it was cooled to 23 °C, acidified with 1 M HCl, and diluted with 8 mL of ethyl acetate. The organic layer was washed with brine (1 × 5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting compound, 3-methoxy-6-methylhept-6-enoic acid, was dissolved in 9 mL of CH_2Cl_2 and cooled to −78 °C, at which point ozone was bubbled through the solution until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated, at which time dimethyl sulfide (0.3 mL, 4.0 mmol) was added and the reaction was allowed to stir overnight (10 h) while warming to 23 °C. The solution was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) to afford ketoacid **6f** as a pale yellow liquid (0.15 g, 43% over three steps): IR (thin film) 3128, 2936, 2373, 2334, 1708 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 3.68−3.63 (m, 1H), 3.34 (s, 3H), 2.60−2.51 (m, 3H), 2.44 (ddd, J = 15.5, 5.6, 0.9 Hz, 1H), 2.14 (s, 3H), 1.90 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 176.3, 76.4, 57.0, 38.9, 38.8, 30.0, 27.4; HRMS (ESI+) calcd. for $C_8H_{14}O_{4Li}$ (M + Li) 181.1052, found 181.1049.

Representative Procedure for 4-DMAP Promoted Aldol-Lactonization of Ketoacids: (1*S*,2*R*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)-6-oxabicyclo[3.2.0]heptan-7-one (7a). To a mixture of TsCl (9.12 g, 47.9 mmol), 4-DMAP (8.0 g, 65.4 mmol), and *N*,*N*-diisopropylethylamine (30.5 mL, 174 mmol) in CH_2Cl_2 (80 mL) was added a solution of ketoacid **6a** (8.02 g, 43.6 mmol) in CH_2Cl_2 (10 mL) dropwise. The reaction mixture was stirred at 23 °C for 1 h, and then powdered anhydrous K_2CO_3 (18.1 g, 131 mmol) was added in one portion. The reaction slurry was stirred at 23 °C for 4 h and then diluted with hexanes and passed through a pad of silica gel to remove excess solids. The volatiles were removed by rotary evaporator, and the residue was purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) to afford β-lactone **7a** as a colorless liquid (5.50 g, 76%). All spectral data were in accordance with that previously reported.[6f]

Dimethyl 5-Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate (7b). β-Lactone **7b** was prepared according to the representative procedure from ketoacid **6b** (47 mg, 0.18 mmol), *p*-TsCl (38 mg, 0.2 mmol), 4-DMAP (33 mg, 0.27 mmol), *N*,*N*-diisopropylethylamine (0.126 mL, 0.72 mmol), and K_2CO_3 (75 mg, 0.54 mmol) in CH_2Cl_2 (0.6 mL) after a reaction time of 1 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) those previously reported.[6c]

Dimethyl 5-Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-3,3-dicarboxylate (7c). β-Lactone **7c** was prepared according to the representative procedure from ketoacid **6c** (111 mg, 0.43 mmol), *p*-TsCl (90 mg, 0.47 mmol), 4-DMAP (79 mg, 0.65 mmol), diisopropylethylamine (0.22 mL, 1.72 mmol), and K_2CO_3 (177 mg, 1.28 mmol) in CH_2Cl_2 (1.4 mL) after a reaction time of 0.5 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) afforded β-lactone **7c** as a colorless liquid (69 mg, 67%). All spectra data were in accordance with those previously reported.[6c]

Methyl 5-Methyl-7-oxo-6-oxabicyclo[3.2.0]heptane-2-carboxylate (7d). β-Lactone **7d** was prepared according to the representative procedure from ketoacid **6d** (121 mg, 0.6 mmol), *p*-TsCl (126 mg, 0.66 mmol), 4-DMAP (110 mg, 0.91 mmol), *N*,*N*-diisopropylethylamine (0.42 mL, 2.4 mmol), and K_2CO_3 (248 mg, 1.8 mmol) in CH_2Cl_2 (1.8 mL) after a reaction time of 1 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) afforded β-lactone **7d** as a colorless liquid (83 mg, 75%): IR (thin film) 2985, 2936, 1822, 1734, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 1H), 3.73 (s, 3H), 3.23 (d, J = 7.0 Hz, 1H), 2.14−2.30 (m, 4H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 169.3, 88.0, 61.3, 52.4, 44.3, 34.2, 28.3, 21.4; HRMS (ESI+) calcd. for $C_9H_{13}O_4$ (M + H) 185.0814, found 185.0821.

