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Facile Chemo-, Regio-, and Diastereoselective Approach to *cis*-3,5-Disubstituted γ-Butyrolactones and Fused γ-Butyrolactones

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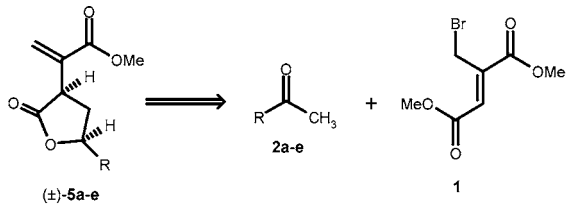

a, R = CH_2CH_3; **b**, R = $(CH_2)_3CH_3$; **c**, R = $(CH_2)_6CH_3$; **d**, R = $(CH_2)_9CH_3$; **e**, R = Ph.

Chemoselective S_N2' condensation of primary enolates of alkyl methyl ketones **2a**−**e** with dimethyl bromomethylfumarate (**1**) followed by highly diastereoselective $NaBH_4$ reduction of the ketone function in the formed ketodiesters **3a**−**e** and the regioselective in situ lactonization of the unisolable intermediates **4a**−**e** exclusively furnished the *cis*-3,5-disubstituted γ-butyrolactones (±)-**5a**−**e** in very good yields. Similarly, the face-selective coupling reaction of cyclohexanone enolate with **1** to form a mixture of diastereomers in an 8:2 ratio followed by a highly selective reductive cyclization of **9** plus **10** exclusively provided the *cis*-octahydrobenzofuran (±)-**12** in 70% overall yield.

The natural and unnatural γ-butyrolactones are an important class of compounds that find major applications in organic, medicinal, and polymer chemistry.[1] A broad range of biological properties has been conferred on them that includes strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, anti-inflammatory, cytostatic, antiallergenic, and anti-HIV activities.[1−4] From the bioactivity point of view, among all types of butyrolactones, the α-methylene γ-butyrolactones are of special interest as alkylating agents via Michael-type acceptor of biological cellular nucleophiles or cysteine residues of functional proteins.[4] A very large number of such γ-butyrolactones has been synthesized during the past century using several elegant synthetic strategies.[5] Basically, the diverse range of γ-butyrolactone skeletons has been designed by employing new C−O bond construction reactions and metal-catalyzed C−C bond formations via the carbocyclization of enynes. All these studies indicate that the development of new potential routes to γ-butyrolactones is still a challenging task of current interest. The S_N2' coupling reaction is a very important tool to form new carbon−carbon bonds in synthetic organic chemistry. Retrosynthetically, the S_N2' coupling reactions of alkyl methyl ketones with dimethyl bromomethylfumarate followed by a reductive regioselective cyclization would constitute a simple two-step approach to 3,5-disubstituted γ-butyrolactones via the [3 + 2] annulation pathway. We herein report our results on the synthesis of the target molecules (Schemes 1 and 2).

In continuation of our studies[6] on cyclic anhydrides to bioactive natural products, we recently synthesized dimethyl bromomethylfumarate (**1**) starting from citraconic anhydride in two steps.[7] We could perform a very chemoselective S_N2' coupling reaction of primary enolates of alkyl methyl ketones **2a**−**e** with **1** at −78 °C in 70−85% yields (Scheme 1). In the present S_N2' coupling of **1** with ketone enolates, the migration of the stable trisubstituted carbon−carbon double bond with the sole formation of the relatively less stable *gem*-disubstituted carbon−carbon double bond takes place as a result of excellent Michael acceptor capacity of the substrate **1** and a better leaving group ability of the bromide group.

The spectral characterization of these newly formed ketodiesters (±)-**3a**−**e** was easily possible on the basis of the appearance of two vinylic proton singlets for one hydrogen each in the ^{1}H NMR spectra of **3a**−**e** at ca. δ 5.27 and ca. δ 6.28. Upon treatment of the ketodiesters **3a**−**e** with $NaBH_4$ (1.50 equiv) in methanol at room temperature, a highly diastereoselective reduction of the ketone carbonyl group took place with the attack of the hydride ion from the less hindered side (Cram addition) to generate the unisolable pair of enantiomers of hydroxydiesters (±)-**4a**−**e**, which on an in situ regioselective lactonization with the more reactive non-conjugated ester moiety furnished the *cis*-3,5-disubstituted lactones (±)-**5a**−**e** in 80−90% yields. The ^{1}H NMR data of these lactones **5a**−**e** revealed that they are formed with ∼100% diastereoselectivity. Treatment of the lactonylacrylate **5e** with $NaBH_4$ in methanol at room temperature for 1 h facilitated the reduction of the carbon−carbon double bond with a Michael-type addition of the hydride

