Use of In Situ Generated Ketene in the Wynberg β-Lactone Synthesis: New Transformations of the Dichlorinated β-Lactone Products

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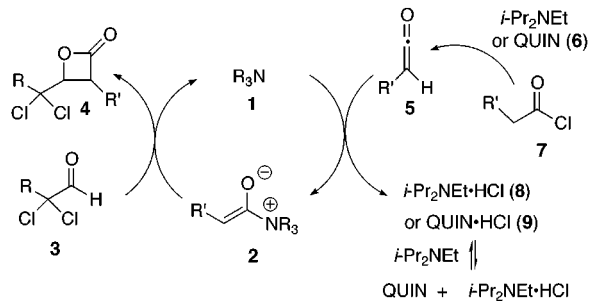
Introduction

β-Lactones are useful synthetic intermediates since they are in fact masked aldol products and thus are important synthons in natural and unnatural product synthesis.[1] However, there are relatively few direct methods for the synthesis of these heterocycles in optically pure form. Recent studies have begun to address this lack of direct methods.[2] In 1982, Wynberg and Staring disclosed one of the first catalytic, asymmetric reactions.[3] They showed that various cinchona alkaloids, such as quinidine and quinine, are excellent catalysts for the net [2 + 2] cycloaddition of highly activated carbonyl compounds, such as chloral, and ketene to form β-lactones with excellent yields and enantioselectivity. Although this method is efficient, there are serious limitations including the use of activated aldehydes and a ketene generator. To begin addressing these limitations, we first sought to develop reaction conditions that would allow the use of in situ generated ketene.[4] The use of triethylamine as both a base to effect dehydrochlorination and a nucleophile to promote the reaction of ketene and activated aldehydes has been previously demonstrated.[5] Swiss chemists have also shown the compatibility of in situ ketene generation in the Wynberg procedure with chloral and trichloroacetone as carbonyl substrates.[6] We were interested in studying the scope of this process further. Furthermore, while the utility of the chlorinated β-lactones obtained via the Wynberg procedure has been explored to some extent,[7] a number of other useful transformations can be envisioned. With these considerations in mind, we have developed a modified and simplified Wynberg procedure for the synthesis of optically active dichlorinated-β-lactones. We have also developed new transformations of the chlorinated β-lactones leading to useful chiral synthons including chloro epoxides, α-azido ketones, vinyl chlorides, and propargylic benzyl ethers.

Scheme 1



The use of in situ generated ketene has been widely employed in synthesis,[8] and one of the simplest and most practical methods involves the action of tertiary amines on acid chlorides.[4b] There are at least two concerns in using a tertiary amine base for dehydrochlorination leading to in situ ketene generation in conjunction with the Wynberg method (Scheme 1). The first concern is the possibility that the tertiary amine used as a base may also act as a nucleophilic catalyst **1** thus leading to racemic product. The second concern is the possiblity of the nucleophilic catalyst (i.e. (−)-quinidine (**6**), QUIN) acting as a base leading to dehydrochlorination of the acid chloride **7** and rendering it unavailable for catalysis. The proposed catalytic cycle for the Wynberg procedure is shown in Scheme 1. The sequence is proposed to involve the ammonium enolate **2** that reacts with an aldehyde in a tandem aldol−lactonization process to give β-lactone **4**.[3c]

Results and Discussion

Control experiments indicated that use of Hunig's base alone with acetyl chloride and α,α-dichlorooctanal did not lead to β-lactone formation as has previously been noted in related reactions.[2b,6] Furthermore, we determined that use of toluene as solvent led to immediate formation of a precipitate when acetyl chloride was added to Hunig's base at −25 °C. The precipitate was identified as the hydrochloride salt of Hunig's base (**8**). Pleasingly when the reaction was repeated in the presence of 2 mol % quinidine (**6**), β-lactone was produced with enantioselectivities similar to those reported by Wynberg (vide infra). In contrast to previous studies,[6] diethyl ether and tetrahydrofuran were found to be inferior solvents relative to toluene. After extensive experimentation, we found

(1) For a review describing transformations of β-lactones, see: (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−449. For a lead reference to more recent transformations, see: (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657−7660.

(2) (a) For a recent review of methods for the synthesis of optically active β-lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434. (b) For a recently described elegant method, see: Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743.

(3) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979. (c) Wynberg, H. *Topics in Stereochemistry* **1986**, *16*, 87−130.

(4) (a) Tidwell, T. T. *Ketenes*; John Wiley&Sons: New York, 1995. For the first report of ketene synthesis from an α-chloro acid choride using Zn dust, see: (b) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735−1739. For the first report of a tertiary amine induced dehydrochlorination to give ketene, see: Wedekind, E. *Ann. Chim.* **1902**, *323*, 246−257.