2-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-6-oxabicyclo-[3.2.0]heptan-7-one (7e). β-Lactone **7e** was prepared according to the representative procedure from ketoacid **6e** (75 mg, 0.27 mmol), *p*-TsCl (59 mg, 0.31 mmol), 4-DMAP (49 mg, 0.41 mmol), *N*,*N*-diisopropylethylamine (0.19 mL, 1.1 mmol), and K_2CO_3 (111 mg, 0.81 mmol) in CH_2Cl_2 (0.9 mL) after a reaction time of 2 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) afforded β-lactone **7e** as a colorless liquid (47 mg, 68%). All spectral data were in accordance with those previously reported.[8]

2-Methoxy-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one (7f). β-Lactone **7f** was prepared according to the representative procedure from ketoacid **6f** (61 mg, 0.35 mmol), *p*-TsCl (74 g, 0.39 mmol), 4-DMAP (64 mg, 0.53 mmol), *N*,*N*-diisopropylethylamine (0.24 mL, 1.4 mmol), and K_2CO_3 (144 mg, 1.1 mmol) in CH_2Cl_2 (1.2 mL) after a reaction time of 2 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) afforded β-lactone **7f** as a colorless liquid (35 mg, 64%): IR (thin film) 2998, 2945, 1828, 1552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (d, J = 3.5 Hz, 1H), 3.59 (s, 1H), 3.30 (s, 3H), 2.11−2.21 (m, 2H), 1.86−2.06 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 87.8, 81.7, 64.0, 56.5, 33.7, 30.0, 21.9; HRMS (ESI+) calcd for $C_8H_{13}O_3$ (M + H) 157.0865, found 157.0881.

2,5-Dimethyl-6-oxabicyclo[3.2.0]heptan-7-one (7g). β-Lactone **7g** was prepared according to the representative procedure from ketoacid **6g** (84 mg, 0.53 mmol), *p*-TsCl (112 g, 0.58 mmol), 4-DMAP (97 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (0.37 mL, 2.1 mmol), and K_2CO_3 (220 mg, 1.59 mmol) in CH_2Cl_2 (1.7 mL) after a reaction time of 6 h. Purification by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) afforded β-lactone **7g** as a colorless liquid (42.3 g, 57%): IR (thin film) 2996, 2943, 1823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.14 (s, 1H), 2.50−2.58 (m, 1H), 2.01−2.13 (m, 2H), 1.75−1.85 (m, 1H), 1.72 (s, 3H), 1.62−1.68 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 87.4, 65.5, 34.2, 33.0, 30.5, 22.1, 18.6; HRMS (ESI+) calcd. for $C_8H_{13}O_2$ (M + H) 141.0916, found 141.0934.

(1*S*,2*R*,5*R*)-5-Methyl-2-(2-methyloxiran-2-yl)-6-oxabicyclo-[3.2.0]heptan-7-one (14). β-Lactone **7a** was dissolved in CH_2Cl_2 (5 mL) and taken to 0 °C, Na_2HPO_4 (24 mg, 1.71 mmol) and *m*-CPBA (15 mg, 0.853 mmol) were added, and the reaction was allowed to warm to 23 °C overnight (~8 h). The reaction mixture was then filtered to remove excess solids and washed with an aqueous solution of saturated K_2CO_3 (2 × 5 mL) and brine (5 mL). It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, eluting with 10 → 40% EtOAc/hexanes) afforded an inseparable, diastereomeric mixture of epoxy β-lactones **14** (dr 4:1) as a colorless liquid (16 mg, 98%): IR (thin film) 2976, 2925, 1818 cm^{-1}. Data for major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) 3.43 (s, 1H), 2.66−2.60 (m, 2H), 2.51 (d, J = 4.5, 1H), 2.18−2.08 (m, 3H), 2.00−1.96 (m, 1H), 1.72 (s, 3H), 1.71−1.65 (m, 2 H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 88.3, 66.1, 57.2, 51.8, 44.7, 35.0, 27.2, 21.7, 15.5; HRMS (ESI+) calcd for $C_{10}H_{14}O_{3Li}$ (M + Li) 189.1103, found 189.1111.