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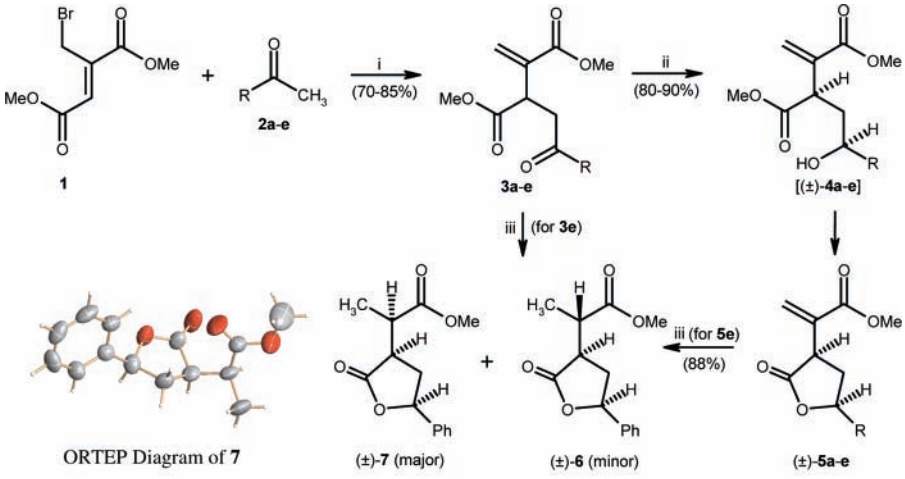
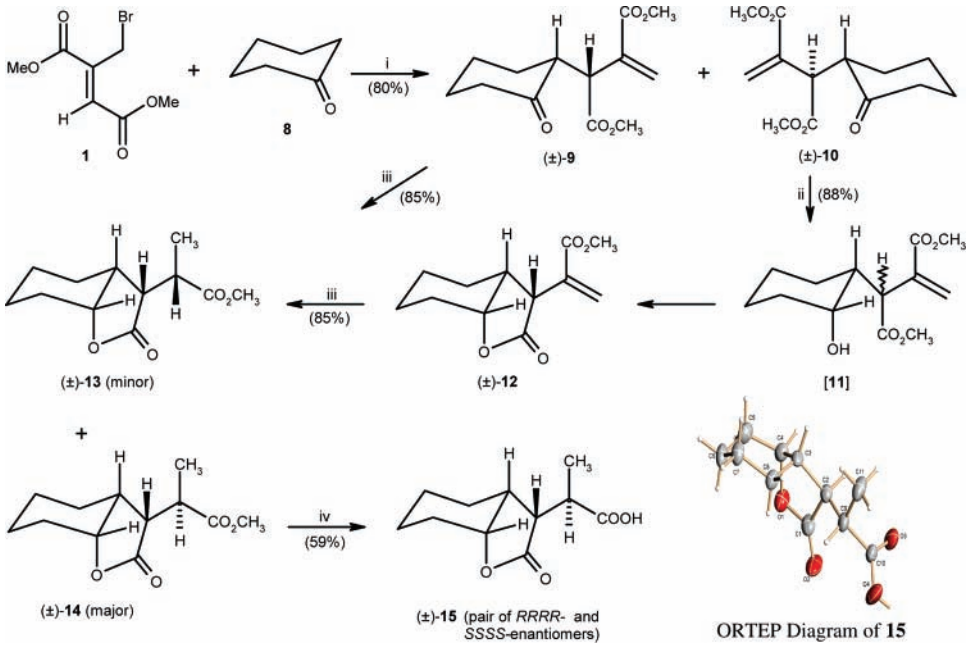
SCHEME 1[a]



a, R = CH_2CH_3; **b**, R = $CH_2(CH_2)_2CH_3$; **c**, R = $CH_2(CH_2)_5CH_3$; **d**, R = $CH_2(CH_2)_8CH_3$; **e**, R = Ph.