(5) Borrman, D.; Wegler, R. German Patent DE-PS 1 214 211, 1966.

(6) Jackson, B. Swiss Patent CH681 302 A5, 1993.

(7) (a) Fujisawa, T.; Ito, T.; Fujimoto, K.; Shimuzu, M., Wynberg, H.; Staring, E. G. J. *Tetrahedron Lett.* **1997**, *38*, 1593−1596. (b) Fujisawa, T.; Ito, T.; Nishiura, S.; Shimuzu, M. *Tetrahedron Lett.* **1998**, *39*, 9735−9738 and references cited. (c) Song, C. E.; Lee, J. K.; Kim, I. O.; Choi, J. H. *Synth. Commun.* **1997**, *27*, 1009−1014. (d) Song, C. E.; Lee, J. K.; Lee, S. H.; Lee, S. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1063−1066.

(8) (a) Brady, W. T.; Giang, Y. F.; Marchand, A. P.; Wu, A. *J. Org. Chem.* **1987**, *52*, 3457−3461 and references cited. For some recent examples, see: (b) Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573−2584. (c) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726−9727. (d) ref 2b.

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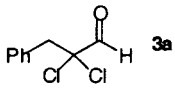
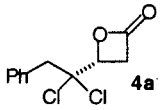
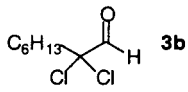
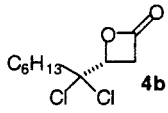
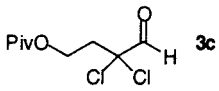
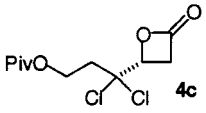
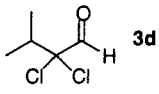
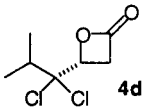
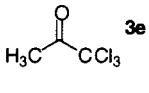
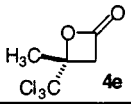
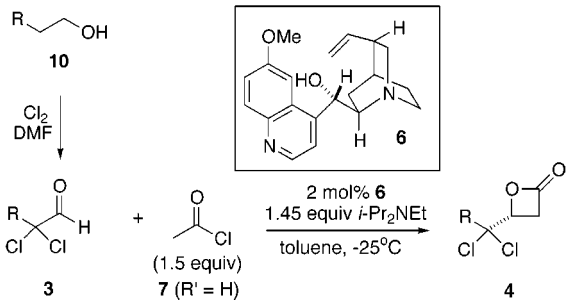
Table 1. β-Lactones Obtained via Nucleophilic Catalytic, Net [2 + 2] Cycloadditions Using In Situ Generated Ketene (Scheme 2)

entry	carbonyl precursor	β-lactone[a]	% yield[b]	% ee[c]
1	 **3a**	 **4a**	85	94
2	 **3b**	 **4b**	73	93
3	 **3c**	 **4c**	80	94
4	 **3d**	 **4d**	40	98
5	 **3e**	 **4e**	25	ND[d]

[a] Absolute configuration of β-lactone **4b** was determined by comparison of optical rotations to published data (ref 13). β-Lactones **4a**, **4c**, and **4d** are assumed to be of the same configuration. [b] Yields refer to isolated, purified products. [c] Optical purity was determined by chiral phase GC (TBS-β-cyclodextrin column). [d] The enantiomeric purity was not determined however comparison of optical rotations with known values indicated the (*R*)-configured β-lactone was obtained.

Scheme 2



that optimal yields were obtained by addition of 1.0 equiv of acetyl chloride to a mixture of the aldehyde, Hunig's base, and 2 mol % quinidine in toluene at −25 °C (Scheme 2). This contrasts to previous related studies in which simultaneous addition of acid chloride and aldehyde was required for optimal yields.[6] Precipitation of the amine hydrochloride was instantaneous, and after 15 min, an additional 0.5 equiv acetyl chloride was added to ensure near complete consumption of aldehyde.[9] Performing the reaction at 0 °C or 25 °C led to similar enantioselectivities (92−93% ee); however, lower yields of β-lactone **4b** (39−42%) were obtained suggestive of the instability of ketene at these temperatures. Thus, in this reaction sequence, Hunig's base does not catalyze formation of the β-lactone nor does quinidine become ineffective as a nucleophilic catalyst due to protonation. It is likely that quinidine also leads to dehydrochlorination of the acid chloride or is protonated to give salt **9**. However, possibly due to the greater solubility of QUIN·HCl relative to EtN*i*-Pr$_2$·HCl in toluene, the QUIN·HCl remains in solution and is free-based by excess Hunig's base. This implies that the requirement for an effective catalyst in this type of reaction is not an appropriate pK_a differential but rather an appropriate solubility differential of the respective hydrochloride salts of the base and catalyst used.

