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Ring Expansions of β-Keto Lactones with Zinc Carbenoids: Syntheses of (+)-Patulolide A and (±)-Patulolide B

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Received September 25, 2002

A one-pot ring expansion/oxidation/elimination method has been developed in which β-keto lactones are converted efficiently to α,β-unsaturated-γ-keto lactones. The reaction can be successfully applied to a variety of ring sizes. Alkene stereochemistry is dependent upon ring size and reaction conditions. The method was applied to the synthesis of (+)-patulolide A.

As part of a research program directed toward the development of zinc-mediated chain extension reactions,[1] we recently developed a one-pot chain extension/oxidation/elimination sequence for the generation of α,β-unsaturated-γ-keto esters and amides (Scheme 1).[2] The successful application of this methodology to a formal synthesis of the dilactone pyrenophorin **3**[3] through the interception of an acyclic precursor was described. Pyrenophorin is one of a large number of natural products that possesses an α,β-unsaturated-γ-keto ester structural unit. In most instances this functionality is found in macrocyclic compounds such as (+)-patulolide A (**4**) and (−)-patulolide B (**5**),[4] (+)-macrosphelide B (**6**),[5] (−)-grahamimycin A (**7**),[6] and others (Figure 1).[7−9] In an effort to advance the scope of this zinc-mediated methodology, we undertook its application to macrocyclic ring expansion.

Patulolides A (**4**) and B (**5**) were selected as the synthetic targets. A macrolide isolated from the culture broth of *Penicillium urticae* mutant S11R59 by Yamada and co-workers, patulolide A possesses antifungal, antibacterial, and antiinflammatory activities.[10] Patulolide B, isolated concurrently with patulolide A, is isomeric with respect to the olefin and was reported to possess a similar biological activity profile. A number of synthetic approaches to patulolides A and B have been reported.[11−13] Most strategies have relied upon lactonization as the

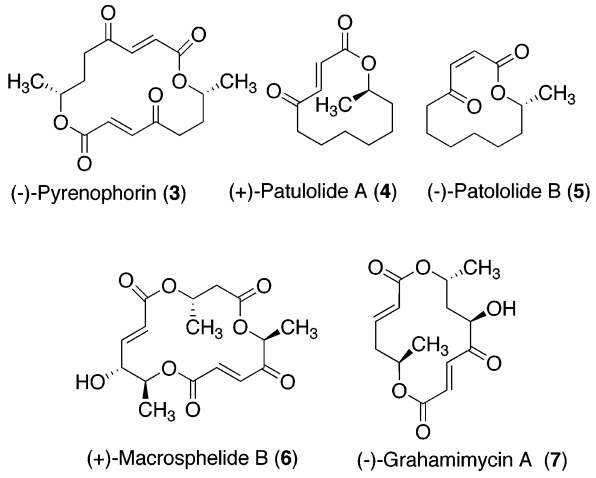
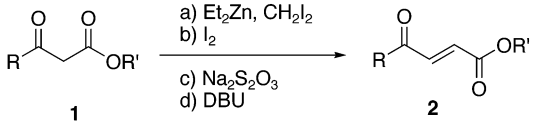


FIGURE 1. Structures of macrocyclic natural products.

SCHEME 1. Chain Extension/Oxidation/Elimination Reaction



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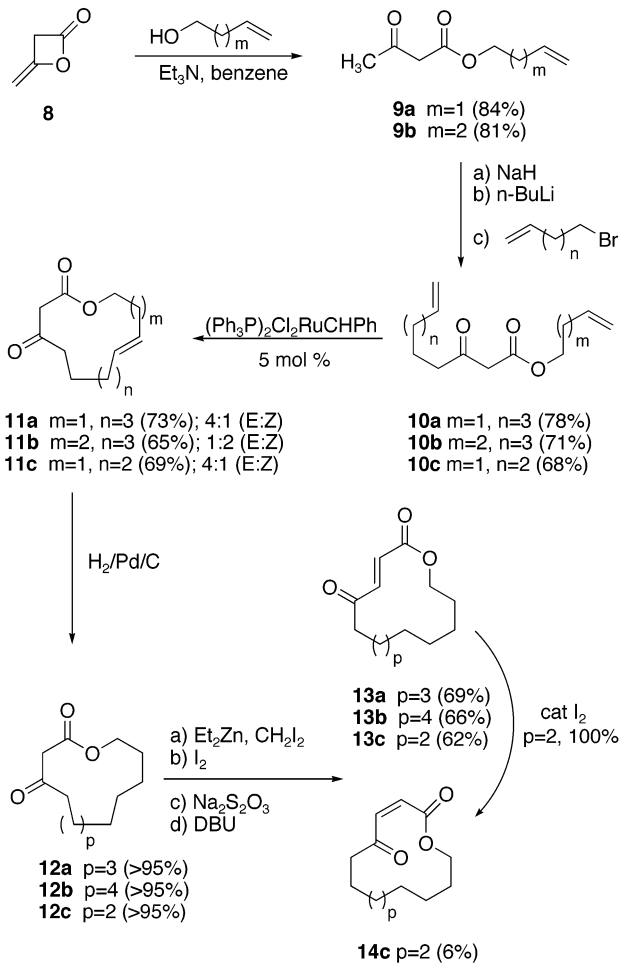
10.1021/jo0264776 CCC: $25.00
Published on Web 01/30/2003

preferred method for macrocycle formation.[14] Alternatively, formation of the macrocycle with concomitant incorporation of the α,β-unsaturated-γ-keto functionality was used effectively by a number of research groups,[15] including a recent report by Doyle in which macrocyclization of a bis-diazo precursor was induced.[16]

We anticipated that olefin metathesis could be used to generate a macrocyclic β-keto lactone. Following reduction of the newly generated olefin, formation of the α,β-unsaturated-γ-keto ester by application of the chain extension/oxidation/elimination methodology would result in ring expansion and formation of the desired macrocycle. Application of this reaction to macrocyclic substrates would encounter issues unique to macrocyclic skeletons. Most importantly, it was unknown how ring size would influence the chain extension portion of the reaction, since simple ring expansions of β-keto lactones had not been studied. Furthermore, the role of the macrocyclic substrate in affecting olefin generation and selectivity was another unknown issue.