[a] Conditions: (i) LDA, THF, −78 °C, 20 min (**3a**, 80%; **3b**, 78%; **3c**, 72%; **3d**, 70%; and **3e**, 85%); (ii) $NaBH_4$ (1.50 equiv), MeOH, rt, 15 min (**5a**, 88%; **5b**, 85%; **5c**, 82%; **5d**, 80%; and **5e**, 90%); (iii) $NaBH_4$ (3.00 equiv), MeOH, rt, 1 h (88%, **6**/**7** = 1:9).

SCHEME 2[a]



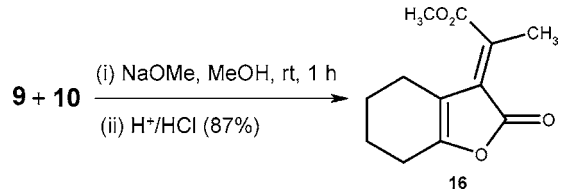
[a] Conditions: (i) LDA, THF, −100 °C, 20 min (**9**/**10** = 8:2, 80%); (ii) $NaBH_4$ (1.50 equiv), MeOH, rt, 15 min (88%); (iii) $NaBH_4$ (3.00 equiv), MeOH, rt, 1 h (85%, **13**/**14** = 15:85); (iv) (a) AcOH/HCl (3:1), reflux, 6 h (92%) and (b) recrystallization from EtOAc (64%).

ion followed by a highly diastereoselective acquisition of a proton from the less hindered side leading to the formation of a mixture of diastereomers (±)-**6** and (±)-**7** in a 1:9 ratio (by ^{1}H NMR) with 88% yield. Similarly, (±)-**3e** too, on treatment with an excess of $NaBH_4$, directly furnished the mixture of (±)-**6** and (±)-**7** in nearly the same ratio and yield. The mixture of **6** and **7** on recrystallization from dichloromethane provided analytically pure (±)-**7** with 69% recrystallization yield. The structure of (±)-**7** thus obtained was established on the basis of analytical and spectral data, and it was unambiguously confirmed on the basis of X-ray crystallographic data.[8]

Next, we prepared a plan to synthesize the fused γ-butyrolactones using the present S_N2' coupling reaction. Toward this, we performed the S_N2' coupling of cyclohexanone enolate with **1** at −78 °C and obtained the coupling product in 80% yield (Scheme 2). The ^{1}H and ^{13}C NMR spectrum of the previously coupled product showed two sets of signals with nearly equal intensities, suggesting that a column inseparable mixture of diastereomers is formed in nearly equal proportions. However, the S_N2' coupling of **1** and the cyclohexanone enolate, with an attack of the expected axial carbanion, was partly diastereoselective at −100 °C, resulting in a mixture of diastereomers **9** and **10** in a nearly 8:2 ratio. The observed face selective coupling could be ascribed to the steric interactions between **1** and axial carbanionic species of **8** and/or the thermodynamic stability of the formed major diastereomer **9**. It was not possible for us to still lower the temperature of the reaction mixture to obtain the complete diastereoselectivity, as the THF solution began solidifying below −105 to −110 °C. Interestingly, the mixture of diastereomers **9** and **10** (1:1/8:2) underwent a very stereospecific $NaBH_4$ reduction of the ketone group at room temperature

(8) The compounds **5a**−**d** were formed as a pair of *RR*- and *SS*-enantiomers, while **5e** was formed as a pair of *RS*- and *SR*-enantiomers.

SCHEME 3



with a less hindered equatorial approach of the hydride ion to generate the axial alcohols, which, upon in situ cyclization, exclusively furnished the octahydrobenzofuran (±)-**12** (pair of *RRR*- and *SSS*-lactones) in 88% yield. Herein, we surmise that during the course of the reaction, the formed lactone from (±)-**10** undergoes an instantaneous epimerization at an allylic carbon, with the catalytic amount of sodium methoxide generated in situ from $NaBH_4$ and methanol, thus providing the single diastereomer (±)-**12** in 88% yield. However, the mixture of **9** plus **10** on treatment with equimolar amounts of sodium methoxide in methanol at room temperature directly furnished the lactone **16** in 87% yield, via the enolization, cyclization, and isomerization of the carbon−carbon double bond (Scheme 3).

