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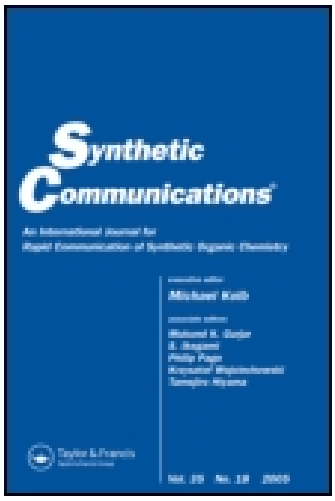

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Synthesis of Fused Tetrahydrofuran-γ-lactone Motifs via One-Pot Ring Expansion of Cyclopropane Rings

Charles Kim [a] , Thomas Brady [a] , Sun Hee Kim [a] & Emmanuel A. Theodorakis [a]

[a] Department of Chemistry , University of California San Diego , 9500 Gilman Drive, La Jolla, California, 92093-0358, USA

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Synthesis of Fused Tetrahydrofuran-γ-lactone Motifs via One-Pot Ring Expansion of Cyclopropane Rings

Charles Kim, Thomas Brady, Sun Hee Kim, and Emmanuel A. Theodorakis*

Department of Chemistry, University of California San Diego, La Jolla, California, USA

ABSTRACT

An efficient method for constructing fused tetrahydrofuran-γ-lactone scaffolds, such as **8**, is presented. Key to this strategy is an acid-catalyzed ring expansion of cyclopropyl precursor **6** that proceeds in the presence of $MeSO_3H$ in acetone and produces the desired bicyclic system in good to excellent yields.

Key Words: Cyclopropanation; Ring expansion; Tetrahydrofuran-γ-lactone; Bicyclic system.

*Correspondence: Emmanuel A. Theodorakis, Department of Chemistry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0358, USA; E-mail: etheodor@ucsd.edu or etheodorakis@ucsd.edu.

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INTRODUCTION

A wide range of linear, angular, and fused γ-butyrolactone ring systems are encountered in natural product structures. Among them, fusion of the γ-butyrolactone onto a substituted tetrahydrofuran (THF) ring creates a distinctive motif that features as a substructure in an interesting but underexplored class of natural diterpenes. Representative members of this family include the marine diterpenes spongionelin (**1**),[1] macfarlandin C (**3**),[2] norrisolide (**4**),[3] and the fungal metabolite dermatolactone (**2**)[4] (Fig. 1).

The interesting chemical architecture of this bicyclic motif, referred to also as perhydrofuran [2,3-*b*] furan moiety, have prompted several approaches toward its synthesis. These are based on enzymatic Baeyer–Villiger oxidation of fused cyclobutanones,[5] oxyselenylation of 2,3 dihydrofurans,[6] radical cyclizations of substituted furans,[7] and acid-catalyzed cyclization of cyclohexanone carboxaldehydes.[8] Nonetheless, all reported strategies suffer from the multiple steps and the low overall yields.

RESULTS AND DISCUSSION

Attracted by the topological characteristics of such fused bicyclic system and faced with the limitations of established strategies, we sought to examine an alternative synthetic entry. Key to this approach was the recognition that the γ-butyrolactone unit can arise from ring expansion of a cyclopropyl carboxylate ester, such as **6** (Fig. 2). It is well established that the strained three-membered ring of cyclopropanes can lead, upon activation, to a variety of ring cleavage and ring expansion reactions (for selected references on ring expansion of cyclopropanes see Ref.[9]). Based on this, we expected that the presence of both electron withdrawing and electron donating substituents at

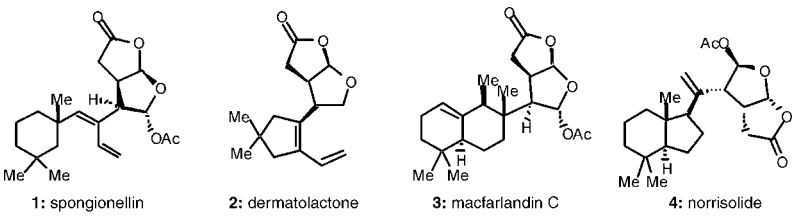

Figure 1. Representative natural products containing a fused tetrahydrofuran-γ-lactone ring system.