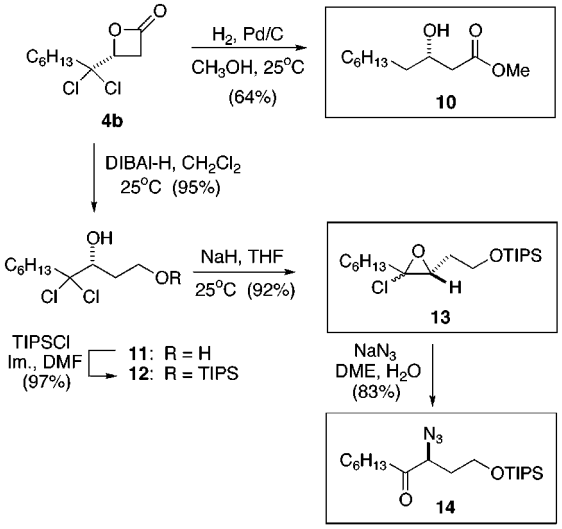
Using the optimized conditions described above, several β-lactones were prepared using in situ ketene generation with acetyl chloride (Table 1). The enantiomeric purity was determined by chiral GC (β-cyclodextrin) on comparison with racemic β-lactones obtained using the same procedure but with quinuclidine (1.0 equiv) as the nucleophilic reagent. The enantiomeric β-lactones should also be available using quinine as demonstrated previously.[3b] Current limitations of this modified Wynberg procedure remain to be the need for activated (i.e., dichlorinated) aldehydes which, however, are available in one step from the corresponding alcohols **10** by the oxidation of De Buyck.[10] Side chain functionality must be compatible with this oxidation and, for example, this mandated the use of a pivalate in aldehyde **3c**.[11] β-Substitution on the aldehyde led to a decrease in yield of β-lactone (Table 1, entry 4). The use of trichloroacetone gave comparable yields of β-lactone using our developed conditions compared to those obtained previously (entry 5).[12,13] Studies with other acid chlorides

(9) Small quantities of unreacted aldehyde (<10%) were commonly detected on analysis of the crude reaction mixture.

(10) (a) De Buyck, L.; Veske, R.; Cantheyn, D.; Schamp, N. *Bull. Soc. Chim. Belg.* **1980**, 89, 441−458. (b) De Buyck, L.; Casaert, F.; De Lepeleire, C. Schamp, N. *Bull. Soc. Chim. Belg.* **1988**, *97*, 525−533.

(11) For example, a primary triisopropylsilyl ether was found to be incompatible with these oxidation conditions.

Scheme 3

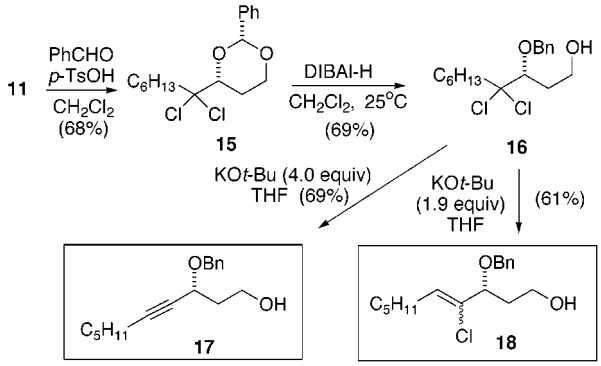


including α-acetoxy, α-methoxy, propionyl, and α-azido acetyl chloride gave only trace quantities (≤5%) of *β*-lactone.

Although we have not yet identified conditions to dechlorinate the *β*-lactone products while maintaining the integrity of the lactone ring,[14] we were able to convert *β*-lactone **4b**[15] to the corresponding *β*-hydroxy ester **10** in a single step. Wynberg and co-workers had previously accomplished this transformation in two steps in similar overall yield.[13] We were also interested in identifying transformations of the dichlorinated *β*-lactones that would make use of the resident chlorine atoms. Toward this goal, we reduced *β*-lactone **4b** to the diol **11**[7b] and selectively protected the primary alcohol as the triisopropylsilyl ether **12** (Scheme 3). Treatment of this alcohol with NaH led to formation of chloroepoxide **13** in good yield as a 38:1 ratio of diastereomers.[16] Transformation of epoxide **13** to the α-azido ketone **14** was accomplished by treatment with NaN_3 in aqueous DME[17] with no loss in optical purity as determined by chiral phase HPLC.[18]