Finally, further reduction of the carbon−carbon double bond in (±)-**12** with $NaBH_4$ was also diastereoselective (70% de, by ^{1}H NMR) with abstraction of the proton occurring predominantly from the less hindered site giving rise to a mixture of (±)-**13** (minor) and (±)-**14** (major, pair of *RRRR*- and *SSSS*-isomers) as a thick oil in 85% yield. Acid-catalyzed ester hydrolysis of **13** plus **14** furnished a diastereomeric mixture of corresponding carboxylic acids in 92% yield. Recrystallization of the previous diastereomeric mixture of acids in ethyl acetate gave the analytically pure single diastereomer with 64% recrystallization yield. The X-ray crystallographic data of the analytically pure diastereomer revealed that a (±)-lactone **15** is formed. Finally, on the basis of X-ray data, we could postulate the complete mechanistic and stereochemical aspects of the present conversion of **1** plus **8** to (±)-**15** as indicated in Scheme 2.

In summary, we have demonstrated a simple, efficient as well as highly chemo-, regio- and diastereoselective approach to *cis*-3,5-disubstituted γ-butyrolactones for the first time by employing the S_N2'-coupling reactions of ketones with dimethyl bromomethylfumarate (**1**) followed by reductive cyclization pathway. In the present approach, the face selective condensation of primary enolate of cyclohexanone with **1** and the diastereoselective reduction of the ketone moiety are noteworthy. We feel that our present approach is general in nature and the natural stereochemical outcome in the present approach to obtain γ-butyrolactones, which is interesting, would be useful to design a large number of desired substituted and bicyclic/fused structurally complex γ-butyrolactones. We also feel that the independent acrylate moiety at the 3-position in **5a-e** and **12** will be useful for further synthetic structural elaborations and their Michael acceptor capacity might be an added advantage from the bioactivity point of view.

Experimental Procedures

(±)-Dimethyl 2-Methylene-3-(2-oxobutyl)succinate (3a). To a stirred solution of 2-butanone (144 mg, 2.00 mmol) in THF (5 mL) at −78 °C was added freshly prepared LDA (214 mg, 2.00 mmol) in THF (5 mL) in a dropwise fashion under argon atmosphere. The reaction mixture was stirred at −78 °C temperature for 1 h, and the reaction mixture was added to a stirred solution of dimethyl bromomethylfumarate (**1**, 474 mg, 2.00 mmol) at −78 °C under argon atmosphere in a dropwise fashion. Stirring was continued for a further 20 min at the same temperature. The reaction was then quenched with a saturated solution of NH_4Cl. The reaction mixture was extracted with ethyl acetate (30 mL × 4), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (2:8) as an eluant gave **3a** as a thick oil (365 mg, 80%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00 (t, J = 8 Hz, 3H), 2.25−2.50 (m, 2H), 2.56 (dd, J = 18 and 4 Hz, 1H), 3.14 (dd, J = 18 and 10 Hz, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 4.03 (dd, J = 10 and 4 Hz, 1H), 5.68 (s, 1H), 6.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.4, 35.8, 42.5, 43.4, 51.9, 52.1, 127.5, 137.8, 165.9, 172.6, 208.2; IR (neat) υ_{max} 1740, 1730, 1717, 1630, 1437, 1231 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.69; H, 7.18.

The compounds **3b**−**e** and **9** + **10** were prepared similarly using the previous procedure. The mixture of diastereomers **9** + **10** (2:8) was prepared similarly using the previous procedure at −100 °C.

(±)-Dimethyl 2-Methylene-3-(2-oxohexyl)succinate (3b). Starting from **1** (474 mg, 2.00 mmol) and 2-hexanone (200 mg, 2.00 mmol), **3b** was obtained as a thick oil (400 mg, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, J = 8 Hz, 3H), 1.27 (sextet, J = 8 Hz, 2H), 1.53 (quintet, J = 8 Hz, 2H), 2.30−2.50 (m, 2H), 2.58 (dd, J = 18 and 6 Hz, 1H), 3.16 (dd, J = 18 and 8 Hz, 1H), 3.63 (s, 3H), 3.73 (s, 3H), 4.04 (dd, J = 8 and 4 Hz, 1H), 5.70 (s, 1H), 6.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 22.1, 25.6, 42.5 (2 carbons), 43.9, 52.0, 52.2, 127.7, 137.8, 166.0, 172.6, 208.0; IR (neat) υ_{max} 1742, 1728, 1715, 1632, 1439, 1232 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 61.13; H, 7.77.