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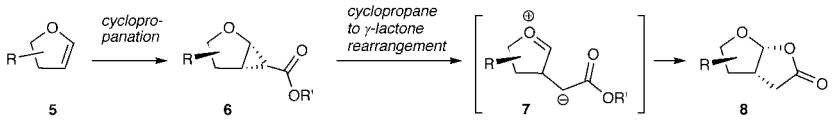

Figure 2. Strategy for the construction of fused tetrahydrofuran-γ-lactone motifs.

vicinal positions of the cyclopropyl ring of **6** would allow the cleavage of the anomeric bond to occur under mild acidic conditions (for selected reviews on this topic see Ref.[10]). The transiently produced 1,3-dipolar synthon **7** could then cyclize in situ at the anomeric center to produce the desired bicyclic ring system of **8**. An important advantage of this strategy is that one can benefit from the existing stereochemistry of the substituted dihydrofuran **5** to install the cyclopropane ring, eventually accessing enantiomerically pure perhydrofuran [2,3-*b*] furans (for references on cyclopropyl ring opening see Ref.[11]). In this manuscript, we present the synthesis and one-step ring expansion of cyclopropanes of generic structure **6** to form the fused tetrahydrofuran γ-lactone structures, such as **8**.

The synthesis of cyclopropane derivatives **11**, **13**, **14**, **15**, and **16** is shown in Sch. 1 and departed with transformation of D-mannose (**9**) to the known glycal **10**.[12] We expected that both the acetonide and the benzyl ether functionalities will shield the top face of vinyl ether **10** and direct the cyclopropanation from the β-face. Indeed, slow addition of ethyl diazoacetate into a concentrated mixture of **10** and rhodium (II) acetate afforded cyclopropane **11** in 59% yield (4 : 1 ratio of isomers in favor of the exo adduct) (for selected references on cyclopropanation chemistry see Ref.[13]). Exposure of **11** to mildly acidic conditions allowed the deprotection of the acetonide unit without opening the cyclopropyl ring. The resulting diol was then oxidatively cleaved ($NaIO_4$) to produce aldehyde **12**, which after methylation (MeMgBr) and subsequent oxidation afforded cyclopropane **13** in 58% combined yield. Alternatively, reduction of aldehyde **12** ($NaBH_4$), followed by silylation of the resulting alcohol (TBDPSCl, imidazole) gave rise to cyclopropyl derivative **14**. Reductive debenzylation of **14** (H_2, Pd/C), followed by oxidation of the resulting alcohol produced ketone **15** (59% yield), which was further subjected to modified Wittig olefination conditions to form alkene **16**. Cyclopropanes **20**,[14a] **22**,[14b] and **24**[14c] were obtained in good yields via a rhodium catalyzed cyclopropanation of ethyl diazoacetate with the corresponding dihydrofurans, following literature procedures.

The results from the cyclopropane to γ-lactone rearrangement are summarized in Table 1. During our initial studies we examined the conversion

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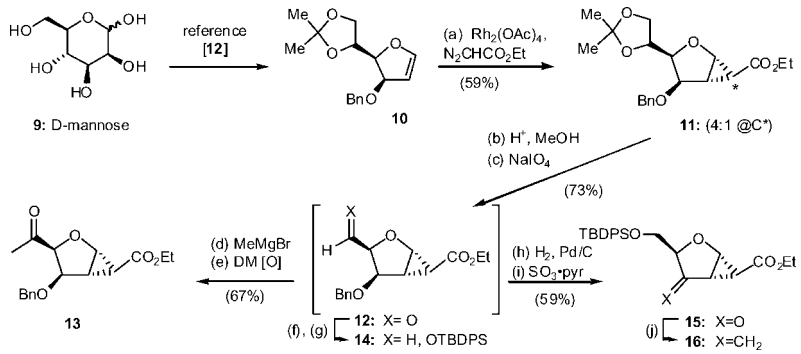

Scheme 1. Reagents and conditions: (a) 0.01 equiv. $Rh_2(OAc)_4$, 1.1 equiv. N_2CHCO_2Et (0.1 M in CH_2Cl_2, syringe pump addition), CH_2Cl_2, 25°C, 14 hr, 59%; (b) HCl (10% aq), MeOH/THF: 1/10, 25°C, 6 hr, 87%; (c) 3.0 equiv. $NaIO_4$, THF/H_2O: 3/1, 2 hr, 25°C, 85%; (d) 1.3 equiv. MeMgBr (1 M in THF), THF, −78°C, 1 hr, 72%; (e) 2.5 equiv. Dess–Martin periodinane, CH_2Cl_2, 2 hr, 93%; (f) 1.0 equiv. $NaBH_4$, THF/MeOH: 5/1, 25°C, 0.5 hr, 73%; (g) 1.5 equiv. TBDPSCl, 2.0 equiv. imid, THF, 25°C, 4 hr, 95%; (h) 0.1 equiv. Pd/C (10%), H_2 (1 atm), 25°C, 24 hr, 84%; (i) 3.0 equiv. SO_3·pyr, 3.0 equiv. Et_3N, CH_2Cl_2/DMSO: 1/1, 0°C, 5 hr, 71%; (j) 1.5 equiv. Ph_3PCH_3Br, 1.5 equiv. *t*BuOK (1 M in THF), THF, 60°C, 12 hr, 34%.