We selected as our initial target a 14-membered-ring unsaturated lactone, which required the generation of a 13-membered β-keto lactone precursor (Scheme 2). Treatment of diketene **8** with 3-buten-1-ol provided unsaturated β-keto ester **9a** in 84% yield. Dianion formation and alkylation with 6-bromohex-1-ene provided the metathesis precursor **10a** in 78% yield. Treatment with the first generation Grubb's metathesis catalyst resulted in efficient formation of the β-keto lactone **11a** in 73% as an inseparable mixture of olefin isomers. Olefin selectivity was determined through NOESY analysis, with the E-isomer dominating in a 4:1 ratio. Quantitative reduction of the alkenes provided access to the thirteen-membered β-keto lactone **12a**. Exposure of **12a** to chain extension/oxidation/elimination reaction conditions provided the α,β-unsaturated-γ-keto lactone **13a** in 69% as a single isomer, which was assigned the E-configuration due to the 15.5 Hz coupling constant. Chain extension of this macrocyclic substrate (as well as the other substrates discussed herein) proceeded more slowly than that of their acyclic analogues; however, the rate of chain extension could be enhanced by exposure of the β-keto lactone to diethyl zinc prior to the addition of the methylene iodide. The use of diethyl zinc to facilitate enolate formation has been applied with success in other chain extension studies,[1c] but it is particularly advantageous in systems where enolate formation is slow. A protocol that involved treatment of the β-keto lactone with excess diethyl zinc prior to addition of methylene iodide (in situ carbenoid formation) was used throughout this study, although similar results with longer reaction times could be obtained by direct exposure of the β-keto lactone to the preformed carbenoid.

SCHEME 2. Formation of Macrocycles



The formation of 13- and 15-membered α,β-unsaturated-γ-keto lactones was undertaken through application of the identical strategy (Scheme 2). A mixture of 14-membered β-keto lactones **11b** was produced through metathesis in a combined 65% yield. The olefin selectivity was once again assigned through NOESY analysis and was quite different (1:1.5; E:Z) from that of the previous system. Both olefins were reduced efficiently through catalytic hydrogenation, and the resulting β-keto lactone **12b** was exposed to the one-pot chain extension/oxidation/elimination sequence. Formation of the 15-membered-ring **13b** was facilitated in 66% yield, once again as the E-isomer exclusively.

An approach to the 13-membered γ-keto lactone **13c** required formation of a 12-membered β-keto lactone **12c**. Metathesis provided an inseparable mixture of olefin isomers **11c** in which the E-isomer was favored (4:1). Reduction of the olefin and exposure to chain extension/oxidation/elimination reaction conditions provided, for the first time, two isomeric products in an approximate 10:1 ratio. Structural assignment was made on the basis of ^{1}H NMR coupling, and indicated that the major product **13c** possessed the anticipated E-olefin configuration. Olefinic protons in the minor product **14c** possessed a

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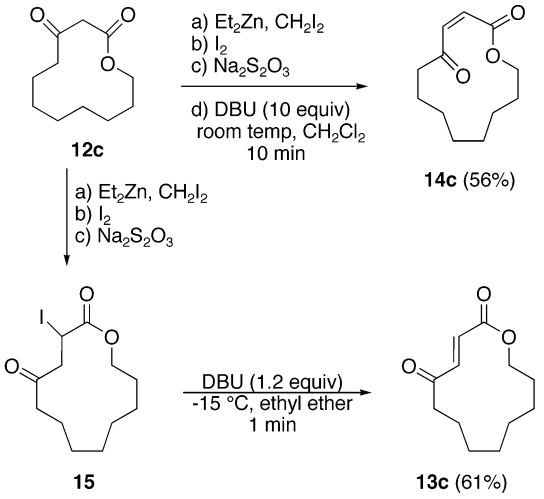
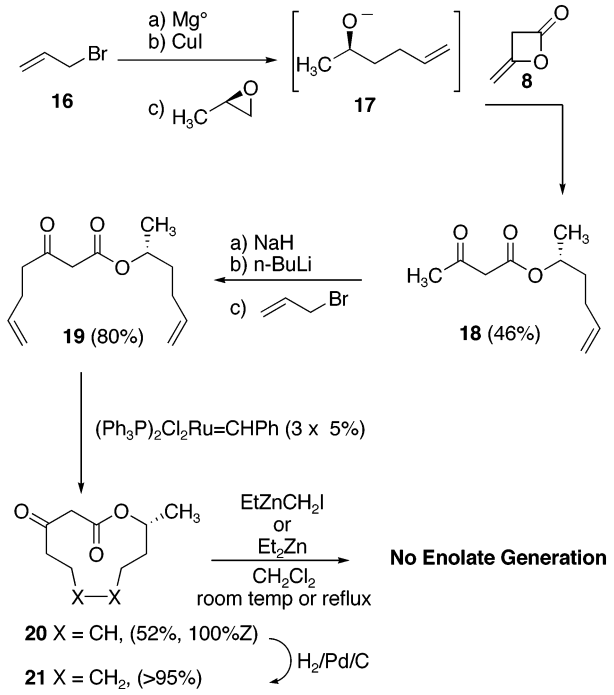
SCHEME 3. Formation of the Kinetic and Thermodynamic Products



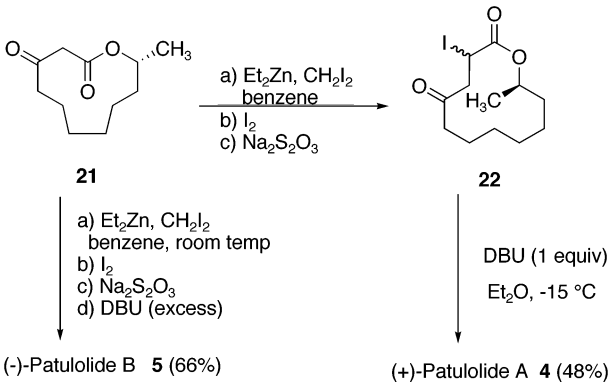
12.7 Hz coupling constant, which led to its assignment as the Z-isomer. The unprecedented appearance of the Z-isomer in the ring expansion of **12c** raised questions regarding the comparative thermodynamic stability of the two isomers, **13c** and **14c**. In their investigation of patulolides A and B (12-membered rings), Doyle and coworkers utilized iodine-mediated isomerization to probe the relative energies of macrocyclic α,β-unsaturated-γ-keto lactones. In a similar fashion, exposure of **13c** to catalytic iodine for 3 days resulted in complete isomerization to the thermodynamically more stable Z-isomer (**14c**). Since the chain extension/oxidation/elimination reaction of **12c** resulted in a 10:1 mixture of E- and Z-isomers, the reaction was either operating under kinetic control or only partial isomerization had taken place. During optimization studies of acyclic substrates,[2] elimination of the iodide had been determined to proceed most efficiently when the intermediate iodide was exposed to excess DBU (10 equiv) for between 30 and 60 s. We anticipated that stirring the reaction mixture for a greater period of time in the presence of the iodide salts and DBU would facilitate isomerization of the E-isomer **13c** to the thermodynamically more stable Z-olefin isomer **14c**. Repeating the chain extension/oxidation/ elimination reaction and allowing the reaction mixture to stir for 10 min after addition of excess DBU resulted in (Scheme 3) exclusive formation of the Z-olefin isomer **14c** in 56% yield. In contrast, exclusive formation of the E-olefin isomer **13c** was possible through a kinetically controlled elimination reaction. Isolation of the intermediate iodide **15** and exposure of the iodide to DBU (1.2 equiv in ether) facilitated formation of the **13c**.