(±)-Dimethyl 2-Methylene-3-(2-oxononyl)succinate (3c). Starting from **1** (474 mg, 2.00 mmol) and 2-nonanone (284 mg, 2.00 mmol), **3c** was obtained as a thick oil (430 mg, 72%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 8 Hz, 3H), 1.26 (bs, 8H), 1.57 (quintet, J = 8 Hz, 2H), 2.35−2.50 (m, 2H), 2.61 (dd, J = 18 and 6 Hz, 1H), 3.19 (dd, J = 18 and 8 Hz, 1H), 3.67 (s, 3H), 3.76 (s, 3H), 4.07 (dd, J = 10 and 4 Hz, 1H), 5.73 (s, 1H), 6.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 23.7, 29.0, 29.1, 31.6, 42.6, 42.9, 44.0, 52.3 (2 carbons), 127.8, 137.9, 166.1, 172.8, 208.2; IR (neat) υ_{max} 1740, 1720, 1630, 1437, 1231 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.32; H, 8.59.

(±)-Dimethyl 2-Methylene-3-(2-oxododecyl)succinate (3d). Starting from **1** (474 mg, 2.00 mmol) and 2-dodecanone (360 mg, 2.00 mmol), **3d** was obtained as a thick oil (476 mg, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (t, J = 8 Hz, 3H), 1.22 (bs, 14H), 1.53 (quintet, J = 8 Hz, 2H), 2.30−2.50 (m, 2H), 2.58 (dd, J = 18 and 6 Hz, 1H), 3.16 (dd, J = 18 and 8 Hz, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 4.04 (dd, J = 8 and 4 Hz, 1H), 5.70 (s, 1H), 6.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 23.6, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8, 42.6, 42.9, 43.9, 52.2 (2 carbons), 127.7, 137.9, 166.1, 172.7, 208.1; IR (neat) υ_{max} 1740, 1720, 1630, 1462, 1437, 1232 cm^{-1}; Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.95; H, 9.58.

(±)-Dimethyl 2-Methylene-3-(2-oxo-2-phenylethyl)succinate (3e). Starting from **1** (474 mg, 2.00 mmol) and acetophenone (240 mg, 2.00 mmol), **3e** was obtained as a thick oil (470 mg, 85%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.24 (dd, J = 18 and 4 Hz, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.77 (dd, J = 18 and 8 Hz, 1H), 4.27 (dd, J = 8 and 6 Hz, 1H), 5.81 (s, 1H), 6.34 (s, 1H), 7.35−7.60 (m, 3H), 7.90−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.2, 42.6, 52.2 (2 carbons), 127.9, 128.0, 128.5, 133.1, 136.3, 137.8, 166.0, 172.7, 197.1; IR (neat) υ_{max} 1736, 1720, 1686, 1630, 1448, 1437, 1260 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.90.

(±)-Dimethyl 2-Methylene-3-(2-oxocyclohexyl)succinate (9 and 10). Starting from **1** (474 mg, 2.00 mmol) and cyclohexanone (196 mg, 2.00 mmol), the mixture of compounds **9** and **10** was obtained as a thick oil (mixture of diasteriomers in the ratio of 1:1, 406 mg, 80%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50−2.50 (m, 16H), 2.80−3.15 (m, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.89 (d, J = 10 Hz, 1H), 4.06 (d, J = 8 Hz, 1H), 5.66 (s, 1H), 5.79 (s, 1H), 6.30 (s, 1H), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.9, 25.3, 27.4, 28.2, 30.6, 31.4, 42.0, 42.1, 45.2, 45.8, 52.0, 52.1, 52.2 (2 carbons), 52.6, 52.8, 126.5, 128.4, 136.7, 137.3, 166.4, 166.6, 172.8, 172.9, 210.0, 211.1; IR (neat) υ_{max} 1734, 1713, 1628, 1437 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.33; H, 7.25.

(±)-Methyl 2-(5-Ethyl-2-oxo-tetrahydrofuran-3-yl)acrylate (5a). To a solution of **3a** (228 mg, 1.00 mmol) in methanol (15 mL) was added $NaBH_4$ (60 mg, 1.50 mmol) at 0 °C, and the reaction mixture was stirred for 15 min. The reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (25 mL × 4), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (3:7) as an eluant gave **5a** as a thick oil (174 mg, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 8 Hz, 3H), 1.55−2.10 (m, 3H), 2.53 (ddd, J = 12, 10, and 6 Hz, 1H), 3.66 (dd, J = 12 and 8 Hz, 1H), 3.77 (s, 3H), 4.25−4.50 (m, 1H), 5.84 (s, 1H), 6.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.3, 28.2, 35.0, 44.9, 52.1, 80.0, 129.2, 136.1, 165.7, 175.8; IR (neat) υ_{max} 1771, 1720, 1634, 1439 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.76; H, 7.03.