Unsaturation could also be introduced by controlled eliminations of the dichlorinated products. To prevent competing epoxide formation, the secondary alcohol of diol **11** was first protected as the benzyl ether in a two-step process proceeding through benzylidene acetal **15** to give alcohol **16** (Scheme 4). Treatment of this alcohol with 1.9 equiv of KO*t*-Bu gave the vinyl chloride **18** as a 7.2:1 ratio of geometrical isomers contaminated with trace amounts of alkyne **17**. Conversion to the alkyne **17** was accomplished using 4.0 equiv of KO*t*-Bu.

Scheme 4



In summary, Wynberg's procedure for the asymmetric synthesis of *β*-lactones has been extended to the use of in situ generated ketene with dichlorinated aldehydes. The use of toluene as solvent to precipitate the hydrochloride salt of Hunig's base and in this way free-base the nucleophilic catalyst, quinidine, was crucial for the success of this reaction. Several transformations of the resulting optically active dichlorinated *β*-lactones are described that extend the utility of these products.

Experimental Section

General. Solvent purification/drying, flash chromatography, spectroscopy, and thin-layer chromatography were performed as previously described.[19] All reactions were carried out under N_2 in oven-dried glassware unless noted otherwise. Diisopropylethylamine was distilled from potassium hydroxide, and acetyl chloride was distilled from PCl_5. (−)-Quinidine and anhydrous dimethylformamide were purchased from Aldrich Chemical Co. and used as received. All other commercially available materials were purchased from Aldrich Chemical Co. or Fluka and used as received. GC analyses were performed using a 20 m 30% *tert*-butyldimethylsilyl-*β*-cyclodextrin in a OV1701 column (kindly provided by Prof. Gyula Vigh, Texas A&M) at an oven temperature of 140 °C and H_2 carrier pressure of 5 psi. HPLC analyses were performed using a Chiracel OD column. Known aldehydes **3a**, **3b**, and **3d** were prepared by the method of De Buyck[10] from commercially available alcohols.

Aldehyde 3c. 4-Pivaloyloxy-1-butanol[20] (2.30 g, 13.2 mmol) and DMF (6.66 mL) were added to a three-neck flask equipped with a vent outlet leading to a mineral oil bubbler, glass stopper, and a plastic tube with attached needle for chlorine gas introduction. Chlorine gas was bubbled through the solution for 15 min. The flask was cooled with an ice/water bath to maintain a reaction temperature of 50−60 °C. The green reaction mixture was stirred at room temperature for 8 h. The reaction was then extracted with ether (3 × 10 mL), and the combined organic layers were washed with concentrated HCl (30 mL) and 50% H_2SO_4 (30 mL). The organic layer was then neutralized with solid $CaCO_3$ and concentrated in vacuo. Purication of the residue by distillation gave the aldehyde **3c** (0.85 g, 21% yield) which distilled at 110 °C (5 mmHg) as a clear liquid: R_f 0.20 (EtOAc/hexanes = 1:3); IR (thin film) 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 4.37 (t, J = 6.3 Hz, 2H), 2.71 (t, J = 6.3 Hz, 2H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 178.3, 86.0, 60.1, 40.1, 38.9, 27.3; FAB HRMS calcd for [M + H] 241.0394, found 241.0398.

General Procedure for the Modified Wynberg Procedure As Described for *β*-Lactone 4b. Aldehyde **3b** (0.50 g, 2.54 mmol, 1.00 equiv) was added to a 25 mL round-bottomed flask followed by quinidine (0.02 g, 0.05 mmol, 0.02 equiv), toluene (3.60 mL), and Hunig's base (0.64 mL, 3.68 mmol, 1.45 equiv). The flask was cooled to −25 °C, and then acetyl chloride (0.18 mL, 2.54 mmol, 1.00 equiv) was added dropwise over a

(12) In this case, reaction in diethyl ether gave a comparable yield (ref 6).

(13) Ketelaar, P. E. F.; Staring, E. G. J.; Wynberg, H. *Tetrahedron Lett.* **1985**, *26*, 4665−4668.

(14) For a report describing selective radical dehalogenation of one or two chlorine atoms from (*R*)-4-(trichloromethyl)oxetan-2-one following lactone cleavage, see ref 7d.

(15) We utilized *β*-lactone **4b** in further transformations because the derived products were nonvolatile.

(16) The stereochemistry of the major diastereomer has not been determined.