Application of this strategy to the preparation of the 12-membered-ring macrolides patulolides A (**4**) and B (**5**) mandated the use of a smaller ring system (Scheme 4). The preparation of the 11-membered-ring precursor through ring-closing metathesis and the selection of appropriate elimination conditions for control of olefin geometry were anticipated to be strongly influenced by the smaller ring size. The R-stereocenter was incorporated through opening of R-propylene oxide with an organocuprate derived from allyl bromide **16**. To avoid

SCHEME 4. Preparation of the Patulolide Ring System



SCHEME 5. Formation of Patulolides A and B



potential problems in the isolation of a low molecular weight alcohol, we captured the intermediate alkoxide **17** with diketene **8** to form the desired β-keto ester **18**. Dianion formation and alkylation with allyl bromide provided the desired olefin **19** in an 80% yield. Exposure of **19** to our standard olefin metathesis conditions did not produce the 11-membered ring in an acceptable yield. When the catalyst load was increased to 15%, added in three portions over a 24-h period, formation of the desired 11-membered ring **20** was accomplished. Although significant oligomerization was observed, the lactone was isolated in 52% with exclusive formation of the Z-isomer. Hydrogenation of the olefin provided the β-keto lactone **21**.

Exposure of **21** to chain extension/iodination/ elimination reaction conditions returned only starting material. No reaction, including ring expansion, was observed under these conditions. As mentioned earlier, chain extension (ring expansion) of these macrocyclic systems is more sluggish than that of the acyclic systems,

presumably due to the decreased acidity of the α-methylene protons. Attempts to deprotonate the β-keto lactone by refluxing the methylene chloride solution of **21** with diethyl zinc or carbenoid were unsuccessful.

In an effort to obtain higher reaction temperatures that might facilitate deprotonation of **21**, benzene was selected. Surprisingly, deprotonation and subsequent ring expansion was observed to occur *at room temperature in benzene*. The precise role benzene plays in facilitating the acid−base reaction is unclear, yet additional experiments revealed the general phenomenon that benzene accelerates the chain extension. The chain extension/oxidation/iodination reaction of racemic **21** resulted in clean formation of patulolide B **5** in 66% yield. Doyle[16] reported that patulolide B is the more stable isomer, and the results obtained in our studies of **12c** confirmed that the elimination reaction was operating under thermodynamic control. However, the conformational biasing inherent to the smaller ring system raised the possibility that the Z-isomer might, in fact, be the kinetically controlled product. Isolation of the intermediate iodide **22** proceeded efficiently. Application of optimized kinetically controlled elimination conditions provided a 48% yield of (+)-patulolide A **4** as a single isomer.

In conclusion, we have demonstrated that application of a chain extension/oxidation/elimination reaction to macrocyclic β-keto lactones provides access to analogous α,β-unsaturated-γ-keto lactones. Olefin stereochemistry is affected by the interplay of ring size and reaction conditions, but can be influenced by selection of conditions that operate under kinetic or thermodynamic control.

Experimental Section

General Experimental Details. Unless otherwise noted, all reactions were run under a nitrogen atmosphere in oven-dried glassware and stirred with Teflon-coated magnetic stir bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator or vacuum pump. Tetrahydrofuran (THF) and diethyl ether were distilled from purple benzophenone ketyl prior to use. Benzene was distilled from calcium hydride prior to use. Methylene chloride (CH_2Cl_2) was distilled from P_2O_5 prior to use. Ethyl acetate (EtOAc) was distilled prior to use. Hexanes were distilled prior to use. Diethylzinc was purchased and used as a solution (1.0 M in hexanes). Iodine was sublimed prior to use. Column chromatography was performed with flash silica gel (32−63μm), for which mobile phases were used as noted. Thin layer chromatography (TLC) was visualized by UV and anisaldehyde or $KMnO_4$ stains. The R_f values were determined with the same solvent used for column chromatography. Unless otherwise noted, all NMR experiments were carried out in deuteriochloroform ($CDCl_3$) solvent. Low-resolution mass spectroscopy was performed by the University of New Hampshire Instrumentation. High-resolution mass spectroscopy was performed at Merck Pharmaceutical Co. Optical rotations were conducted in the specified solution and concentrations are given in g/mL. Melting points are uncorrected.

But-3-enyl 3-Oxo-butanoate (9a).[17] A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of benzene (20 mL), diketene (1.0 mL, 13.0 mmol), and 3-buten-1-ol (0.86 mL, 10 mmol) under an atmosphere of N_2 at 0 °C. Triethylamine was added (2.1 mL, 15 mmol) slowly and the solution was allowed to warm to room temperature. The solution was allowed to stir for 2 h and, washed with 20 mL of sat. aqueous NH_4Cl (20 mL). The organic layer was washed with sat. aqueous Na_2HCO_3 (20 mL) and the layers were separated. The combined aqueous washings were extracted (3 × 20 mL) with Et_2O and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f 0.23) to yield 1.31 g (84%) of **9a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) keto form δ 5.75 (tdd, 1H, J = 6.8, 10.5, 17.2 Hz), 5.14−5.07 (m, 2H), 4.20 (t, 2H, J = 6.6 Hz), 3.46 (s, 2H), 2.44−2.38 (m, 2H), 2.27 (s, 3H); visible resonances corresponding to enol form include δ 12.1 (s), 4.99 (s), 1.96 (s); ^{13}C NMR (100 MHz, $CDCl_3$) keto and enol resonances δ 200.7, 175.8, 167.3, 133.8, 117.7, 117.5, 89.9, 64.5, 63.2, 50.2, 33.2, 33.1, 30.3, 21.4.

