Reactivity of α-(Benzoyloxy)crotylstannane with Aldehydes in Liquid Phase and on Solid Support. Synthesis of Substituted Lactones

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Solid-phase synthesis[1] has gained in popularity as a result of its relative ease of automation and the emergence of high-throughput screening. Combinatorial chemistry had its beginnings with the sequential synthesis of peptide libraries on solid supports and is now being applied to the synthesis of catalysts, polymers, pharmaceutical lead compounds, and more recently, complex natural products such as epothilone.[2] The application of combinatorial synthesis methods to various classes of chiral organic backbone structures such as polypropionates, which are present in a great number of biologically interesting natural products, represents a challenge for modern organic chemistry. Although these compounds can be synthesized in solution, the workup and removal of byproducts can be tedious.

Recent studies by Marshall[3] and Gung[4] have shown that in the presence of a Lewis acid α-(alkoxy)crotylstannanes add to aldehydes to produce polypropionate intermediates with high stereoselectivity. However, the purification of these adducts can be difficult because of tin byproducts, which are often not easily removed. Thus, by developing a solid-support application of these reactions we could expect to solve this purification problem.

Our initial plan was to prepare the α-oxygenated crotylstannane reagent of type **A** through addition of the hydroxy stannane **1**[5] (from crotonaldehyde and Bu_3SnLi)[6] to a polystyrene-supported chloropyran[7] (Scheme 1, eq 1). However, the tetrahydropyranyl ethers **A** could not be prepared.

It is possible that polymeric resins incorporating a $ROCH_2Cl$ grouping would permit the preparation of supported α-oxygenated crotylstannanes, but instead of exploring this option, we elected to examine supported benzoate derivatives of type **B**. These could be readily prepared through esterification of the α-hydroxy stannane **1** with a readily available polystyrene carboxylic acid (Scheme 1, eq 2).

However, as Lewis acid-promoted additions of α-acyloxyallylic stannanes to aldehydes had not previously been examined, we felt it was necessary to first carry out preliminary solution-phase studies to establish the scope and feasibility of such additions. Accordingly, the benzoate reagent **2**[8] was prepared by benzoylation of the hydroxycrotylstannane **1** (Scheme 2). This stannane was treated with a series of aldehydes in the presence of excess $BF_3{\cdot}OEt_2$ at −78 °C in CH_2Cl_2 to afford various enol benzoate adducts (Table 1).

Table 1. Synthesis of Enol Benzoate Adducts

series	R	yield (%)	**3**:**4**:**5**[a]
a	Ph	70	74:9:17
b	*p*-ClC_6H_4	58	84:8:8
c	*p*-$NO_2C_6H_4$	62	67:20:13
d	*n*-C_6H_{13}	48	63:<1:37
e	*c*-C_6H_{11}	52	36:<1:64

[a] Ratios determined by ^1H NMR spectra on the crude.

The stereochemistry of the double bond in adducts **3**−**5** was deduced from the ^1H NMR spectrum of each mixture. These spectra also provided the isomer ratios. The relative stereochemistry was initially assigned by analogy with the previously reported reactions of the OMOM or OBOM analogues.[3,4] The assignments were confirmed by conversion to the known lactones **7** and **8** after cleavage of the enol benzoates with NaOMe and oxidation of the resulting lactols **6** with PCC as summarized in Scheme 3 and Table 2. These findings show that the reactivity of α-(benzoyloxy)crotylstannanes in Lewis acid promoted additions to aldehydes is similar to that of α-(alkoxy)-crotylstannanes, except for *p*-nitrobenzaldehyde, which gave more of the *anti-Z* isomer **4c** (Table 1) than that obtained with the α-(alkoxy)crotylstannanes.[4c]

Since α-(benzoyloxy)crotylstannanes and α-(alkoxy)-crotylstanannes behave similarly in Lewis acid promoted additions to aldehydes, we decided to examine the solid-phase reactions. The commercially available carboxylic polystyrene resin[13] was treated with stannane **1**, 1-(3-

(1) For reviews, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. (c) Blackburn, C.; Albericio, F.; Kates, S. A. *Drugs Future* **1997**, *22*, 1007. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (e) Balkenhohl, F.; Von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (f) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. (g) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (h) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (i) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (j) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (k) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233.

(2) (a) Cargill, J. F.; Lebl, M. *Curr. Opin. Chem. Biol.* **1997**, *1*, 67. (b) Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47. (c) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (d) Pirrung, M. C. *Chem. Rev.* **1997**, *97*, 473. (e) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (f) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2097.