of cyclopropane **11** to lactone **17** using a variety of acids, such as 10% H_2SO_4 or 1 N HCl in refluxing dioxane, or ethanol. In all these cases, we observed the formation of multiple products, presumably arising from concomitant deprotection of the acetonide group. In order to suppress acetonide deprotection we subjected **11** to 10% methanesulfonic acid in acetone and found that, after only 6 hr at 25°C, the starting cyclopropyl ester was completely converted to the desired product **17**, which was isolated in 77% yield. The structure and relative stereochemistry of **17** was unambiguously established by a single crystal x-ray analysis, and confirmed that the cyclopropanation in precursor **11** occurred from the more accessible α-face of the cyclopropyl ring.[a] Under identical acidic treatment the TBDPS group of cyclopropane adduct **14** was not cleaved (Table 1, entry 3), allowing isolation of the desired lactone **19** in 83% yield. Similar yields were obtained during the acid-catalyzed ring expansion of cyclopropanes **13**, **20**, **22**, and **24**, indicating that this one-pot reaction is general and synthetically useful.

[a]The crystallographic data for structure **17** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication No: CCDC 212319. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

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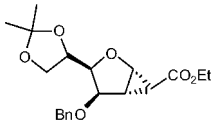
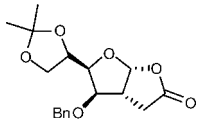
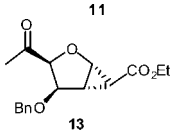
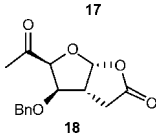
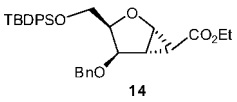
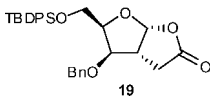
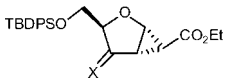
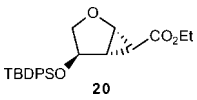
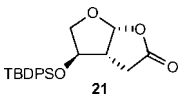
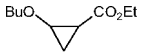
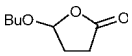
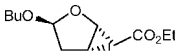
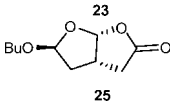
Table 1. The results from the cyclopropane to γ-lactone rearrangement.

Entry	Cyclopropane	γ-Lactone	Yield (%)
1	 **11**	 **17**	77
2	 **13**	 **18**	62
3	 **14**	 **19**	83
4	 **15**: X=O **16**: X=CH_2	*Decomposition*	N/A
5			
6	 **20**	 **21**	79
7	 **22**	 **23**	48
8	 **24**	 **25**	72

However, cyclopropanes **15** and **16** having an sp^2 hybridized center at the α-carbon of the cyclopropyl ring led to decomposition under the above conditions.

CONCLUSION

In summary, we describe herein an efficient and general procedure for the preparation of fused tetrahydrofuran-γ-lactone motifs, based on a $MeSO_3H$ catalyzed one-pot ring expansion of the corresponding cyclopropanes.

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SELECTED EXPERIMENTAL PROCEDURES/DATA

General Techniques

All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45°C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. THF, diethyl ether (ether, Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$), and benzene (PhH) were purified by passage through a bed of activated alumina. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative TLC separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX 3 kW Sealed Tube x-ray diffraction system.