But-3-enyl 3-Oxo-dec-9-enoate (10a). A 100-mL round-bottom flask containing a suspension of NaH (60% in hexanes, 134 mg, 3.3 mmol) in THF (10 mL) was cooled to 0 °C under a blanket of N_2. A solution of β-keto ester **9a** (468 mg, 3.0 mmol) dissolved in THF (5 mL) was added slowly and the solution was allowed to stir for 30 min until the suspension became a clear yellow solution. The solution was cooled to −15 °C and *n*-BuLi (1.3 M in hexanes, 2.5 mL, 3.3 mmol) was added slowly. The solution was allowed to stir for an additional 20 min, at which time 6-bromo-1-hexene (0.44 mL, 3.3 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The resulting thick suspension was quenched with sat. aqueous NH_4Cl (20 mL) and washed successively with D.I. H_2O (20 mL) and brine (20 mL). The organic layer was separated and the combined aqueous washings were extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.21) to yield 510 mg (78%) of **10a** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) keto form δ 5.83−5.73 (m, 2H), 5.14−4.92 (m, 4H), 4.19 (t, 2H, J = 6.5 Hz), 3.43 (s, 2H), 2.54 (t, 2H, J = 7.5 Hz), 2.43−2.39 (m, 2H), 2.07−2.02 (m, 2H), 1.63−1.57 (m, 2H), 1.43−1.27 (m, 4H); ^{1}H NMR (500 MHz, $CDCl_3$) visible resonances corresponding to enol form include δ 2.23−2.17 (m); ^{13}C NMR (125 MHz, $CDCl_3$) keto and enol resonances δ 202.9, 167.4, 139.0, 139.0, 134.2, 133.9, 117.7, 117.5, 114.7, 114.6, 89.1, 64.5, 63.2, 49.4, 43.2, 35.2, 33.8, 33.7, 33.3, 33.1, 28.8, 28.8, 28.7, 28.6, 26.3, 23.5; HRMS (CI) $[M + NH_4]^+$ calcd for $C_{14}H_{26}NO_3$ 256.1907, found 256.1909.

Oxacyclotridec-10-ene-2,4-dione (11a). To a solution of β-keto ester **10a** (102 mg, 0.43 mmol) in dry CH_2Cl_2 (250 mL) was added bis(cyclohexylphosphine)benzylidine ruthenium(IV) dichloride (35 mg, 0.043 mmol). This solution was heated to reflux for 4 h. The solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f 0.19) to yield 66 mg (73%) of **11a** as an inseparable 4:1 mixture of E- and Z-isomers, respectively. ^{1}H NMR (500 MHz, $CDCl_3$) major isomer δ 5.50−5.43 (m, 1H), 5.32−5.28 (m, 1H), 4.23−4.21 (m, 2H), 3.39 (s, 2H), 2.51 (t, 2H, J = 7.0 Hz), 2.38−2.35 (m, 2H), 2.02−1.99 (m, 2H), 1.66 (m, 2H, J = 6.5 Hz), 1.47−1.31 (m, 4H); ^{1}H NMR (500 MHz, $CDCl_3$) minor isomer δ 4.26−4.24 (m), 3.42 (s), 2.55−2.52 (m), 2.43−2.40 (m), 2.09−2.05 (m); ^{13}C NMR (125 MHz, $CDCl_3$) visible signals corresponding to both E- and Z-isomers δ 203.3, 167.1, 134.6, 132.5, 127.2, 127.1, 65.4, 64.3, 50.2, 50.0, 43.5, 42.3, 32.4, 32.1, 27.8, 27.4, 27.2, 26.6, 26.4, 25.3, 23.1, 23.0; IR (film) 2929.6, 2856.0, 1743.0, 1713.4, 1254.5; HRMS (EI) $[M + H]^+$ calcd for $C_{12}H_{19}O_3$ 211.1642, found 211.1604.

Oxacyclotridecane-2,4-dione (12a). To a 100-mL round-bottom flask containing β-keto lactone **11a** (53 mg, 0.25 mmol) in MeOH (5 mL) under a blanket of N_2 was added 10% Pd on carbon (25 mg). The vessel was purged with hydrogen via a balloon and the nitrogen inlet was removed. The suspension

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was allowed to stir at room temperature with the balloon attached for 4 h. The suspension was filtered and concentrated in vacuo to yield 50 mg (95%) of **12a** as a white solid; mp 39.0−40.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21−4.19 (m, 2H), 3.44 (s, 2H), 2.63−2.61 (m, 2H), 1.71−1.62 (m, 4H), 1.44−1.36 (m, 2H), 1.34−1.28 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 166.8, 65.5, 50.5, 42.0, 26.5, 25.9, 25.2, 25.1, 24.9, 23.2, 21.8.

***E*-Oxacyclotetradec-3-ene-2,5-dione (13a).**[18] A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and β-keto lactone **12a** (39 mg, 0.19 mmol). To this solution was added diethyl zinc (1.0 M in hexanes, 1.14 mL, 1.14 mmol) under an atmosphere of N_2 at 0 °C. This solution was allowed to stir for 5 min and CH_2I_2 (0.95 mL, 1.18 mmol) was added. The solution was monitored by TLC until starting material was no longer visible (approximately 45 min). Iodine (300 mg, 1.18 mmol) was added to the reaction mixture in a single portion. The reaction mixture turned pink and was allowed to stir for an additional 30 s. A saturated solution of sodium thiosulfate (10 mL) was added and the mixture was stirred until the pink color had disappeared. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.28 mL, 1.9 mmol) was added and the mixture was stirred for 1 min and washed with saturated aqueous ammonium chloride (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.19) to yield 30 mg (69%) of **13a** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 1H, J = 15.6 Hz), 6.60 (d, 1H, J = 15.6 Hz), 4.33−4.31 (m, 2H), 2.55−2.52 (m, 2H), 1.77−1.70 (m, 4H), 1.56−1.52 (m, 2H), 1.46−1.35 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 165.3, 138.0, 130.5, 66.8, 42.3, 28.6, 27.5, 27.5, 26.8, 26.7, 26.5, 23.6; HRMS (CI) $[M + Na]^+$ calcd for $C_{13}H_{20}O_3Na$ 247.1304, found 247.1317.