(3) (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A.; Jablonowski, J. A.; Welmaker, G. J. *J. Org. Chem.* **1996**, *61*, 2904. (c) Marshall, J. A.; Yashunsky, D. V. *J. Org. Chem.* **1991**, *56*, 5493. (d) Marshall, J. A.; Welmaker, G. J. *Tetrahedron Lett.* **1991**, *32*, 2101. (e) Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043. (f) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. (g) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616. (h) Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527.

(4) (a) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370. (b) Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron* **1992**, *48*, 5455. (c) Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron Lett.* **1991**, *32*, 13. (d) Gung, B. W.; Peat, A. J.; Snook, B. M.; Smith, D. T. *Tetrahedron Lett.* **1991**, *32*, 453.

(5) Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1115.

(6) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(7) Cossy, J.; Rasamison, C.; Gomez Pardo, D. Unpublished results.

(8) Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1521.

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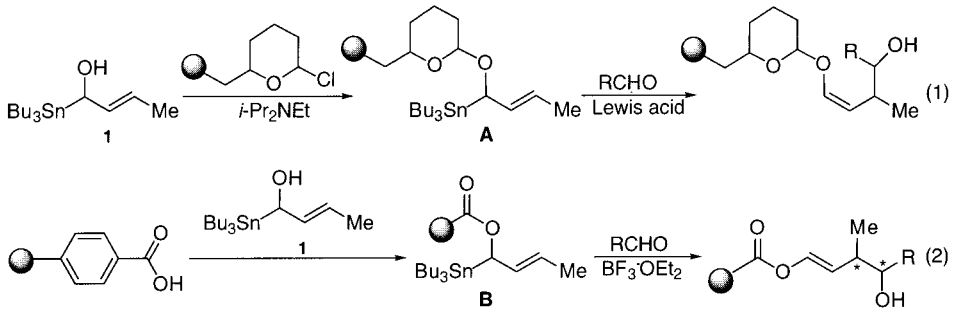
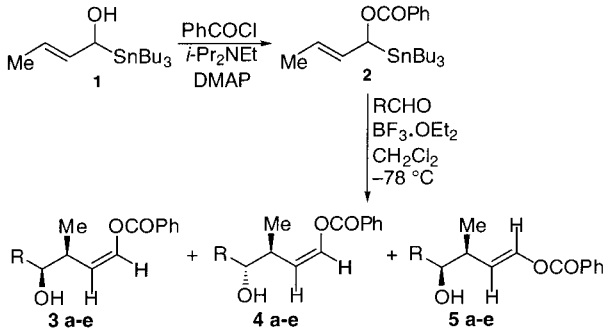
Scheme 1



Scheme 2



Scheme 3

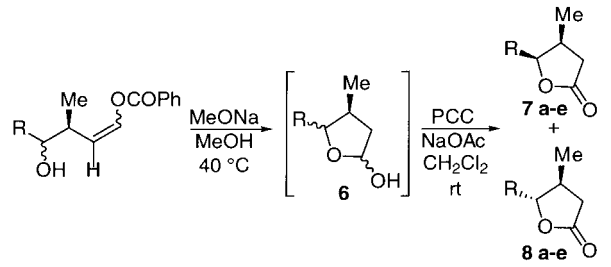


Table 2. Synthesis of Lactones 7a−e and 8a−e

series	R	yield[a] (%)	**7**:**8**[b]
a	Ph[8,9]	66	93:7
b	*p*-ClC_6H_4[8,10]	47	90:10
c	*p*-$NO_2C_6H_4$[8]	70	72:28
d	*n*-C_6H_{13}[8,11]	40	100:0
e	*c*-C_6H_{11}[12]	60	100:0

[a] The yields are reported for the two-step process. [b] Ratios determined by ^1H NMR spectra on the crude.

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 to give the supported ester derivative **B**.[14] The aldehyde was introduced at room temperature, and $BF_3 \cdot OEt_2$ was added dropwise at −78 °C. After 5 h, the resin was washed, and then the enol ester **C** was cleaved with