(17) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906−1908.

(18) The %ee of the corresponding, chromophore-containing TBDPS-protected azido ketone was determined by chiral HPLC analysis after reduction and in situ Boc protection by the literature procedure: Saito, S.; Nakajma, H.; Inabe, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(19) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471−16488.

(20) Wu, Y.; Ahlberg, P. *Acta Chem. Scand.* **1995**, *49*, 364−374.

1−2 min period. A precipitate formed immediately, the heterogeneous mixture was stirred for 15 min, and then more acetyl chloride (0.09 mL, 1.27 mmol, 0.50 equiv) was added slowly. The resulting heterogeneous, light-yellow mixture was stirred an additional 45 min at −25 °C and then warmed to 25 °C. After dilution with 10 mL of Et_2O, the mixture was transferred to a separatory funnel, and additional Et_2O was used to transfer all the solids. The organics were washed with 4 N HCl (3 × 10 mL) and brine (10 mL). The organic layers were dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (EtOAc/hexanes = 1:20 to 1:3) to afford *β*-lactone **4b** (0.45 g, 73% yield) as a light-yellow oil in 93% ee: GC, t_R (*R*) = 17.9 ± 0.1 min, t_R (*S*) = 19.7 ± 0.1 min; R_f 0.58 (EtOAc/hexanes = 1:3); $[\alpha]^{25}_D$ +1.40° (*c* 4.37, $CHCl_3$); IR (thin film) 1844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 4.69 (dd, *J* = 4.2, 5.7 Hz, 1H), 3.70 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.62 (dd, *J* = 5.7, 16.8 Hz, 1H), 2.11−2.32 (m, 2H), 1.59−1.79 (m, 2H), 1.29−1.40 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.6, 91.7, 723.3, 43.9, 41.6, 31.3, 28.4, 24.3, 22.3, 13.8; FAB HRMS calcd for [M + Na] 239.06056, found 239.06061.

***β*-Lactone 4a.** This *β*-lactone was prepared from aldehyde **3a** (0.50 g, 2.46 mmol). Purification by flash chromatography (EtOAc/ hexanes = 1:20 to 1:3) gave *β*-lactone **4a** (0.52 g, 85%) as a light-yellow oil in 93% ee: GC, t_R (*R*) = 31.0 ± 0.1 min, t_R (*S*) = 33.6 ± 0.1 min;: R_f 0.56 (EtOAc/hexanes = 1:3); $[\alpha]^{25}_D$ −111° (*c* 5.49, $CHCl_3$); IR (thin film) 1839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.36 (s, 5H), 4.58 (dd, *J* = 3.9 Hz, 5.7 Hz, 1H), 3.62 (app d, *J* = 0.9 Hz, 2H), 3.66 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.50 (dd, *J* = 5.7, 16.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.4, 132.7, 131.2, 128.4, 128.2, 90.2, 71.4, 49.8, 41.4; FAB HRMS calcd for [M + Na] 266.9955, found 266.9951

***β*-Lactone 4c.** This *β*-lactone was prepared from aldehyde **3c** (0.50 g, 2.07 mmol). Purification by flash chromatography (EtOAc/ hexanes = 1:20 to 1:3) gave *β*-lactone **4c** (0.47 g, 80% yield) as a white solid in 94% ee: GC, t_R (*R*) = 39.0 ± 0.1 min, t_R (*S*) = 45.2 ± 0.1 min; R_f 0.60 (EtOAc/ hexanes = 1:3); $[\alpha]^{25}_D$ +7.99° (*c* 5.71, $CHCl_3$); IR (thin film) 1844 cm^{-1} and 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 4.75 (dd, *J* = 3.9, 5.4 Hz, 2H), 4.38−4.52 (m, 2H), 3.72 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.64 (dd, *J* = 5.4, 16.8 Hz, 1H), 2.59−2.78 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 178.1, 165.2, 88.6, 73.0, 59.9, 42.7, 41.7, 38.6, 27.0; FAB HRMS calcd for [M + Na] 305.0323, found 305.0337.