Compounds **5b**−**e** and **12** were prepared similarly using the previous procedure.

(±)-Methyl 2-(5-Butyl-2-oxo-tetrahydrofuran-3-yl)acrylate (5b). Starting from **3b** (256 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol), **5b** was obtained as a thick oil (192 mg, 85%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 8 Hz, 3H), 1.15−1.50 (m, 4H), 1.50−1.85 (m, 2H), 1.85−2.07 (m, 1H), 2.53 (ddd, J = 13, 8 and 6 Hz, 1H), 3.55−3.75 (m, 1H), 3.75 (s, 3H), 4.30−4.50 (m, 1H), 5.83 (s, 1H), 6.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 22.3, 27.2, 35.0, 35.4, 44.9, 52.0, 78.8, 129.1, 136.0, 165.6, 175.8; IR (neat) υ_{max} 1771, 1720, 1634, 1439 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.61; H, 7.92.

(±)-Methyl 2-(5-Heptyl-2-oxo-tetrahydrofuran-3-yl)acrylate (5c). Starting from **3c** (298 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol), **5c** was obtained as a thick oil (220 mg, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.27 (bs, 10H), 1.40−1.85 (m, 2H), 1.85−2.10 (m, 1H), 2.54 (ddd, J = 12, 10, and 6 Hz, 1H), 3.66 (dd, J = 12 and 8 Hz, 1H), 3.78 (s, 3H), 4.30−4.50 (m, 1H), 5.85 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 25.2, 29.1, 29.2, 31.7, 35.4, 35.6, 44.9, 52.1, 78.9, 129.2, 136.1, 165.7, 175.8; IR (neat) υ_{max} 1771, 1720, 1632, 1439 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.98; H, 8.93.

(±)-Methyl 2-(5-Decyl-2-oxo-tetrahydrofuran-3-yl)acrylate (5d). Starting from **3d** (340 mg, 1.00 mmol) and $NaBH_4$ (60 mg, 1.50 mmol), **5d** was obtained as a thick oil (248 mg, 80%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.25 (bs, 16H), 1.40−1.85 (m, 2H), 1.85−2.10 (m, 1H), 2.54 (ddd, J = 12, 10, and 6 Hz, 1H), 3.55−3.75 (m, 1H), 3.78 (s, 3H), 4.30−4.50 (m, 1H), 5.85 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 25.2, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 35.4, 35.6, 44.9, 52.1, 78.9, 129.1, 136.1, 165.7, 175.8; IR (neat) υ_{max} 1774, 1734, 1634, 1439 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.57; H, 9.88.

(±)-Methyl 2-(2-Oxo-5-phenyl-tetrahydrofuran-3-yl)acrylate (5e). Starting from **3e** (200 mg, 0.72 mmol) and $NaBH_4$ (45 mg, 1.10 mmol), **5e** was obtained as a white solid (160 mg, 90%). Mp 127−128 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.30−2.50 (m, 1H), 2.83 (ddd, J = 12, 10, and 6 Hz, 1H), 3.65−3.75 (m, 1H), 3.80 (s, 3H), 5.42 (dd, J = 10 and 6 Hz, 1H), 5.91 (s, 1H), 6.45 (s, 1H), 7.30−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.1, 45.6, 52.2, 79.7, 125.9, 128.6, 128.7, 129.7, 135.7, 138.8, 165.5, 175.5; IR (neat) υ_{max} 1771, 1728, 1632, 1439 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.22; H, 5.71.

(±)-Methyl 2-(2-Oxo-octahydrobenzofuran-3-yl)acrylate (12). Starting from a mixture of **9** and **10** (150 mg, 0.60 mmol) and $NaBH_4$ (36 mg, 0.90 mmol), **12** was obtained as a thick oil (116 mg, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15−1.65 (m, 4H), 1.75−2.35 (m, 4H), 3.36 (d, J = 14 Hz, 1H), 3.65−3.90 (m, 2H), 3.79 (s, 3H), 5.77 (s, 1H), 6.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.0, 25.1, 27.4, 30.1, 50.1, 50.3, 52.2, 83.0, 129.2, 134.9, 166.0, 175.5; IR (neat) υ_{max} 1769, 1732, 1632, 1445 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.23.