Scheme 4

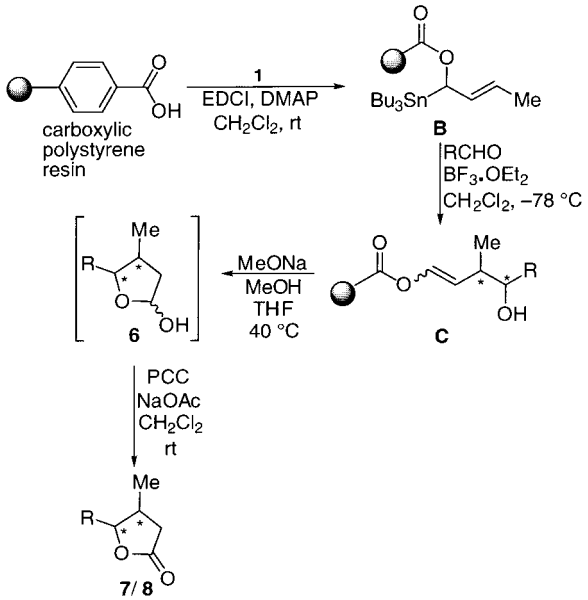


Table 3. Synthesis of Lactones on Solid Support

series	R	yield[a] (%)	**7**:**8**[b]
a	Ph	70	93:7
b	*p*-ClC_6H_4	82	89:11
c	*p*-$NO_2C_6H_4$	72	75:25
d	*n*-C_6H_{13}	63	100:0
e	*c*-C_6H_{11}	61	100:0

[a] The yields are reported for the four-step process. [b] Ratios determined by ^1H NMR spectra on the crude.

NaOMe in MeOH−THF (1/4) at 40 °C[15] to yield the lactol products **6**, which were directly oxidized to the corresponding lactones **7** and **8** in 60%-80% overall yield over four steps (Scheme 4). The results are summarized in Table 3.

The lactones were obtained with a diastereoselectivity similar to that of the liquid-phase synthesis. Yields were high (60−80%), and the products were not contaminated by tin byproducts. Thus, it is clear that this solid-phase strategy could be useful for the preparation of lactone libraries.

Experimental Section

General Methods. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from Na/benzophenone-ketyl immediately prior to use. CH_2Cl_2, *i*-Pr_2NH, and *i*-Pr_2NEt

(9) (a) Frenette, R.; Kakushima, M.; Zamboni, R.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1987**, *52*, 304. (b) Tokuda, M.; Yokoyama, Y.; Taguchi, T.; Suzuki, A.; Itoh, M. *J. Org. Chem.* **1972**, *37*, 1859.

(10) Satoh, M.; Washida, S.; Takeuchi, S.; Asaoka, M. *Heterocycles* **2000**, *52*, 227.

(11) Fukuzawa, S.-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.

(12) (a) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. B. *J. Org. Chem.* **1991**, *56*, 3083. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.

(13) The carboxylic polystyrene resin (1% DVB cross-linked) with a loading of 2 mmol/g was purchased from Advanced Chemtech.

(14) Cossy, J.; Rasamison, C.; Gomez Pardo, D.; Marshall, J. A. *Synlett* **2001**, 629.

(15) Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Mol. Div.* **1995**, *1*, 13.

were distilled from calcium hydride under argon. Moisture-sensitive reactions were conducted in oven-dried glassware under an argon atmosphere. Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates, and flash column chromatography was accomplished on Merck Kieselgel 60 (230−400 mesh). HRMS were obtained from Centre de Spectrochimie Organique de l'Ecole Normale Supérieure de Paris. NMR spectra were recorded at 300 MHz (^{1}H) or 75 MHz (^{13}C) in $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm relative to residual $CHCl_3$ at $\delta = 7.27$ for ^{1}H and to $CDCl_3$ at $\delta = 77.1$ for ^{13}C. MS: Mass spectra were obtained by GC/MS with electron-impact ionization at 70 eV. Only selected ions are reported.