Pent-4-enyl 3-oxo-butanoate (9b).[19] A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of benzene (20 mL). Diketene (1.0 mL, 13.0 mmol) and 4-penten-1-ol (1.03 mL, 10 mmol) were added under an atmosphere of N_2 at 0 °C. Triethylamine was added (2.1 mL, 15 mmol) slowly and allowed to warm to room temperature. The solution was allowed to stir for 2 h and washed with 20 mL of sat. aqueous NH_4Cl (20 mL). The organic layer was washed with sat. aqueous Na_2HCO_3 (20 mL) and the layers were separated. The combined aqueous washings were extracted (3 × 20 mL) with Et_2O and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f 0.23) to yield 1.38 g (81%) of **9b** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) keto form δ 5.85 (tdd, 1H, J = 6.8, 10.0, 17.2 Hz), 5.07−4.98 (m, 2H), 4.16 (t, 2H, J = 6.8 Hz), 3.46 (s, 2H), 2.27 (s, 3H), 2.15 (q, 2H, J = 6.8 Hz), 1.78 (p, 2H, J = 6.8 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) visible resonances corresponding to enol form include δ 1.96 (s); ^{13}C NMR (100 MHz, $CDCl_3$) keto and enol resonances δ 200.8, 167.3, 137.4, 115.6, 64.9, 63.8, 50.3, 30.3, 30.1, 27.8, 21.7; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_9H_{18}NO_3$ 188.1284, found 188.1281.

Pent-4-enyl 3-Oxo-dec-9-enoate (10b). A 100-mL round-bottom flask containing a suspension of NaH (60% in hexanes, 193 mg, 4.8 mmol) in THF (15 mL) was cooled to 0 °C under a blanket of N_2. A solution of β-keto ester **9b** (680 mg, 4.0 mmol) dissolved in THF (5 mL) was added slowly and the solution was allowed to stir for 30 min until the suspension became a clear yellow solution. The solution was cooled to −15 °C and *n*-BuLi (1.3 M in hexanes, 4.0 mL, 5.2 mmol) was added slowly and allowed to stir for an additional 20 min, at which time 6-bromo-1-hexene (0.59 mL, 4.4 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The resulting thick suspension was quenched with sat. aqueous NH_4Cl (20 mL) and washed successively with D.I. H_2O (20 mL) and brine (20 mL). The organic layer was separated and the combined aqueous washings were extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.21) to yield 721 mg (71%) of **10b** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) keto form δ 5.81−5.76 (m, 2H), 5.06−4.93 (m, 4H), 4.15 (t, 2H, J = 6.0 Hz), 3.43 (s, 2H), 2.54 (t, 2H J = 7.5 Hz), 2.15−2.10 (m, 2H), 2.07−2.02 (m, 2H), 1.78−1.72 (m, 2H), 1.65−1.58 (m, 2H), 1.41−1.29 (m, 4H); ^{1}H NMR (500 MHz, $CDCl_3$) visible resonances corresponding to enol form include δ 2.22−2.17 (m); ^{13}C NMR (125 MHz, $CDCl_3$) keto and enol resonances δ 202.9, 167.4, 138.9, 137.4, 115.6, 114.6, 89.1, 64.9, 63.2, 49.5, 43.2, 35.2, 33.7, 30.1, 28.8, 28.7, 28.1, 27.9, 26.3, 23.5; IR (film) 2977.6, 2936.8, 2360.2, 2342.5, 1734.1, 1717.4; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{15}H_{28}NO_3$ 270.2063, found 270.2066.

E*-Oxacyclotetradec-10-ene-2,4-dione (*E*-11b) and *Z*-Oxacyclotetradec-10-ene-2,4-dione (*Z*-11b).** To a solution of β-keto ester **10b** (200 mg, 0.79 mmol) in dry CH_2Cl_2 (250 mL) was added bis(cyclohexylphosphine)benzylidine ruthenium(IV) dichloride (33 mg, 0.040 mmol). This solution was heated to reflux for 3 h. The solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (13:1, hexanes/ethyl acetate) to yield 77 mg (44%) of the less polar isomer (R_f 0.19) (Z*-11b**) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49−5.44 (m, 1H), 5.31−5.26 (m, 1H), 4.18−4.16 (m, 2H), 3.42 (s, 2H), 2.56−2.53 (m, 2H), 2.23−2.19 (m, 2H), 2.03−1.99 (m, 2H), 1.77−1.64 (m, 4H), 1.37−1.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 167.5, 131.1, 128.9, 64.3, 50.6, 41.2, 28.5, 27.6, 26.9, 25.9, 23.5, 22.3. The more polar isomer (R_f 0.17) (***E*-11b**) was isolated (38 mg, 21%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45−5.28 (m, 2H), 4.21−4.18 (m, 2H), 3.44 (s, 2H), 2.50−2.46 (m, 2H), 2.22−2.17 (m, 2H), 2.06−2.01 (m, 2H), 1.81−1.64 (m, 4H), 1.44−1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 167.4, 131.2, 130.3, 66.7, 49.2, 43.0, 31.9, 30.7, 28.3, 27.3, 26.3, 24.1; IR (film) 2928.4, 2855.6, 1743.5, 1714.0; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{13}H_{24}NO_3$ 242.1750, found 242.1759.

The residue described in the previous reaction (preparation of ***E*-11b**) was chromatographed on silica (13:1, hexanes/ethyl acetate; R_f 0.19) to yield 77 mg (44%) of the less polar component (***Z*-11b**) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49−5.44 (m, 1H), 5.31−5.26 (m, 1H), 4.18−4.16 (m, 2H), 3.42 (s, 2H), 2.56−2.53 (m, 2H), 2.23−2.19 (m, 2H), 2.03−1.99 (m, 2H), 1.77−1.64 (m, 4H), 1.37−1.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 167.5, 131.1, 128.9, 64.3, 50.6, 41.2, 28.5, 27.6, 26.9, 25.9, 23.5, 22.3.

Oxacyclotetradecane-2,4-dione (12b).[20] To a 100-mL round-bottom flask containing β-keto lactone ***E*-11b** and ***Z*-11b** (99 mg, 0.44 mmol) in EtOH (10 mL) under a blanket of N_2 was added 10% Pd on carbon (40 mg). The vessel was purged with hydrogen via a balloon and the nitrogen inlet was removed. The suspension was allowed to stir at room temperature with the balloon attached for 4 h. The suspension was filtered and concentrated in vacuo to yield 94 mg (94%) of **12b** as a white solid; mp 34.0−35.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21−4.19 (m, 2H), 3.43 (s, 2H), 2.59 (t, 2H, J = 7.0 Hz), 1.72−1.66 (m, 4H), 1.42−1.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 167.3, 65.2, 50.2, 41.1, 27.5, 26.3, 25.9, 25.5, 25.2, 24.7, 23.9, 21.2; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{13}H_{26}NO_3$ 244.1907, found 244.1913.