(1*S*,2*R*,5*R*)-2-Acetyl-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one (15). β-Lactone **7a** was dissolved in CH_2Cl_2 (9 mL) and taken to −78 °C, at which point ozone was bubbled through the solution until it turned a deep blue color. Then oxygen was bubbled through until the color dissipated, at which time dimethyl sulfide was added (0.2 mL, 2.66 mmol) and the reaction was allowed to stir overnight (10 h)

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while warming to 23 °C. The solution was concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, eluting with 10 → 30% EtOAc/hexanes) to afford β-lactone **15** as a colorless liquid (55 mg, 65%): $[\alpha]^{19}_D$ +50 (*c* 1.5 $CHCl_3$); IR (thin film) 2984, 2937, 1815, 1702 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$): δ 3.66 (s, 1H), 3.30 (d, *J* = 8.0 Hz, 1H), 2.24−2.20 (m, 1H), 2.20 (s, 3H), 2.12−2.03 (m, 2H), 1.67 (s, 3H), 1.55−1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 170.5, 88.2, 60.4, 52.0, 33.9, 28.2, 27.6, 21.4; HRMS (ESI+) calcd for $C_9H_{12}O_{3Li}$ (M + Li) 175.0946, found 175.0950.

(1*S*,2*R*,5*R*)-Methyl 2-hydroxy-2-methyl-5-(prop-1-en-2-yl)-cyclopentanecarboxylate (16). A reaction mixture of **7a** (20 mg, 0.12 mmol), MeOH (0.5 mL), and triethylamine (0.5 mL) was stirred at 23 °C for 24 h. The volatiles were removed by rotovap, and the residue was purified by flash column chromatography (SiO_2, eluting with 20%→50% EtOAc/hexanes) to afford hydroxyl ester **16** as a colorless liquid (21.7 mg, 92%): $[\alpha]^{19}_D$ +14.2 (*c* 0.4, $CHCl_3$); IR (thin film) 2965, 1734, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.73 (s, 1H), 3.73 (s, 3H), 3.31 (s, 1H), 3.20−3.24 (m, 1H), 2.59 (d, *J* = 11.5 Hz, 1H), 2.06−2.18 (m, 1H), 1.84−1.94 (m, 1H), 1.70−1.78 (m, 4H), 1.50−1.62 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 145.8, 110.4, 80.4, 57.3, 51.8, 49.6, 40.0, 28.3, 27.1, 19.6; HRMS (ESI+) calcd. for $C_{11}H_{19}O_3$ (M + H) 199.1334, found 199.1352.

1-((1*S*,2*R*,5*R*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)-cyclopentyl)pent-4-en-1-one (17). To a suspension of CuBr·DMS (74 mg, 0.36 mmol) in THF (1.0 mL) at 23 °C was added Me_2S (0.062 mL, 0.84 mmol). After this mixture was cooled to −42 °C, a solution of vinylmagnesium bromide in THF (0.7 mL, 0.7 mmol, 1.0 M in THF) was added dropwise. After 30 min at −42 °C and 30 min at −30 °C, it was cooled back to −42 °C. A solution of **7a** (20 mg, 0.12 mmol) in THF (0.5 mL) was added dropwise via cannula. After 10 min, TMSCl (0.023 mL, 0.18 mmol) was added dropwise, and the reaction was slowly warmed to 0 °C over 2 h and quenched with 1 N HCl and satd aq NH_4Cl . The mixture was extracted with Et_2O, dried with $MgSO_4$, and purified by flash column chromatography (SiO_2, eluting with 20 → 50% EtOAc/hexanes) to afford vinyl ketone **17** as a colorless liquid (19.8 mg, 75%): $[\alpha]^{19}_D$ +25.4 (*c* 0.8, $CHCl_3$); IR (thin film) 2965, 2957, 1721, 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74−5.86 (m, 1H), 4.96−5.04 (m, 2H), 4.78 (s, 2H), 3.86 (s, 1H), 3.08−3.18 (m, 1H), 2.73 (d, *J* = 11.0 Hz, 1H), 2.52−2.58 (m, 2H), 2.26−2.36 (m, 2H), 2.05−2.15 (m, 1H), 1.80−1.85 (m, 1H), 1.77 (s, 3H), 1.50−1.72 (m, 2H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.1, 146.0, 136.9, 115.3, 111.6, 81.2, 62.5, 50.6, 44.4, 40.7, 28.5, 27.2, 26.9, 19.1; HRMS (ESI+) calcd for $C_{14}H_{23}O_2$ (M + H) 223.1698, found 223.1681.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: romo@tamu.edu.

Notes

The authors declare no competing financial interest.

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