(*E*)-1-Benzoyloxy-2-butenyl(tributyl)stannane (2). Tributyltin hydride (6.7 mL, 24.9 mmol, 1 equiv) was added to a solution of LDA (24.9 mmol, 1 equiv) in THF (50 mL) at 0 °C. After 15 min, the solution was cooled to −78 °C, and crotonaldehyde (2.06 mL, 24.9 mmol, 1 equiv) was added dropwise. After 30 min, the reaction was quenched by addition of an aqueous NH_4Cl solution (0.9 M, 60 mL) and warmed to 20 °C. The aqueous layer was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo, and (*E*)-1-(tributylstannyl)-2-buten-1-ol **1** was obtained as an unstable yellow oil used immediately without purification. Crude **1** was added to a solution of DMAP (1.5 g, 12.48 mmol, 0.5 equiv), *i*-Pr_2NEt (8.9 mL, 50 mmol, 2 equiv), and benzoyl chloride (4.4 mL, 37.4 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature. After 16 h at room temperature, the organic layer was washed with an aqueous HCl solution (0.5 M). After drying over $MgSO_4$, the solvent was removed in vacuo to afford an oil that was purified by flash column chromatography on silica gel (eluting with a gradient of 0−0.5% of EtOAc in cyclohexane) to give **2** (10.4 g, 22.4 mmol, 90% yield) as a yellow oil. IR (neat): 1702, 1450, 1335, 1271, 1115, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.04 (m, 2 H), 7.59−7.51 (m, 1 H), 7.49−7.40 (m, 2 H), 5.82 (ddq, J = 15.1, 6.6, 1.5 Hz, 1 H), 5.60 (dt, J = 7.0, 1.5 Hz, 1 H), 5.58−5.44 (m, 1 H), 1.75 (dt, J = 6.6, 1.5 Hz, 3 H), 1.60−1.47 (m, 6 H), 1.38−1.23 (m, 6 H), 1.03−0.82 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (s), 132.6 (d), 130.5 (d), 130.0 (s), 129.4 (d), 128.1 (d), 119.6 (d), 72.2 (d), 28.7 (t), 27.6 (t), 17.6 (q), 13.5 (q), 7.9 (t). MS (EI, relative intensity): *m*/*z* 409 ($M^{\cdot+}$ − Bu·, 99), 353 (24), 291 (32), 235 (80), 179 (99), 121 (24), 105 (100), 77 (40), 69 (35). HRMS (EI): calcd for $C_{23}H_{38}O_2Sn$ ($M^{\cdot+}$) 467.1972, found 467.1991.

3-Methyl-4-phenyl-1-butene-1,4-diol Monobenzoate (3a, 4a, 5a). To a solution of benzaldehyde (0.13 mL, 1.3 mmol, 1.5 equiv) and (*E*)-1-benzoyloxy-2-butenyl(tributyl)stannane **2** (0.40 g, 0.87 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.16 mL, 1.3 mmol, 1.5 equiv). After 5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ (5 mL), extracted with ether, washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 9/91) to give an inseparable mixture (ratio 74/9/17 according to ^{1}H NMR) of diastereomers *syn*-(*Z*) **3a**, *anti*-(*Z*) **4a**, and *syn*-(*E*) **5a** (0.17 g, 0.61 mmol, 70% yield) as an oil. IR (neat): 3446, 1728, 1451, 1268, 1111, 1026 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11−8.03 (m, 2 H), 7.65−7.46 (m, 1 H), 7.40−7.20 (m, 2 H), 7.30−7.00 (m, 7 H), 5.46 (dd, J = 12.5, 8.5 Hz, 0.17 H), 4.92 (dd, J = 9.6, 6.3 Hz, 0.09 H), 4.79 (dd, J = 9.6, 6.3 Hz, 0.74 H), 4.54 (m, 0.91 H), 4.44 (dd, J = 7.0, 2.6 Hz, 0.09 H), 3.20 (m, 1 H), 1.10 (d, J = 6.6 Hz, 2.22 H), 1.05 (d, J = 6.6 Hz, 0.51 H), 0.95 (d, J = 7.0 Hz, 0.27 H).^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ: 163.2 (s), 142.5 (s), 134.2 (d), 133.4 (d), 129.8 (d), 129.0 (s), 128.4 (d), 128.1 (d), 128.0 (d), 126.4 (d), 116.1 (d), 78.2 (d), 37.4 (d), 17.1 (q).

4-(4-Chlorophenyl)-3-methyl-1-butene-1,4-diol Monobenzoate (3b, 4b, 5b). Following the procedure outlined above for benzaldehyde, *p*-chlorobenzaldehyde (0.18 g, 1.3 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 8/92) to give an inseparable mixture (ratio 84/8/8 according to ^{1}H NMR) of diastereomers *syn*-(*Z*) **3b**, *anti*-(*Z*) **4b**, and *syn*-(*E*) **5b** (0.16 g, 0.50 mmol, 58% yield) as an oil. IR (neat): 3456, 1732, 1266, 1113, 1070 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−7.97 (m, 2 H), 7.66−7.56 (m, 1 H), 7.53−7.40 (m, 2 H), 7.35−7.15 (m, 5 H), 5.52 (dd, J = 12.5, 8.5 Hz, 0.08 H), 4.97 (dd, J = 9.6, 6.2 Hz, 0.08 H), 4.84 (dd, J = 9.9, 6.6 Hz, 0.84 H), 4.65−4.50 (m, 1 H), 3.29−3.09 (m, 1 H), 2.85 (bs, 1 H), 1.17 (d, J = 6.6 Hz, 2.52 H), 1.05 (d, J = 6.6 Hz, 0.24 H), 1.01 (d, J = 7.0 Hz, 0.24 H).^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$): δ 163.2 (s), 141.1 (s), 134.4 (d), 133.5 (d), 133.1 (s),129.8 (d), 128.9 (s), 128.4 (d), 128.2 (d), 127.8 (d), 115.9 (d), 76.8 (d), 37.4 (d), 16.0 (q).