***E*-Oxacyclopentadec-3-ene-2,5-dione (13b).** A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and β-keto ester **12b** (87 mg, 0.39 mmol). To this solution was added diethyl zinc (1.0

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M in hexanes, 2.3 mL, 2.3 mmol) under an atmosphere of N_2 at 0 °C. This solution was allowed to stir for 5 min and CH_2I_2 (0.20 mL, 2.4 mmol) was added. The solution was monitored by TLC until starting material was no longer visible (approximately 45 min). Iodine (616 mg, 2.4 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 s. A saturated solution of sodium thiosulfate (10 mL) was added and the mixture was stirred until the pink color had disappeared. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) (0.58 mL, 3.9 mmol) was added, the mixture was stirred for 1 min and washed with saturated aqueous ammonium chloride (20 mL), and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.19) to yield 62 mg (66%) of **13b** as a yellow solid, mp 41.7−43.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 1H, J = 15.6 Hz), 6.64 (d, 1H, J = 16.1 Hz), 4.27−4.25 (m, 2H), 2.57−2.55 (m, 2H), 1.76−1.71 (m, 4H), 1.49−1.32 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 165.4, 138.5, 130.9, 66.5, 41.3, 28.9, 27.9, 27.6, 27.5, 27.1, 27.0, 26.5, 25.0; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{14}H_{26}NO_3$ 256.1907, found 256.1912.

But-3-enyl 3-oxo-non-8-enoate (10c). A 100-mL round-bottom flask containing a suspension of NaH (60% in hexanes, 480 mg, 12 mmol) in THF (30 mL) was cooled to 0 °C under a blanket of N_2. A solution of β-keto ester **9a** (1.56 g, 10 mmol) dissolved in THF (5 mL) was added slowly and the solution was allowed to stir for 30 min until the suspension became a clear yellow solution. The solution was cooled to −15 °C and *n*-BuLi (1.3 M in hexanes, 9.2 mL, 12 mmol) was added slowly and allowed to stir for an additional 20 min after which time 5-bromo-1-pentene (1.3 mL, 11 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The resulting thick suspension was quenched with sat. aqueous NH_4Cl (30 mL) and washed successively with D.I. H_2O (30 mL) and brine (30 mL). The organic layer was separated and the combined aqueous washings were extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.23) to yield 1.53 g (68%) of **10c** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) keto form δ 5.83−5.73 (m, 2H), 5.10−4.94 (m, 4H), 4.19 (t, 2H, J = 6.8 Hz), 3.43 (s, 2H), 2.56−2.53 (m, 2H), 2.43−2.39 (m, 2H), 2.08−2.04 (m, 2H), 1.64−1.61 (m, 2H), 1.45−1.37 (m, 2H); ^{1}H NMR (500 MHz, $CDCl_3$) visible resonances corresponding to enol form include δ 2.22−2.19 (m); ^{13}C NMR (125 MHz, $CDCl_3$) keto and enol resonances δ 202.7, 167.4, 138.5, 134.1, 133.9, 117.6, 114.9, 89.2, 64.5, 63.2, 49.4, 43.0, 35.1, 33.6, 33.3, 33.1, 28.4, 25.9, 23.1; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{13}H_{24}NO_3$ 242.1750, found 242.1753.

Oxacyclododec-9-ene-2,4-dione (11c). To a solution of β-keto ester **10c** (236 mg, 1.05 mmol) in dry CH_2Cl_2 (250 mL) was added bis(cyclohexylphosphine)benzylidine ruthenium(IV) dichloride (42 mg, 0.050 mmol). This solution was heated to reflux for 4 h. The solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f 0.20) to yield 143 mg (69%) of **11c** as an inseparable 6:1 mixture of E- and *Z*-isomers, respectively. ^{1}H NMR (500 MHz, $CDCl_3$) major isomer δ 5.46−4.42 (m, 1H), 5.35−5.29 (m, 1H), 4.32−4.28 (m, 2H), 3.35 (s, 2H), 2.65−2.62 (m, 2H), 2.44−2.39 (m, 2H), 2.14−2.08 (m, 2H), 1.70−1.64 (m, 2H), 1.55−1.50 (m, 2H); ^{1}H NMR (500 MHz, $CDCl_3$) visible signals corresponding to minor isomer δ 3.93 (s), 2.53−2.50 (m); ^{13}C NMR (120 MHz, $CDCl_3$) visible signals corresponding to both E- and Z-isomers δ 202.8, 167.1, 135.3, 132.8, 127.0, 126.5, 64.7, 63.3, 50.7, 50.3, 40.7, 40.5, 33.3, 32.0, 27.6, 26.5, 25.3, 24.4, 23.1, 22.2; IR (film) 2929.6, 2856.0, 1743.0, 1713.4; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{11}H_{20}NO_3$ 214.1440, found 214.1437.

Oxacyclododecane-2,4-dione (12c).[21] To a 100-mL round-bottom flask containing β-keto lactone **11c** (91 mg, 0.46 mmol) in EtOH (10 mL) under a blanket of N_2 was added 10% Pd on carbon (20 mg). The vessel was purged with hydrogen via a balloon and the nitrogen inlet was removed. The suspension was allowed to stir at room temperature with the balloon attached for 3 h. The suspension was then filtered and concentrated in vacuo to yield 86 mg (95%) of **12c** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19−4.17 (m, 2H), 3.43 (s, 2H), 2.65−2.63 (m, 2H), 1.73−1.65 (m, 4H), 1.49−1.44 (m, 2H), 1.37−1.27 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 167.0, 66.5, 50.9, 40.5, 26.5, 26.1, 24.6, 23.5, 23.0, 21.7; HRMS (CI, Na) $[M + Na]^+$ calcd for $C_{11}H_{18}O_3Na$ 221.1148, found 221.1170.