***β*-Lactone 4d.** This *β*-lactone was prepared from aldehyde **3d** (0.50 g, 3.22 mmol). Purification by flash chromatography (EtOAc/ hexanes = 1:20 to 1:3) gave *β*-lactone **4d** (0.25 g, 40%) as a light-yellow oil: GC, t_R (*R*) = 4.20 ± 0.1 min, t_R (*S*) = 4.45 ± 0.1 min; R_f 0.54 (EtOAc/ hexanes = 1:3); $[\alpha]^{25}_D$ +19.4° (*c* 9.65, $CHCl_3$); IR (thin film) 1849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 4.85 (dd, *J* = 3.9, 5.7 Hz, 1H), 3.74 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.63 (dd, *J* = 5.7, 16.8 Hz, 1H), 2.48 (sept, *J* = 6.6 Hz, 1H), 1.24 (d, *J* = 6.6, 3H), 1.18 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 161.5, 97.0, 71.7, 42.2, 40.7, 18.1, 17.9; FAB HRMS calcd for [M + Na] 218.99555, found 218.99484. GC analysis indicated an enantiomeric purity of 99% (*R* enantiomer, t_R = 4.20 min, *S* enantiomer, t_R = 4.45 min.).

***β*-Lactone 4e.** This *β*-lactone was prepared in 25% yield (61.9 mg) as a yellow oil from trichloroacetone (200 mg, 1.24 mmol). Purification by flash chromatography (EtOAc/hexanes = 1:10 to 1:5) gave *β*-lactone **4e**. Spectral data for this compound matched that previously reported.[3] $[\alpha]^{25}_D$ +5.64° (*c* 4.40, $CHCl_3$); lit. $[\alpha]^{25}_D$ +6.20° (*c* 2, EtOH).[3b]

***β*-Hydroxy Ester 10.** The *β*-lactone **4b** (100 mg, 0. 42 mmol) was added to a flask followed by Pd/C (40 mg, 0.04 mmol), K_2CO_3 (0.14 g), $MgSO_4$ (1.00 equiv), and methanol (1.40 mL). A balloon of hydrogen gas was attached and the reaction was stirred for 3.5 h at 25 °C. The mixture was then filtered and concentrated in vacuo. The product was purified by flash chromatography (EtOAc/ hexanes = 1:20 to 1:3) to afford the *β*-hydroxy ester **10** (53.7 mg, 64% yield) as a light-yellow oil. Spectral data for this compound matched that previously reported.[3] $[\alpha]^{25}_D$ +11.4° (*c* 4.19, $CHCl_3$); lit. $[\alpha]^{25}_D$ +25.8 ° (*c* 1.0, cyclohexane).[13]

Diol 11. DIBAl-H (1.86 mL, 10.45 mmol) was added to a flask containing CH_2Cl_2 (10.5 mL). This mixture was added slowly via cannula to a solution of *β*-lactone **4b** (1.00 g, 4.18 mmol) in CH_2Cl_2 (31.3 mL) at 0 °C. The mixture was then warmed to 25 °C and stirred for 3 h. After cooling to 0 °C, the reaction was quenched with acetone (5 mL), 1 M sodium/potassium tartrate solution (30 mL), and EtOAc (20 mL). The mixture was warmed to 25 °C and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to give the diol **12** (0.96 g, 95% yield) as a light-yellow oil which was of sufficient purity to carry on directly to the next step: R_f 0.18 (EtOAc/ hexanes = 1:3); IR (thin film) 3375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 4.10 (dd, *J* = 2.1, 10.2 Hz, 1H), 3.85−4.00 (m, 2H), 3.18 (s, 1H), 2.50 (s, 1H), 2.10−2.27 (m, 3H), 1.80−1.95 (m, 1H), 1.62−1.79 (m, 2H), 1.29−1.41 (m, 6H), 0.94 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 98.8, 78.6, 61.0, 43.5, 33.8, 31.8, 29.1, 25.0, 22.8, 14.3; FAB HRMS calcd for [M + H] 243.0919, found 243.0929.

Mono-TIPS Protected Alcohol 12. The diol **11** (0.75 g, 3.08 mmol) was added to a flask, followed by imidazole (0.25 g, 3.70 mmol), DMF (6.17 mL), and TIPS-Cl (0.79 mL, 3.70 mmol). The mixture was stirred at 25 °C for 9 h and then quenched with saturated $NaHCO_3$ (1 mL). The mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried, and concentrated in vacuo. Purification by flash chromatography (EtOAc/hexanes = 1:20 to 1:5) gave mono-TIPS protected alcohol **12** (1.19 g, 97% yield) as a light-yellow oil: R_f 0.80 (EtOAc/hexanes = 1:3); IR (thin film) 3457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 3.80−4.10 (m, 4H), 2.12−2.35 (m, 3H), 1.82−2.00 (m, 1H), 1.61−1.80 (m, 2H), 1.21−1.40 (m, 6H), 0.99−1.15 (m, 21H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 98.3, 78.8, 62.4, 44.0, 34.1, 31.9, 29.1, 24.9, 22.8, 18.2, 17.9, 14.3, 12.1; FAB HRMS calcd for [M + H] 399.2253, found 399.2266.