3-Methyl-4-(4-nitrophenyl)-1-butene-1,4-diol Monobenzoate (3c, 4c, 5c). Following the procedure outlined above for benzaldehyde, *p*-nitrobenzaldehyde (0.19 g, 1.3 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 20/80) to give an inseparable mixture (ratio 67/20/13 according to ^{1}H NMR) of diastereomers *syn*-(*Z*) **3c**, *anti*-(*Z*) **4c**, and *syn*-(*E*) **5c** (0.18 g, 0.54 mmol, 62% yield) as an oil. IR (neat): 3522, 1729, 1522, 1347, 1265, 1110 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20−7.90 (m, 4 H), 7.67−7.40 (m, 5 H), 7.19−7.14 (m, 0.33 H), 7.18 (dd, J = 6.6, 1.1 Hz, 0.67 H), 5.54 (dd, J = 12.5, 8.1 Hz, 0.13 H), 4.97 (dd, J = 9.6, 6.2 Hz, 0.2 H), 4.87 (dd, J = 9.9, 6.6 Hz, 0.67 H), 4.78 (d, J = 5.2 Hz, 0.13 H), 4.72 (d, J = 6.2 Hz, 0.87 H), 3.20 (m, 1 H), 2.85 (bs, 1 H), 1.15 (d, J = 7.0 Hz, 2.01 H), 1.12−1.02 (m, 0.99 H).^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$): δ 163.1 (s), 150.2 (s), 147.0 (s), 134.7 (d), 133.6 (d), 129.6 (d), 128.6 (d), 127.2 (d), 123.0 (d),115.4 (d), 76.7 (d), 37.5 (d), 15.7 (q).

3-Methyl-1-decene-1,4-diol Monobenzoate (3d, 5d). Following the procedure outlined above for benzaldehyde, heptanal (0.18 mL, 1.3 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 8/92) to give an inseparable mixture (ratio 63/37 according to ^{1}H NMR) of diastereomers *syn*-(*Z*) **3d** and *syn*-(*E*) **5d** (0.12 g, 0.41 mmol, 48% yield) as an oil. IR (neat): 3445, 1729, 1452, 1265, 1113, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13−8.05 (m, 2 H), 7.65−7.55 (m, 1 H), 7.52−7.42 (m, 2 H), 7.38 (dd, J = 12.5, 1.1 Hz, 0.37 H), 7.32 (dd, J = 6.6, 1.1 Hz, 0.63 H), 5.61 (dd, J = 12.5, 8.8 Hz, 0.37 H), 4.93 (dd, J = 9.7, 6.4 Hz, 0.63 H), 3.58−3.45 (m, 1 H), 3.04−2.87 (m, 0.63 H), 2.60 (bs, 1 H), 2.40−2.30 (m, 0.37 H), 1.13 (d, J = 6.6 Hz, 1.89 H), 1.11 (d, J = 7.0 Hz, 1.11 H), 1.75−0.80 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (s), 163.3 (s), 136.0 (d), 134.1 (d), 133.4 (d), 133.3 (d), 129.8 (d), 129.0 (s), 128.4 (d), 128.3 (d), 117.7 (d), 117.0 (d), 75.3 (d), 75.1 (d), 38.5 (d), 36.0 (d), 34.4 (t), 33.9 (t), 31.7 (t), 30.0 (t), 29.5 (t), 29.1 (t), 27.7 (t), 26.7 (t), 25.7 (t), 22.4 (t), 15.9 (q), 15.2 (q), 13.9 (q), 13.4 (q).