(3*E*)-Oxacyclotridec-3-ene-2,5-dione (13c) and (3*Z*)-oxacyclotridec-3-ene-2,5-dione (14c). A 100-mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and β-keto lactone **12c** (96 mg, 0.48 mmol). To this solution was added diethyl zinc (1.0 M in hexanes, 2.9 mL, 2.9 mmol) under an atmosphere of N_2 at 0 °C. This solution was allowed to stir for 5 min and CH_2I_2 (0.24 mL, 2.9 mmol) was added. The solution was monitored by TLC until starting material was no longer visible (approximately 45 min). Iodine (756 mg, 2.9 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 s. A saturated solution of sodium thiosulfate (10 mL) was added and the mixture was stirred until the pink color had disappeared. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.72 mL, 4.8 mmol) was added and the mixture was stirred for 1 min. The mixture was washed with saturated aqueous ammonium chloride (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.21) to yield 63 mg (62%) of **13c** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 15.6 Hz), 6.49 (d, 1H, J = 15.6 Hz), 4.30−4.28 (m, 2H), 2.50−2.48 (m, 2H), 1.75−1.73 (m, 4H), 1.46−1.40 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 165.9, 139.8, 129.4, 65.9, 42.4, 27.7, 27.5, 27.1, 27.1, 23.9, 23.5. The more polar component (15:1, hexanes/ethyl acetate; R_f 0.19) was isolated (6.3 mg, 6%) to yield **14c** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, 1H, J = 12.7 Hz), 6.02 (d, 1H, J = 12.7 Hz), 4.21−4.19 (m, 2H), 2.62−2.60 (m, 2H), 1.76−1.71 (m, 2H), 1.69−1.64 (m, 2H), 1.52−1.44 (m, 4H), 1.37−1.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 165.8, 139.3, 126.5, 66.5, 40.8, 26.3, 26.1, 26.0, 25.1, 24.5, 21.0; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{12}H_{22}NO_3$ 228.1594, found 228.1601.

***Z*-Oxacyclododec-3-ene-2,5-dione (14c).** When the above reaction of **12c** was allowed to stir for 10 min after addition of the DBU, compound **14c** was the sole product and was isolated in 56%.

***E*-Oxacyclododec-3-ene-2,5-dione (13c).** The reaction of **12c** is initiated as described above. After treatment with the saturated sodium thiosulfate solution, the reaction mixture was diluted with diethyl ether and washed with an aqueous solution of ammonium chloride. The layers were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue, which contained **15**, was dissolved in diethyl ether and brought to −15 °C. To this solution was added DBU (1.2 equiv) and the mixture was allowed to stir for approximate 1 min. The mixture was filtered through a plug of silica. The silica plug was washed with diethyl ether and the filtrate was concentrated under reduced pressure at room temperature. Chromatography provided **13c** as the sole product in 61% yield.

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(*R*)-1-Methylpent-4-enyl 3-Oxo-butanoate (18). A 250-mL round-bottom flask was fitted with a 100-mL addition funnel and purged with N_2 for 30 min. The round-bottom flask was charged with Mg° (1.8 g, 75 mmol), THF (50 mL), and a crystal of iodine. The addition funnel was charged with allyl bromide **16** (3.2 mL, 37.5 mmol) and THF (50 mL). A 5-mL portion of the allyl bromide solution was added and the magnesium-containing solution was allowed to stir until the brown color disappeared. After waiting an additional 10 min, the remaining allyl bromide/THF solution was added dropwise over a 1-h period. Following completion of the addition, the mixture was allowed to stir for an additional 1 h. The mixture was brought to −40 °C and CuI (215 mg, 1.13 mmol) was added. The resulting light green mixture was allowed to stir for an additional 10 min, at which time *R*-propylene oxide (1.05 mL, 15 mmol) in THF (10 mL) was added in a single portion. The mixture was allowed to warm to −15 °C and allowed to stir for an additional 2 h. A solution of diketene (2.9 mL, 37.5 mmol) in THF (10 mL) was added dropwise over 15 min. The solution was allowed to stir for an additional 15 min, then allowed to stir at 0 °C for an additional 30 min. The solution was quenched with saturated aqueous ammonium chloride (50 mL). The layers were separated and the organic layer was washed with H_2O (50 mL) and brine (50 mL). The layers were separated, the combined aqueous layers were extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over anhydrous sodium sulfate. The solution was filtered and concentrated in vacuo. The residue was chromatographed on silica (15:1, hexanes/ethyl acetate; R_f 0.18) to yield 1.27 g (46%) of **18** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (tdd, 1H, J = 6.5, 10.0, 17.0 Hz), 5.05−4.95 (m, 3H), 3.43 (s, 2H), 2.27 (s, 3H), 2.26−2.05 (m, 2H), 1.73 (m, 1H), 1.60 (m, 1H), 1.26 (d, 3H, J = 6.5 Hz); ^{1}H NMR (500 MHz, $CDCl_3$) visible resonance corresponding to enol form δ 1.95 (s); ^{13}C NMR (125 MHz, $CDCl_3$) resonances corresponding to keto and enol forms δ 200.8, 166.9, 137.9, 137.7, 115.3, 115.2, 90.3, 72.0, 70.2, 50.6, 35.3, 35.1, 30.3, 29.8, 21.4, 20.2, 20.0. $[\alpha]_D$ −17.1, (*c* 0.0226 g/mL, EtOH).

(*R*)-1-Methylpent-4-enyl 3-Oxo-hept-6-enoate (19). A 100-mL round-bottom flask containing a suspension of NaH (60% in hexanes, 525 mg, 13.1 mmol) in THF (30 mL) was cooled to 0 °C under a blanket of N_2. A solution of β-keto ester **18** (2.19 mg, 11.9 mmol) dissolved in THF (5 mL) was added slowly and the solution was allowed to stir for 30 min until the suspension became a clear yellow solution. The solution was cooled to −15 °C and *n*-BuLi (2.5 M in hexanes, 5.2 mL, 13.1 mmol) was added slowly. The solution was stirred for an additional 20 min, at which time allyl bromide (1.13 mL, 13.1 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The resulting thick suspension was quenched with sat. aqueous NH_4Cl (30 mL) and washed successively with D.I. H_2O (30 mL) and brine (30 mL). The organic layer was separated and the combined aqueous washings were extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica (20:1, hexanes/ethyl acetate; R_f 0.20) to yield 2.12 g (80%) of **19** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85−5.75 (m, 2H), 5.07−4.96 (m, 5H), 3.42 (s, 2H), 2.65 (t, 2H, J = 7.3 Hz), 2.38−2.33 (m, 2H), 2.12−2.06 (m, 2H), 1.73 (m, 1H), 1.59 (m, 1H), 1.25 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 167.0, 137.8, 136.8, 115.8, 115.3, 72.0, 49.9, 42.3, 35.1, 29.8, 27.6, 20.1; IR (film) 2978.8, 2935.5, 1734.8, 1717.4; HRMS (CI, NH_3) $[M + NH_4]^+$ calcd for $C_{13}H_{24}NO_3$ 242.1750, found 242.1755; $[\alpha]_D$ −13.3 (*c* 0.011 g/mL, EtOH).