Cyclopropane 11. Compound **10**[12] (1.1 g, 3.97 mmol) was dissolved in 10 mL of dichloromethane and 5 mg of $Rh_2(OAc)_4$ was added. Ethyl diazoacetate (0.5 g, 4.3 mmol) was dissolved in 10 mL of dichloromethane and added to the stirring 2,3-dihydrofuran/rhodium mixture over a 12-hr period via the syringe pump. The residue was then concentrated and subjected to silica gel chromatography to provide 0.9 g of the title compound **11** (59%). $[\alpha]_D^{25}$: −5.0 ($c = 0.9$, CH_2Cl_2); IR (film) ν_{max} 2984, 2935, 1715, 1268, 1187, 1097; Rf = 0.5 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.71 (d, $J = 11.6$ Hz, 1H), 4.59 (d, $J = 12$ Hz, 1H), 4.35 (m, 2H), 4.18 (d, $J = 4.8$ Hz, 1H), 4.07 (m, 3H), 3.95 (dd, $J = 6.0$, 8.4 Hz, 1H), 3.68 (m, 1H), 2.34 (t, $J = 4.4$, 4.8 Hz, 1H), 1.89 (d, $J = 2.8$ Hz, 1H),

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1.40 (s, 3H), 1.36 (s, 3H), 1.24 (t, $J = 6.8$, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 137.5, 128.2, 127.6, 127.5, 108.6, 81.9, 78.8, 72.7, 72.1, 66.5, 64.9, 60.7, 28.5, 26.7, 25.4, 21.4, 14.3; HRMS, calcd for $C_{20}H_{26}O_6$ ($M + Na^+$): 385.1627, found: 385.1623.

Cyclopropane 13. Compound **11** (1 g, 2.7 mmol) was dissolved in 50 mL of a (1/1) THF/methanol solution and cooled to 0°C. A 20 mL of aqueous HCl (1 M) was added to the cooled, stirring solution and stirring was continued for 6 hr. The solution was diluted with ethyl acetate and carefully neutralized with saturated sodium bicarbonate solution. The diol was extracted three times with 50 mL ethyl acetate, dried over magnesium sulfate and concentrated on the rotary evaporator. The crude residue was purified by silica gel chromatography (60% ether in hexanes) to yield 0.75 g of analytically pure diol (87%). $[\alpha]_D^{25} = -15.1$ ($c = 1.1$, CH_2Cl_2); IR (film) ν_{max} 3393, 2924, 1718, 1449, 1406, 1274; Rf = 0.2 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5H), 4.80 (d, $J = 11.6$ Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.37 (d, $J = 4.8$ Hz, 1H), 4.30 (d, $J = 5.2$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.01–3.97 (m, 1H), 3.76 (dd, $J = 11.6$ Hz, 3.4 Hz, 1H), 3.66–3.61 (m, 2H), 2.40 (t, $J = 4.2$ Hz, 1H), 2.10 (br.s, 2H), 1.88 (d, $J = 4.0$ Hz, 1H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.8, 129.9, 129.0, 82.1, 80.7, 73.2, 70.7, 66.5, 65.3, 62.1, 28.9, 23.0, 15.6; HRMS calcd for $C_{17}H_{22}O_6$ ($M + Na^+$): 345.1314, found: 345.1299.

The diol (0.75 g, 2.3 mmol) was added to a round-bottom flask and dissolved in 50 mL of a 1/1 mixture of THF/H_2O. Sodium periodate (0.5 g, 6.9 mmol) was added and the reaction mixture was stirred for 2 hr. The reaction was cooled to 0°C and quenched with saturated sodium thiosulfate and sodium bicarbonate (50 mL each). The reaction mixture was diluted with ethyl acetate and extracted three times with 75 mL of ethyl acetate. The combined organics were dried over magnesium sulfate and concentrated en vacuo to give ~0.7 g of the crude unstable aldehyde **12**, which was immediately treated with ~1.1 equiv. (0.84 mL, 2.5 mmol) of methylmagnesium bromide (3 M in ether) in 25 mL of THF at 0°C. The reaction was stirred for 30 min at 0°C, then diluted with 50 mL of ether. The organic layer was washed with 100 mL of saturated ammonium chloride. The aqueous layer was extracted twice with 50 mL of ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated on the rotary evaporator. The resulting alcohol, mixture of diastereomers, was dissolved in 50 mL of dichloromethane and treated with Dess–Martin periodinane (2.1 g, 5 mmol) and stirred for 2 hr. The reaction was quenched with sodium thiosulfate and sodium bicarbonate (50 mL each). The aqueous phase was extracted twice with 50 mL of dichloromethane, filtered, dried over magnesium sulfate, and concentrated on the rotary evaporator. The crude ketone was subjected to silica gel chromatography (30% ether in hexanes) to afford

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ketone **13** in 49% yield (four steps). $[\alpha]_D^{25}$: −7.7 ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 1717, 1454, 1183, 1118, 1094; Rf = 0.6 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.63–4.39 (m, 4H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.04 (d, $J = 5.2$ Hz, 1H), 2.37 (t, $J = 4.8$ Hz, 1H), 2.21 (s, 3H), 1.79 (d, $J = 3.6$ Hz, 1H), 1.26 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 170.3, 137.9, 128.5, 126.0, 127.7, 86.1, 80.3, 78.8, 72.3, 65.7, 60.9, 28.3, 27.4, 21.8, 14.2; HRMS, calcd for $C_{17}H_{20}O_5$ ($M + Na^+$): 327.1208, found: 327.1198.