Chloro Epoxide 13. A THF (2.50 mL) solution of the alcohol **12** (100 mg, 0.25 mmol) was added to NaH (60% dispersion in mineral oil, 9.0 mg, 0.38 mmol) which had been washed with hexane (3 × 1 mL), and the mixture was stirred at 25 °C for 7 h. The reaction was washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated to afford the chloroepoxide **13** (83.0 mg, 92% yield) as a light-yellow oil and as a 38:1 ratio of diastereomers. This epoxide was not stable to silica gel chromatography: R_f 0.73 (EtOAc/ hexanes = 1:10); ^1H NMR (300 MHz, $CDCl_3$) *δ* 3.91 (t, *J* = 5.9 Hz, 2H), 3.13 (dd, *J* = 5.3, 6.5 Hz, 1H), 1.92−2.05 (m,4H), 1.50−1.61 (m, 2H), 1.20−1.39 (m, 6H), 0.99−1.15 (m, 21H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 84.6, 61.3, 60.5, 40.7, 32.9, 31.9, 28.9, 25.0, 22.7, 18.2, 14.3, 12.2; FAB HRMS calcd for [M + H] 363.2486, found 363.2485.

α-Azido Ketone 14. The epoxide **13** (50.0 mg, 0.11 mmol) was added to a flask, followed by NaN_3 (36.0 mg, 0.55 mmol), DME (0.69 mL), and H_2O (0.34 mL) at 25 °C. The reaction was stirred at 25 °C for 84 h. The mixture was then diluted with 5 mL EtOAc, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (EtOAc/ hexanes = 1:20 to 1:6) afforded the α-azido ketone **14** (42.1 mg, 83% yield) as a light-yellow oil: R_f 0.74 (EtOAc/ hexanes = 1:3); $[\alpha]^{25}_D$ −2.57° (*c* 1.40, $CHCl_3$); IR (thin film) 2105 and 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 4.10 (dd, *J* = 4.2, 9.3 Hz, 1H), 3.83 (dd, *J* = 4.4, 7.0 Hz, 2H), 2.54 (app dt, *J* = 2.4, 7.5 Hz, 2H), 2.00−2.10 (m, 1H), 1.72−1.83 (m, 1H), 1.49−1.61 (m, 2H), 1.20−1.39 (m, 6H), 0.99−1.15 (m, 21H), 0.88 (t, *J* = 6.6 Hz, 3H); 13C NMR (75 MHz, $CDCl_3$) *δ* 207.8, 64.7, 59.1, 39.8, 33.7, 31.6, 28.8, 23.4, 22.5, 18.0, 14.0, 11.8; FAB HRMS calcd for [M + H] 370.28898, found 370.28956. The enantiomeric purity of the TBDPS protected α-azido ketone was determined to be 85% ee by HPLC analysis (5% 2-propanol/hexane, 1 mL/min) after reduction and in situ protection (H_2, Pd/C, Boc_2O, EtOAc).

Benzylidene Acetal 15. The diol **11** (1.00 g, 4.11 mmol) was added to a flask followed by TsOH (78.2 mg, 0.41 mmol), MgSO4 (0.99 g, 8.23 mmol), CH_2Cl_2 (11.4 mL), and benzaldehyde (0.50 mL, 4.94 mmol) at 25 °C. The mixture was stirred at 25 °C for 4 h and then filtered and extracted with satd $NaHCO_3$ (3 × 10 mL). Drying the organics over $MgSO_4$ and concentration in vacuo was followed by purification by flash chromatography (EtOAc/hexanes = 1:20 to 1:5) gave the benzylidene acetal **15** (0.93 g, 68% yield) as a light-yellow oil: R_f 0.74 (EtOAc/hexanes = 1:3); ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.,47−7.51 (m, 2H), 7.30−7.41 (m, 3H), 5.55 (s, 2H), 4.38 (ddd, *J* = 1.5, 5.1, 11.7 Hz, 1H), 4.10 (dd,

J = 2.4, 11.1 Hz, 1H), 4.00 (app dt, J = 2.7, 12.0 Hz, 1H), 2.22−2.35 (m, 3H), 2.05 (app dq, J = 2.4, 13.2 Hz, 1H), 1.66−1.75 (m, 2H), 1.31−1.39 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 129.2, 128.5, 126.3, 101.5, 94.7, 83.0, 66.9, 43.9, 31.9, 29.0, 26.3, 24.9, 22.8, 14.3; FAB HRMS calcd for [M + H] 331.1232 found 331.1230.