4-Cyclohexyl-3-methyl-1-butene-1,4-diol Monobenzoate (3e, 5e). Following the procedure outlined above for benzaldehyde, cyclohexanecarboxaldehyde (0.16 mL, 1.3 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 8/92) to give an inseparable mixture (ratio 36/64 according to ^{1}H NMR) of diastereomers *syn*-(*Z*) **3e** and *syn*-(*E*) **5e** (0.13 g, 0.45 mmol, 52% yield) as an oil. IR (neat): 3422, 1727, 1451, 1337, 1265, 1120 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 8.5 Hz, 2 H), 7.65−7.35 (m, 3.37 H), 7.28 (d, J = 7.0 Hz, 0.64 H), 5.63 (dd, J = 12.5, 8.5 Hz, 0.64 H), 4.96 (dd, J = 9.7, 6.4 Hz, 0.37 H), 3.30−3.20 (m, 0.64 H), 3.12−3.02 (m, 0.37 H), 2.55−2.45 (m, 1 H), 1.98−1.85 (m, 1 H), 1.80−0.90 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (s), 163.4 (s), 135.7 (d), 133.6 (d), 133.4 (d), 133.3 (d), 129.8 (d), 129.7 (d), 129.0 (s), 128.3 (d), 128.1 (d), 118.7 (d), 117.8 (d), 79.5 (d), 79.3 (d), 40.6 (d), 40.3 (d), 34.9 (d), 32.7 (d), 30.0 (t), 29.7 (t), 27.4 (t), 26.8 (t), 26.6 (t), 26.1 (t), 15.6 (q), 14.4 (q).

General Procedure. Preparation of γ-Butyrolactones from Enol Esters. To a solution of enol esters (0.3 mmol, 1 equiv) in MeOH (5 mL) under an argon atmosphere at room temperature was added MeONa (48 mg, 0.9 mmol, 3 equiv), and the reaction mixture was warmed to 40 °C. After 1 h at 40 °C, the solution was cooled to room temperature and neutralized with aqueous HCl (1.2 M) until pH ∼7. The aqueous layer was extracted with Et_2O, and the combined organic phases were washed with water, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to give the γ-butyrolactol **6** as a mixture of diastereomers. The oxidation of the crude γ-butyrolactol **6** was achieved with pyridinium chlorochromate (194 mg, 0.9 mmol, 3 equiv) and anhydrous sodium acetate (12 mg, 0.15 mmol, 0.5 equiv) in the presence of molecular sieves 3 Å (388 mg) in CH_2Cl_2 (2 mL). After 5 h at room temperature, the reaction mixture was filtered through silica gel and concentrated under reduced

pressure. The crude γ-butyrolactone was purified by flash chromatography.

4-Methyl-5-phenyldihydrofuran-2(3*H*)-one (7a, 8a). An inseparable mixture of enol esters **3a**, **4a**, and **5a** (85 mg, 0.3 mmol) was processed as described in the general procedure above. The crude γ-butyrolactone was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 10/90) to give a mixture (ratio 93/7 according to ^{1}H NMR) of diastereomers *cis*-**7a** and *trans*-**8a** (35 mg, 0.2 mmol, 66% yield). IR (neat): 1780, 1456, 1306, 1217, 1159, 988 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.22 (m, 5 H), 5.61 (d, *J* = 6.3 Hz, 0.93 H), 4.95 (d, *J* = 8.5 Hz, 0.07 H), 2.97−2.75 (m, 1.93 H), 2.55−2.30 (m, 1.07 H), 1.20 (d, *J* = 6.6 Hz, 0.21 H), 0.70 (d, *J* = 7.0 Hz, 2.79 H). ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$): δ 176.6 (s), 136.0 (s), 128.3 (d), 127.9 (d), 125.3 (d), 83.9 (d), 36.6 (t), 34.8 (d), 15.0 (q). ^{13}C NMR for the minor diastereomer (75 MHz, $CDCl_3$): δ 175.9 (s), 137.8 (s), 128.6 (d), 128.6 (d), 125.8 (d), 88.0 (d), 39.7 (d), 37.1 (t), 16.3 (q). MS for the major diastereomer (EI, relative intensity): *m*/*z* 177 ($M^{\cdot+}$ + 1, 8), 176 ($M^{\cdot+}$, 70), 107 (100), 106 (21), 105 (97), 77 (26). MS for the minor diastereomer (EI, relative intensity): *m*/*z* 177 ($M^{\cdot+}$ + 1, 10), 176 ($M^{\cdot+}$, 77), 107 (100), 106 (21), 105 (95), 77 (26).