Cyclopropane 14. The crude aldehyde **12** (0.7 g, ∼2.3 mmol, prepared as previously described for **13**) was dissolved in a 1/1 mixture of isopropanol/THF and cooled to 0°C. Sodium borohydride (0.12 g, 4 mmol) was added to the solution and stirring was continued for 30 min at 0°C. The reaction was then diluted with water and extracted three times with 75 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The crude residue was purified on silica gel (50% ether in hexanes) to yield 0.47 g of the primary alcohol (70%, two steps). $[\alpha]_D^{25}$: −12.7 ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 3444, 2926, 1715, 1412; Rf = 0.2 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H), 4.76 (d, $J = 11.6$ Hz, 1H), 4.48 (d, $J = 11.6$ Hz, 1H), 4.43 (dd, $J = 5.2$, 0.8 Hz, 1H), 4.24 (d, $J = 5.2$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.00 (dd, $J = 10.4$, 6.4 Hz, 1H), 3.85–3.77 (m, 2H), 2.39 (dd, $J = 4.8$, 4.0 Hz, 1H), 1.84 (dd, $J = 4.0$, 1.2 Hz, 1H), 1.25 (t, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 137.1, 128.7, 128.2, 127.7, 81.5, 80.3, 72.0, 65.2, 60.8, 60.7(2), 22.2, 14.2; HRMS, calcd for $C_{16}H_{20}O_5$ ($M + Na^+$): 315.1209, found: 315.1201.

The alcohol (0.47 g, 1.5 mmol) and imidazole (0.11 g, 1.6 mmol) were dissolved in 10 mL THF and TBDPS-Cl (0.44 g, 1.6 mmol) was added to the stirring solution. The reaction was stirred at room temperature for 3 hr and quenched with water. The solution was diluted with ether and extracted three times with 50 mL of ether. The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The product was isolated by silica gel chromatography (25% ether in hexanes) to yield 0.77 g of the protected alcohol **14** (93%). $[\alpha]_D^{25} = -5.3$ ($c = 1.0$, CH_2Cl_2); IR (film); ν_{max} 3065, 2930, 2855, 1697, 1423, 1109; Rf = 0.6 (30% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H) 7.44–7.25 (m, 11H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.54 (d, $J = 12$ Hz, 1H), 4.34 (dd, $J = 4.8$ Hz, 0.6 Hz, 1H), 4.18 (d, $J = 4.8$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.0 (dd, $J = 10.4$ Hz, 6.2 Hz, 1H), 3.85–3.75 (m, 2H), 2.34 (t, $J = 4.4$ Hz, 1H), 1.91 (dd, $J = 3.6$ Hz, 1.0 Hz, 1H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8. 137.6, 135.4, 135.3, 134.5, 133.3, 133.1, 129.6 129.5, 129.4, 128.3, 127.6, 127.5, 127.4, 82.1, 78.7, 72.0, 64.8, 64.7, 61.2, 60.7, 28.4, 26.9, 26.7, 21.6, 21.5, 19.3, 14.4; HRMS calcd for $C_{32}H_{38}O_5Si$ ($M + Na^+$): 553.2387, found: 553.2367.

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Cyclopropane 15. Compound **14** (5 g, 9.4 mmol) was dissolved in 150 mL of THF, palladium hydroxide, (10% on carbon, 0.5 g) was added and the flask was capped with a septum, evacuated and filled with hydrogen gas from a balloon. The reaction flask was periodically evacuated and replenished with hydrogen gas (four times over a 12 hr period). The reaction was stirred under an argon atmosphere for an additional 12 hr. The solution was filtered through a plug of celite and concentrated on the rotary evaporator. The crude residue was purified on silica gel (50% ether in hexanes) to yield 3 g of the secondary alcohol (75%). $[\alpha]_D^{25} = +10.8$ ($c = 2.0$, CH_2Cl_2); IR (film) ν_{max} 3435, 3074 2930, 1714, 1105; Rf = 0.4 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.45–7.38 (m, 6H), 4.51 (d, $J = 4.8$ Hz, 1H), 4.40 (dd, $J = 5.2$ Hz, 1.2 Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.97–3.95 (m, 2H), 3.68 (q, $J = 9.6$ Hz, 5.0 Hz, 1H), 2.31 (t, $J = 4.6$ Hz, 1H), 1.85 (dd, $J = 3.6$ Hz, 1.2 Hz, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 135.4, 135.3, 135.2, 135.5, 132.2, 129.8, 127.7, 127.6, 81.0, 80.9, 73.7, 73.6, 64.9, 64.8, 62.0, 60.6, 31.3, 31.2, 26.9, 26.8, 22.2, 22.1, 19.2, 14.3; HRMS calcd for $C_{25}H_{32}O_5Si$ ($M + Na^+$): 463.1917, found: 463.1921.