Alcohol 16. To a solution of benzylidene acetal **15** (0.99 g, 2.99 mmol) in CH_2Cl_2 (25.0 mL) was added a solution of DIBAL-H (1.60 mL, 8.96 mmol) in CH_2Cl_2 (4.80 mL) at 0 °C. The mixture was warmed to 25 °C and stirred for 9 h. The reaction was quenched with 1.5 mL acetone, 10 mL of 1 M sodium/potassium tartrate solution, and 10 mL of EtOAc at 0 °C. After allowing the reaction to warm to 25 °C and stirring for 45 min, the reaction was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography (EtOAc/hexanes = 1:20 to 1:3) to give alcohol **16** (0.69 g, 69% yield) as a light-yellow oil: R_f 0.48 (EtOAc/hexanes = 1:3); IR (thin film) 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.96 (d, J = 11.1 Hz, 1H) 4.75 (d, J = 11.1, 1H), 4.04 (dd, J = 2.4, 9.3 Hz, 1H), 3.65−3.83 (m, 2H), 2.17−2.35 (m, 3H), 1.85−1.98 (m, 1H), 1.63−1.79 (m, 2H), 1.41 (s, 1H), 1.25−1.39 (m, 6H), 0.90 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.7, 128.3, 128.2, 98.0, 84.5, 75.8, 60.0, 43.4, 34.6, 31.8, 29.1, 25.0, 22.8, 14.2; FAB HRMS calcd for [M + H] 333.1388, found 333.1387.

Alkene 18. To a THF solution (0.50 mL) of the alcohol **16** (62.0 mg, 0.19 mmol) was added a solution of KO^{t}Bu (39.6 mg, 0.35 mmol) in THF (1.36 mL) slowly over a period of 15 min at 25 °C. The reaction was stirred for 6 h and then quenched with 0.5 mL of 4 N HCl. The mixture was then diluted in 5 mL of EtOAc and washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was then purified by flash chromatography (EtOAc/hexanes = 1:20 to 1:3) to give alkene **18** (33.5 mg, 61% yield) as a yellow oil and a 7.2:1 ratio of stereoisomers: R_f 0.48 (EtOAc/ hexanes = 1:3); $[\alpha]^{25}_D$ +66.9 (c 0.77, $CHCl_3$); IR (thin film) 1650 and 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.40 (m, 5H), 5.80 (t, J = 6.9 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.11 (dd, J = 4.5, 8.4 Hz, 1H), 3.67−3.81 (m, 2H), 2.22−2.39 (m, 2H), 1.99−2.13 (m, 1H),1.81−1.90 (m, 1H), 1.26−1.46 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 133.2, 129.6, 128.5, 128.0, 127.9, 80.7, 70.2, 60.2, 36.2, 31.4, 28.2, 28.0, 22.4, 14.0; FAB HRMS calcd for [M + Na] 319.1443, found 319.1442.

Alkyne 17. The alcohol **16** (46.0 mg, 0.14 mmol) was added to a flask followed by KO^{t}Bu (61.9 mg, 0.5520 mmol). The flask was then cooled to 0 °C, and then THF (1.4 mL) was added. The mixture was stirred at 0 °C for 30 min and then raised to 25 °C and stirred for an additional 21.5 h. The mixture was cooled to 0 °C and then quenched with 0.5 mL of 4 N HCl. The reaction was diluted in 5 mL of EtOAc, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (1:10 → 1:3 EtOAc/hexanes) afforded alkyne **17** (24.6 mg, 69% yield) as a light-brown oil which was contaminated with inseparable products (∼95% pure). HPLC analysis of this alkyne indicated that it was obtained with <5% racemization. R_f 0.47 (EtOAc/hexanes = 1:3); $[\alpha]^{25}_D$ +102° (c 1.00, $CHCl_3$); IR (thin film) 3450, 2233 and 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.37 (m, 5H), 4.82 (d, 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.30−4.36 (m, 1H), 3.86−3.95 (m, 1H),3.76−3.81 (m, 1H), 2.26 (dt, J = 6.9, 7.2 Hz, 2H), 2.00 (dd, 2H, J = 5.7, 11.1 Hz), 1.51−1.58 (m, 2H),1.26−1.42 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 133.3, 128.7, 128.2, 87.9, 78.3, 70.8, 68.4, 60.6, 38.5, 31.3, 28.6, 22.4, 18.9, 14.3; FAB HRMS calcd for [M + H] 261.18546, found 261.18565.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of β-lactones **4a**−**d**, epoxide **13**, azido ketone **14**, vinyl chloride **18**, and acetylene **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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