Methyl 2-(2-Oxo-octahydrobenzofuran-3-yl)propanoate (13 and 14). To a solution of a mixture of **9** and **10** (150 mg, 0.60 mmol) in methanol (15 mL) was added $NaBH_4$ (72 mg, 1.80 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction was then quenched with water. The reaction mixture was extracted with ethyl acetate (25 mL × 4), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (3:7) as an eluant gave the mixture of **13** and **14** as a thick oil (the mixture of diastereoisomers was formed in the ratio of **13**/**14** = 15:85, 113 mg, 85%). Major isomer (±)-**14**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (d, J = 6 Hz, 3H), 1.20−2.00 (m, 8H), 2.15−2.30 (m, 1H), 2.85 (dd, J = 14 and 4 Hz, 1H), 2.90−3.10 (m, 1H), 3.70 (s, 3H), 3.70−3.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 23.9, 25.1, 28.0, 30.0, 37.3, 45.8, 48.6, 51.9, 82.7, 174.8, 176.7; IR (neat) υ_{max} 1778, 1734, 1450, 1254 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.65; H, 8.14.

Methyl 2-(2-Oxo-5-phenyl-tetrahydrofuran-3-yl)propanoate (6 and 7). Starting from **3e** (200 mg, 0.72 mmol) and $NaBH_4$ (90 mg, 2.20 mmol), the mixture of **6** and **7** was obtained as a white solid (the mixture of diastereoisomers was formed in the ratio of **6**/**7** = 10:90, 158 mg, 88%). Recrystallization from dichloromethane furnished the analytically pure major isomer (±)-**7**: mp 79−80 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (d, J = 6 Hz, 3H), 2.08−2.30 (m, 1H), 2.68 (ddd, J = 12, 8, and 6 Hz, 1H), 2.85−3.20 (m, 2H), 3.69 (s, 3H), 5.37 (dd, J = 12 and 6 Hz, 1H), 7.30−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.1, 34.5, 38.6, 44.1, 51.9, 79.5, 125.7, 128.5, 128.6, 139.1, 173.9, 176.8; IR (neat) υ_{max} 1774, 1732, 1458 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.89; H, 6.47.

(±)-2-(2-Oxo-octahydrobenzofuran-3-yl)propanoic acid (15). A solution of the mixture of **13** and **14** (70 mg, 0.30 mmol) in AcOH/HCl (3:1) (10 mL) was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo, and the resulting solution was washed with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a mixture of diastereomers as a white solid (60 mg, 92%). Recrystalization from ethyl acetate furnished the analytically pure major isomer **15**: mp 215−216 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00−1.30 (m, 2H), 1.29 (d, J = 6 Hz, 3H), 1.35−1.85 (m, 4H), 2.20−2.45 (m, 2H), 2.55−2.75 (m, 1H), 3.00−3.15 (m, 2H), 4.45−4.55 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 16.9, 20.4, 23.0, 23.7, 28.0, 36.5, 38.0, 51.3, 78.1, 176.9, 177.6; IR (neat) υ_{max} 2700−2500, 1757, 1697, 1464, 1377 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.56.

(*E*)-Methyl 2-(2-Oxo-4,5,6,7-tetrahydrobenzofuran-3(2*H*)-ylidene)propanoate (16). To a solution of a mixture of **9** and **10** (125 mg, 0.50 mmol) in methanol (5 mL) was added NaOMe (27 mg, 0.50 mmol) at room temperature, and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate (15 mL), and acidified with 2 N HCl. The aqueous layer was extracted with ethyl acetate (10 mL × 2), and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (2:8) as an eluant gave **16** as a white solid (95 mg, 87%). Mp 88−89 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.55−1.90 (m, 4H), 2.03 (s, 3H), 2.29 (t, J = 6 Hz, 2H), 2.53 (t, J = 6 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 21.4, 21.8, 23.4, 27.3, 52.5, 109.1, 119.6, 145.4, 157.7, 163.3, 166.4; IR ($CHCl_3$) υ_{max} 1736, 1719, 1647 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.03; H, 6.52.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **3a**−**e**, **5a**−**e**, **6** + **7**, **9** + **10**, **12**, **13** + **14**, **15**, and **16**. X-ray crystallographic data for compounds (±)-**7** and (±)-**15** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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