The alcohol (1.2 g, 2.7 mmol) was dissolved in 60 mL of a 1/1 mixture of DMSO/dichloromethane. The reaction was cooled by an ice bath and triethylamine (3.75 mL, 27 mmol) was added followed by addition of sulfur trioxide–pyridine complex (4.34 g, 27 mmol) in four portions over a 2-hr period. The reaction was stirred for an additional 4 hr at 0°C and quenched with brine. The mixture was extracted three times with 125 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The ketone **15** was purified on silica gel (25% ether in hexanes) to yield 0.91 g of analytically pure compound (77%). $[\alpha]_D^{25} = +23.7$ ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 3071, 2931, 2851, 1755, 1725, 1426; Rf = 0.7 (30% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 4H), 7.44–7.38 (m, 6H), 4.88 (td, $J = 4.4$ Hz, 1.2 Hz, 1H), 4.18 (q, $J = 6.8$ Hz, 2H), 3.93 (dd, $J = 10.8$ Hz, 2.8 Hz, 1H), 3.89 (t, $J = 2.8$ Hz, 1H), 3.85 (dd, $J = 10.8$ Hz, 2.4 Hz, 1H), 2.67 (t, $J = 4.4$ Hz, 1H), 2.35 (dd, $J = 3.2$ Hz, 1.6 Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 168.6, 135.9, 133.2, 133.1, 130.1, 130.0, 128.0(2), 127.9, 81.3, 67.1, 64.1, 61.7, 33.0, 28.0, 26.9, 26.8, 19.5, 14.4; HRMS calcd for $C_{25}H_{30}O_5Si$ ($M + Na^+$): 461.1760, found: 461.1767.

Cyclopropane 16. Methyltriphenylphosphonium bromide (10 g, 28 mmol) was dissolved in 10 mL of anhydrous THF in a flame dried flask under an argon atomosphere. NaHMDS (27 mL, 1 M) was added via syringe at room temperature to the Wittig reagent and the mixture was stirred for 30 min. The ketone **15** (3.0 g, 7.1 mmol) was dissolved in anhydrous THF (10 mL) and added dropwise to the bright yellow solution. The reaction was judged complete (by TLC) after 30 min of stirring at room temperature. The

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reaction was diluted with 100 mL of ether followed by 300 mL of brine. The aqueous phase was extracted with 3–150 mL portions of ether. The combined organic layers were dried over magnesium sulfate and concentrated on the rotary evaporator. The residue was purified by silica gel (10% ether in hexanes) to yield 2.1 g of olefin **16** (68%). $[\alpha]_D^{25} = +15.0$ ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 3478, 2924, 2848, 1697; Rf = 0.6 (30% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.41–7.36 (m, 6H), 5.22 (d, $J = 2.4$ Hz, 1H), 4.90 (s, 1H), 4.38 (dd, $J = 4.4$ Hz, 0.4 Hz, 1H), 4.33–4.28 (m, 1H), 4.12 (dq, $J = 6.8$ Hz, 1.2 Hz, 2H), 3.69 (dd, $J = 4.4$ Hz, 3.2 Hz, 2H), 2.67 (t, $J = 4.2$ Hz, 1H), 1.95 (dd, $J = 2.4$ Hz, 0.8 Hz, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 146.6, 135.5, 135.4, 135.1, 134.6, 129.5, 129.4 127.5, 106.7, 82.5(2), 66.3, 66.0, 65.9, 60.7, 32.6, 27.0, 26.9, 26.6, 24.9, 19.3, 19.2, 19.1, 14.3; HRMS calcd for $C_{26}H_{32}O_4Si$ ($M + Na^+$): 459.1967, found: 459.1973.