5-(4-Chlorophenyl)-4-methyldihydrofuran-2(3*H*)-one (7b, 8b). An inseparable mixture of enol esters **3b**, **4b**, and **5b** (95 mg, 0.3 mmol) was processed as described in the general procedure described above. The crude γ-butyrolactone was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 8/92) to give a mixture (ratio 90/10 according to ^{1}H NMR) of diastereomers *cis*-**7b** and *trans*-**8b** (30 mg, 0.14 mmol, 47% yield). IR (neat): 1786, 1493, 1458, 1214, 1157, 1091, 990 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.34 (m, 2 H), 7.27 (d, *J* = 8.1 Hz, 0.2 H), 7.19 (d, *J* = 8.4 Hz, 1.8 H), 5.58 (d, *J* = 5.9 Hz, 0.9 H), 4.91 (d, *J* = 8.1 Hz, 0.1 H), 2.95−2.79 (m, 2 H), 2.43−2.28 (m, 1 H), 1.20 (d, *J* = 6.6 Hz, 0.3 H), 0.70 (d, *J* = 7.3 Hz, 2.7 H). ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$): δ 176.2 (s), 134.5 (s), 133.8 (s), 128.6 (d), 126.7 (d), 83.2 (d), 37.0 (t), 34.7 (d), 14.0 (q). ^{13}C NMR for the minor diastereomer (75 MHz, $CDCl_3$): δ 175.6 (s), 136.3(s), 134.5 (s), 128.8 (d), 127.1 (d), 87.2 (d), 39.8 (d), 37.0 (t), 16.2 (q). MS for the major diastereomer (EI, relative intensity): *m*/*z* 212 ($M^{\cdot+}$ + 2, 17), 210 ($M^{\cdot+}$, 49), 143 (24), 142 (24), 141 (100), 140 (57), 139 (95), 70 (22). MS for the minor diastereomer (EI, relative intensity): *m*/*z* 212 ($M^{\cdot+}$ + 2, 18), 210 ($M^{\cdot+}$, 56), 143 (23), 142 (24), 141 (100), 140 (57), 139 (94), 70(21). HRMS (EI) calcd for $C_{11}H_{11}O_2Cl$ ($M^{\cdot+}$) 210.0448, found 210.0444.

4-Methyl-5-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (7c, 8c). An inseparable mixture of enol esters **3c**, **4c**, and **5c** (98 mg, 0.3 mmol) was processed as described in the general procedure described above. The crude γ-butyrolactone was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 20/80) to give a mixture (ratio 72/28 according to ^{1}H NMR) of diastereomers *cis*-**7c** and *trans*-**8c** (47 mg, 0.21 mmol, 70% yield). IR (neat): 1788, 1524, 1350, 1265, 1158, 994 cm^{-1}. ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$): δ 8.30−8.24 (m, 2 H), 7.50−7.45 (m, 2 H), 5.68 (d, *J* = 5.9 Hz, 1 H), 3.02−2.88 (m, 1 H), 2.38 (dd, *J* = 16.2, 2.2 Hz, 1 H), 0.70 (d, *J* = 7.4 Hz, 3 H). ^{1}H NMR for the minor diastereomer (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 5.04 (d, *J* = 8.1 Hz, 1 H), 2.83 (dd, *J* = 15.4, 5.9 Hz, 1 H), 2.53−2.34 (m, 2 H), 1.26 (d, *J* = 6.2 Hz, 3 H).^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$): δ 175.6 (s), 147.5 (s) 143.4 (s), 126.2 (d), 123.9 (d), 82.6 (d), 37.1 (t), 34.6 (d), 15.0 (q).^{13}C NMR for the minor diastereomer (75 MHz, $CDCl_3$): δ 175.1 (s), 148.0 (s), 145.1 (s), 126.4 (d), 123.9 (d), 86.3 (d), 39.9 (d), 36.7 (t), 16.3 (q). MS for the major diastereomer (EI, relative intensity): *m*/*z* 221 ($M^{\cdot+}$, 4), 152 (100), 115 (19), 107 (33), 70 (45). MS for the minor diastereomer (EI, relative intensity): *m*/*z* 221 ($M^{\cdot+}$, 3), 152 (100), 115 (17), 107 (31), 70 (36). HRMS (CI): calcd for $C_{11}H_{11}O_4N$ (M^+ + H) 222.0766, found 222.0770.