(11*R*)-11-Methyloxacycloundec-7-ene-2,4-dione (20). To a solution of β-keto ester **19** (202 mg, 0.90 mmol) in dry CH_2Cl_2 (250 mL) was added bis(cyclohexylphosphine)benzylidine ruthenium(IV) dichloride (38 mg, 0.047 mmol). This solution was heated to reflux for 8 h and additional catalyst was added (38 mg, 0.047 mmol). Reflux was continued for an additional 8 h, at which time another portion of catalyst was added (38 mg, 0.047 mmol). Following an additional 8 h at reflux, the solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f 0.20) to yield 90 mg (52%) of **20** as a single isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37−5.25 (m, 2H), 5.04−4.98 (m, 1H), 3.39 (d, 1H, J = 11.2 Hz), 3.31 (d, 1H, J = 11.2 Hz), 2.80 (m, 1H), 2.36−2.24 (m, 3H), 2.11 (m, 1H), 1.96 (m, 1H), 1.73−1.60 (m, 2H), 1.20 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 164.7, 133.2, 127.5, 73.8, 54.9, 41.3, 34.9, 32.1, 28.1, 21.7; $[\alpha]_D$ −239 (*c* 0.0155 g/mL, EtOH).

(11*R*)-11-Methyloxacycloundecane-2,4-dione (21). To a 100-mL round-bottom flask containing β-keto lactone **20** (180 mg, 0.92 mmol) in EtOH (10 mL) under a blanket of N_2 was added 10% Pd on carbon (30 mg). The vessel was purged with hydrogen via a balloon and the nitrogen inlet was removed. The suspension was allowed to stir at room temperature with the balloon attached for 4 h. The suspension was then filtered and concentrated in vacuo to yield 173 mg (95%) of **21** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (m, 1H), 3.41 (d, 1H, J = 13.7 Hz), 3.37 (d, 1H, J = 13.7 Hz), 2.69 (ddd, 1H, J = 3.4, 11.2, 15.6 Hz), 2.40 (ddd, 1H, J = 3.4, 10.3, 15.6 Hz), 1.92 (m, 1H), 1.78−1.15 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 166.1, 74.2, 52.5, 39.3, 31.1, 24.8, 24.0, 23.2, 22.9, 20.7; $[\alpha]_D$ −100.0 (*c* 0.0114 g/mL).

(±)-(3*E*)-12-Methyloxacyclododec-3-ene-2,5-dione (5). A 100-mL round-bottom flask was equipped with a stir bar and charged with 10 mL of benzene and diethyl zinc (1.0 M in hexanes, 1.70 mL, 1.70 mmol) under an atmosphere of N_2 at room temperature. Methylene iodide (0.14 mL, 1.73 mmol) was added and the resulting white suspension was stirred for 10 min. A solution of racemic β-keto lactone **21** (34 mg, 0.17 mmol) in benzene (5 mL) was added rapidly by syringe and allowed to stir until the starting material was no longer visible by TLC (approximately 1.5−2.0 h). Iodine (440, 1.73 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 s. A saturated solution of sodium thiosulfate (20 mL) was added and the mixture was stirred until the pink color had disappeared. To this solution was added DBU (0.25 mL, 1.70 mmol) and the mixture was stirred for 1 min, washed with saturated aqueous ammonium chloride (25 mL), and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (2:1, hexanes/Et_2O; R_f 0.22) to yield 24 mg (66%) of **5** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, 1H, J = 13.2 Hz), 6.02 (d, 1H, J = 13.2 Hz), 4.97 (m, 1H), 2.69 (ddd, 1H, J = 3.4, 7.8, 18.1 Hz), 2.54 (ddd, 1H, J = 3.9, 8.3, 18.1 Hz), 1.82−1.29 (m, 10H), 1.27 (d, 3H, J = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 165.5, 139.8, 126.1, 74.8, 40.4, 32.0, 25.0, 24.4, 23.6, 20.6, 19.9.

(+)-(12*R*)-12-Methyloxacyclododec-3*E*-ene-2,5-dione (4). A 100-mL round-bottom flask was equipped with a stir bar and charged with 10 mL of benzene and diethyl zinc (1.0 M in hexanes, 1.90 mL, 1.90 mmol) under an atmosphere of N_2 at room temperature. Methylene iodide (0.16 mL, 1.94 mmol) was added and the resulting white suspension was stirred for 10 min. A solution of β-keto lactone **21** (38.6 mg, 0.19 mmol) in benzene (2.5 mL) was added rapidly by syringe and allowed to stir until the starting material was no longer visible by TLC (approximately 1.5 h). Iodine (495 mg, 1.94 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 s. A saturated solution of sodium thiosulfate (20 mL) was added and the mixture was stirred until the pink color had disappeared. The mixture was diluted with diethyl ether (20 mL) and washed with an aqueous solution of ammonium chloride (25 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue, which contained **24**, was dissolved in

diethyl ether (1 mL) and brought to −15 °C. To this solution was added DBU (0.04 mL, 0.25 mmol) and the mixture was allowed to stir for approximately 2 min. The mixture was filtered through a plug of silica. The silica plug was washed with diethyl ether (3 × 2 mL) and the filtrate was concentrated under reduced pressure in a water bath that was maintained at room temperature. Chromatography on silica (2:1, hexanes/Et_2O, R_f 0.19) yielded **3** (19 mg, 48%) as a white solid (mp 80.2−81.4 °C (lit.[22] mp 83−84 °C)), $[\alpha]_D$ 26.5 (*c* 0.00204 g/mL, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 1H, J = 16.1 Hz), 6.78 (d, 1H, J = 16.1 Hz), 4.89 (m, 1H), 2.73 (ddd, 1H, J = 3.4, 10.7, 14.2 Hz), 2.47 (ddd, 1H, J = 3.4, 10.3, 14.2 Hz), 1.85 (m, 1H), 1.70−1.30 (m, 9H), 1.39 (d, 3H, J = 6.4 Hz).

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Acknowledgment. We thank the University of New Hampshire and the National Institutes of Health (R15 GM060967-01) for supporting this work.

Supporting Information Available: ^{1}H and ^{13}C spectra for compounds **9a**−**13a, 9b**−**13b, 10c**−**14c**, **18**−**21**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0264776