Cyclopropane 20. The cyclopropane, prepared by literature procedure,[14a] (2.5 g, 5.2 mmol) and imidazole (0.36 g, 5.3 mmol) were dissolved in 20 mL THF and TBDPS-Cl (1.4 g, 5.3 mmol) was added to the stirring solution. The reaction was stirred at room temperature for 3 hr and quenched with water. The solution was diluted with ether and extracted three times with 100 mL of ether. The combined organics were dried over magnesium sulfate and concentrated on the rotary evaporator. The product was isolated by silica gel chromatography (25% ether in hexanes) to yield 2.0 g of the protected alcohol **20** (95%). Rf = 0.4 (30% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.68 (m, 4H), 7.48–7.37 (m, 6H), 4.49 (d, $J = 4.4$ Hz, 1H), 4.41 (d, $J = 4.4$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.89 (d, $J = 10.0$ Hz, 1H), 3.35 (dd, $J = 10.8$ Hz, 4.4 Hz, 1H), 2.26 (t, $J = 3.6$ Hz, 1H), 1.64 (dd, $J = 3.6$ Hz, 1.2 Hz, 1H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 135.6, 134.8, 129.8 129.5, 127.8, 127.6, 75.1, 74.1, 72.0, 65.2, 60.6, 31.3, 26.8, 26.5, 21.4, 19.0, 14.1; HRMS calcd for $C_{24}H_{30}O_4Si$ ($M + Na^+$): 433.1811, found: 433.1979.

Cyclopropane 22. This compound was prepared by the rhodium catalyzed cyclopropanation of *n*-butyl vinyl ether and ethyl diazoacetate following a literature procedure.[14b] *Z*-**22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, $J = 7.2$ Hz, 2H), 3.57–3.47 (m, 2H), 3.41–3.34 (m, 1H), 1.72–0.82 (m, 13H); *E*-**22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, $J = 6.9$ Hz, 2H), 3.59–3.49 (m, 3H), 1.76–0.82 (m, 13H); HRMS calcd for $C_{10}H_{18}O_3$ ($M + Na^+$): 209.1154, found: 209.1159.

Cyclopropane 24. 2-Butoxy-2,3-dihydrofuran[14c] (1.0 g, 7.0 mmol) was dissolved in 50 mL of dichloromethane and $Rh_2(OAc)_4$ ($\sim$15 mg, 0.03 mmol) was added. Ethyl diazoacetate (0.85 g, 7.4 mmol) dissolved in 8 mL of dichloromethane was added via syringe pump over 8 hr. The dichloromethane was removed on the rotary evaporator and the residue was purified by silica

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gel chromatography (25% ether in hexanes) to yield 1.2 g of cyclopropane **24**. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (dd, $J = 6.8$, 1.2 Hz, 1H), 4.27–4.21 (m, 1H), 4.15–4.06 (m, 2H), 3.71–3.63 (m, 1H), 3.40–3.25 (m, 1H), 2.23–2.19 (m, 1H), 2.15–2.07 (m, 2H), 2.01 (dd, $J = 13.6$, 1.2 Hz, 1H), 1.58–1.21 (m, 7H), 0.91 (t, $J = 7.2$ Hz, 3H); HRMS calcd for $C_{12}H_{20}O_4$ ($M + Na^+$): 251.1259, found: 251.1262.

General Procedure for the Conversion of Cyclopropane Derivatives to γ-Lactones

To a solution of the cyclopropyl adduct (0.44 mmol) in acetone (1 mL) was added 1.0 mL of 10% methanesulfonic acid solution in acetone at 25°C. The reaction mixture was stirred overnight, quenched by triethylamine (0.26 mL) in an ice bath and then stirred for 30 min. The solution was concentrated in vacuo and purified by column chromatography (ether/petroleum ether) to give the corresponding γ-lactone.

Lactone 17. $[\alpha]_D^{25}$: −21.7 ($c = 1.68$, CH_2Cl_2); IR (film) ν_{max} 1785, 1067, 982; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 6.16 (d, $J = 5.6$ Hz, 1H), 4.63 (d, $J = 1.6$ Hz, 2H), 4.43 (q, $J = 7.6$ Hz, 1H), 4.14 (dd, $J = 8.8$, 6.0 Hz, 1H), 4.02–3.99 (m, 2H), 3.91 (d, $J = 2.8$ Hz, 1H), 3.22–3.19 (m, 1H), 2.84 (dd, $J = 18.8$, 11.6 Hz, 1H), 2.35 (dd, $J = 18.8$, 5.2 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 137.3, 128.5, 128.0, 127.6, 109.3, 107.2, 83.4, 81.9, 72.1, 67.2, 45.0, 31.4, 26.8, 25.4; HRMS, calcd for $C_{18}H_{22}O_6$ ($M + Na^+$): 357.1314, found: 357.1330.