5-Hexyl-4-methyldihydrofuran-2(3*H*)-one (7d). An inseparable mixture of enol esters **3d** and **5d** (87 mg, 0.3 mmol) was processed as described in the general procedure described above. The crude γ-butyrolactone was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 13/87) to give **7d** (22 mg, 0.12 mmol, 40% yield). IR (neat): 1772, 1421, 1265, 1169, 896 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49−4.39 (m, 1 H), 2.70 (dd, *J* = 16.9, 7.7 Hz, 1 H), 2.66−2.51 (m, 1 H), 2.20 (dd, *J* = 16.5, 3.7 Hz, 1 H), 1.77−1.59 (m, 1 H), 1.57−1.45 (m, 1 H), 1.40−1.23 (m, 8 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 0.94−0.84 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (s), 83.5 (d), 37.4 (t), 32.9 (d), 31.5 (t), 29.7 (t), 29.0 (t), 25.7 (t), 22.4 (t), 13.9 (q), 13.7 (q). MS (EI, relative intensity): *m*/*z* 184($M^{\cdot+}$, 0,1), 142 (19), 99 (100), 97 (19), 71 (21).

5-Cyclohexyl-4-methyldihydrofuran-2(3*H*)-one (7e). An inseparable mixture of enol esters **3e** and **5e** (86 mg, 0.3 mmol) was processed as described in the general procedure described above. The crude γ-butyrolactone was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 15/85) to give **7e** (33 mg, 0.18 mmol, 60% yield). IR (neat): 1774, 1458, 1174, 1148, 984, 936 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02 (dd, *J* = 9.6, 4.4 Hz, 1 H), 2.72 (dd, *J* = 16.9, 7.3 Hz, 1 H), 2.62−2.49 (m, 1 H), 2.20 (dd, *J* = 16.5, 1.1 Hz, 1 H), 2.10−0.80 (m, 8 H), 1.00 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (s), 87.7 (d), 38.6 (t), 37.3 (d), 31.8 (d), 27.9 (t), 27.7 (t), 26.1 (t), 25.3 (t), 17.4 (t), 13.3 (q). MS (EI, relative intensity): *m*/*z* 182 ($M^{\cdot+}$, 1), 154 (22), 111 (19), 99 (100), 83 (24), 71 (24), 55 (22).

Preparation of Support-Bound α-(Benzoyloxy)crotylstannane (B). To a suspension of carboxypolystyrene (1.0 g, 2 mmol/g, 2 mmol) in CH_2Cl_2 (20 mL) at room temperature were added successively EDCI (1.9 g, 10 mmol, 5 equiv), DMAP (0.74 g, 6 mmol, 3 equiv), and **1** (3.6 g, 10 mmol, 5 equiv). After 16 h, the resin was filtered, alternately thoroughly washed with CH_2Cl_2 and Et_2O, and dried in vacuo to give the crotylstannane-supported reagent **B**. IR (KBr): 3022, 2922, 2844, 1728, 1700, 1350 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 130.6 (d), 127.8 (m, polystyrene), 119.4 (d), 71.9 (d), 40.3 (m, polystyrene), 28.8 (t), 27.2 (t), 17.7 (q), 13.6 (q), 9.5 (t).

General Conditions for Preparation of γ-Butyrolactones 7 and 8 from Resin B. The resin **B** (0.10 g, 0.12 mmol, 1 equiv) was washed with anhydrous CH_2Cl_2 to remove water under an argon atmosphere at room temperature. To a suspension of resin **B** and RCHO (1.2 mmol, 10 equiv) in CH_2Cl_2 (3 mL) at −78 °C was added dropwise $BF_3{\cdot}OEt_2$ (0.02 mL, 0.18 mmol, 1.5 equiv) with stirring. After 5 h at −78 °C, the mixture was allowed to reach room temperature, and the resin was filtered, washed with saturated aqueous $NaHCO_3$, then alternately thoroughly washed with CH_2Cl_2 and Et_2O, and dried in vacuo. Resin **C** was then suspended in MeOH/THF (1/4) (5 mL) at room temperature. After addition of NaOMe (0.13 g, 2.4 mmol, 20 equiv), the resulting slurry was stirred at 40 °C for 1 h, before neutralization by an aqueous solution of HCl (1.2 M). The mixture was filtered, and the filtrate was dried over $MgSO_4$. The solvent was removed in vacuo to give the γ-butyrolactol **6** as a mixture of diastereomers. The crude γ-butyrolactol **6** was oxidized by using pyridinium chlorochromate (78 mg, 0.36 mmol, 3 equiv) in the presence of anhydrous sodium acetate (5 mg, 0.06 mmol, 0.5 equiv) and molecular sieves 3 Å (156 mg) in CH_2Cl_2 (2 mL). After 6 h at room temperature, the reaction mixture was filtered through silica gel and concentrated under reduced pressure to produce γ-butyrolactones **7** and **8**.

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Supporting Information Available: ^{1}H NMR spectra of **7b**,**c** and **8c** and GC/MS spectra of **7b**, **8b**, **7c**, and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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