Lactone 18. $[\alpha]_D^{25}$: −53.5 ($c = 0.85$, CH_2Cl_2); IR (film) ν_{max} 3634, 3528, 2918, 2861, 1780, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.23 (m, 2H), 6.33 (d, $J = 5.6$ Hz, 1H), 4.54 (m, 2H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.15 (d, $J = 4$ Hz, 1H), 3.23 (m, 1H), 2.84 (dd, $J = 19.2$, 11.6 Hz, 1H), 2.33 (dd, $J = 5.2$, 18.8 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 173.5, 136.2, 128.5, 128.2, 127.6, 107.4, 85.4, 85.1, 72.2, 44.3, 31.1, 28.4; HRMS, calcd for $C_{15}H_{16}O_5$ ($M + Cs^+$): 409.0052, found: 409.0055.

Lactone 19. $[\alpha]_D^{25}$: −18.0 ($c = 1.3$, CH_2Cl_2); IR (film) ν_{max} 2931, 2857, 1784, 1427, 1109; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 4H), 7.43–7.10 (m, 11H), 6.16 (d, $J = 5.6$ Hz, 1H), 4.60 (d, $J = 12$ Hz, 1H), 4.53 (d, $J = 12$ Hz, 1H), 4.42 (m, 1H), 4.03–4.09 (m, 3H), 3.19 (m, 1H), 2.83 (dd, $J = 18.8$, 11.6 Hz, 1H), 2.35 (dd, $J = 18.4$, 5.2 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 137.2, 135.5, 134.8, 133.0, 132.8, 129.8, 129.7, 129.6, 129.5, 128.5, 128.0, 127.8, 127.7, 127.6, 107.2, 83.2, 81.3, 72.1, 60.7, 44.6, 31.8, 26.7, 26.5, 19.1; HRMS, calcd for $C_{30}H_{34}O_5Si$ ($M + Na^+$): 525.2073, found: 525.2069.

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Lactone 21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.61 (m, 4H), 7.47–7.39 (m, 6H), 6.21 (d, $J = 5.6$ Hz, 1H), 4.15 (d, $J = 3.2$ Hz, 1H), 4.00 (d, $J = 10.4$ Hz, 1H), 3.83 (dd, $J = 10.4$, 3.6 Hz, 1H), 2.98–2.94 (m, 1H), 2.50 (dd, $J = 19.2$, 11.6 Hz, 1H), 2.00 (dd, $J = 19.2$, 4.80 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 135.6, 135.5, 133.0, 132.7, 130.2, 130.1, 128.0, 127.9, 108.0, 78.7, 74.0, 48.4, 31.4, 26.7, 19.0; HRMS, calcd for $C_{22}H_{26}O_4Si$ ($M + Na^+$): 405.1498, found: 405.1502.

Lactone 23. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (dd, $J = 5.4$, 2.1 Hz, 1H), 3.83–3.76 (m, 1H), 3.55–3.48 (m, 1H), 2.72–2.61 (m, 1H), 2.46–2.39 (m, 2H), 2.27–2.07 (m, 1H), 1.59–1.20 (m, 4H), 0.91 (t, $J = 7.5$ Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 104.2, 69.4, 31.5, 28.8, 26.9, 19.1, 13.8; HRMS, calcd for $C_8H_{14}O_3$ ($M + Na^+$): 181.0841, found: 181.0844.

Lactone 25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, $J = 7.4$ Hz, 1H), 5.27 (d, $J = 6.0$ Hz, 1H), 3.79 (dd, $J = 7.2$, 4.8 Hz, 1H), 3.37 (dd, $J = 7.2$, 4.8 Hz, 1H), 3.19–3.14 (m, 1H), 2.80 (dd, $J = 14.4$, 6.8 Hz, 1H), 2.64 (dd, $J = 14.0$, 2.4 Hz, 1H), 2.19–2.12 (m, 1H), 2.01 (d, $J = 12.8$ Hz, 1H), 1.55–1.20 (m, 4H), 0.90 (t, $J = 4.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 134.2, 108.4, 105.7, 67.9, 39.3, 36.9, 36.0, 19.4, 14.0; HRMS, calcd for $C_{10}H_{16}O_4$ ($M + Na^+$): 223.0946, found: 223.0949.

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