A Versatile Route to Functionalized Dilactones as Monomers for the Synthesis of Poly(α-hydroxy) Acids

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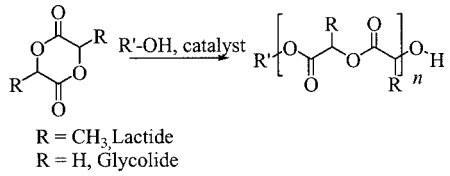
A synthetic pathway to functionalized six-membered dilactones structurally analogous to lactide is described. Through the use of orthogonal protecting groups, the synthesis of functionalized dilactones was performed in a straightforward way by cyanuric chloride-mediated cyclization of the corresponding linear α-hydroxy acid dimers. The synthesis of three different dilactones – methylglycolide, benzyloxymethylglycolide, and 2-benzyloxymethyl-5-methylglycolide – by the same procedure demonstrated the versatility of this route.

Introduction

Poly(α-hydroxy) acids such as polylactic acid and polyglycolic acid are widely under investigation, particularly for biomedical and pharmaceutical applications, because of their good biocompatibility and biodegradability.[1] Derivatives bearing functional groups along the main chain would be a valuable extension of the present arsenal of biodegradable polymers. In particular, the introduction of hydrophilic functional groups would open a considerable range of potential for the design of new poly(α-hydroxy) acids that should, for example, display enhanced hydrophilicity and compatibility with living cells and blood components. Such polymers can also be used for the formation of supramolecular structures such as polymeric micelles and hydrogels.[2,3] Moreover, it is to be expected that the degradation time could be tailored and that non-toxic degradation products should be formed through proper selection of the monomers. Another advantage is that the functional groups can be further derivatized with − for example − cytostatic agents to yield biodegradable polymeric prodrugs.[4]

Polylactic acid can be synthesized by a polycondensation reaction of lactic acid at high temperature. This route, however, yields relatively low molecular weight polymers.[5] High molecular weight polylactic acid and polyglycolic acid, as well as their copolymers, can be routinely synthesized by ring-opening polymerization of the dilactone of lactic acid or glycolic acid with stannous 2-ethyl hexanoate or zinc powder as catalysts.[6] Moreover, the synthesis of poly(α-hydroxy) acids by controlled ring-opening polymerization allows polymers with a low polydispersity to be made, and block copolymers of well defined structure also become available.[7] Scheme 1 shows a simplified representation of the ring-opening polymerization of lactide/glycolide.



Scheme 1

The two substituents in the dilactone can be identical (homodimers) or different (heterodimers). Homodimers are usually prepared by thermal catalytic depolymerization of low molecular weight polycondensate with transition metal complexes as transesterification catalysts (e.g., synthesis of lactide and glycolide).[8] A homobislactone was also obtained by ring-closure mediated by reagents such as HOAt and HOBt.[9] Heterodimers, however, cannot be prepared easily by this route. Few methods for the synthesis of this kind of unsymmetrical dilactones have been reported,[10−12] and, importantly, those that are currently known are not very efficient. Drawbacks include limited availability of starting materials, the need for long oxidation periods, and low overall yields.

Here we propose a versatile route to substituted glycolides and lactides starting from α-hydroxy acids. These are converted into linear dimers, which are subsequently cyclized by a lactonization reaction. Furthermore, to prevent side reactions during polymerization of the functionalized dilactones, it is essential to introduce protecting groups. These groups should be inert to the polymerization reaction conditions. To achieve these structures, mild conditions for

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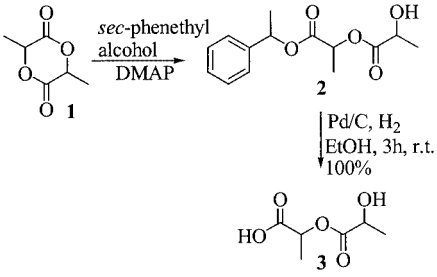
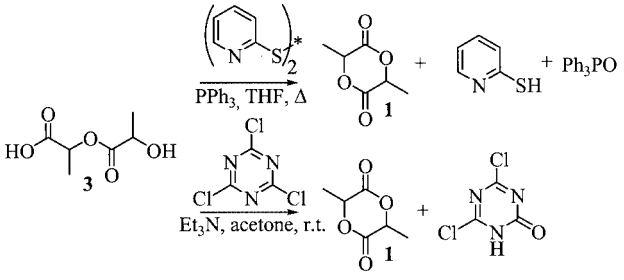
ring-closure are required. Several complex macrolides have been synthesized via 2-pyridinethiol esters, an approach also known as the Corey−Nicolaou lactonization.[13−15] This method involves the activation both of the hydroxyl group and of the carboxylic acid. The use of cyanuric chloride for the synthesis of macrolactones has also been reported.[16] These reports all deal with the synthesis of lactones containing one ester function and 5−20 (mostly aliphatic) carbon atoms in the ring. This tempted us to apply these methods for the preparation of six-membered dilactones that do not have two or more aliphatic carbon atoms next to each other.

Results and Discussion

To investigate whether the six-membered ring structure of the objected dilactones could be synthesized from its linear precursor through lactonization, lactic acid was used as a model compound. Its linear dimer was prepared first, by treatment of lactide (**1**) with *sec*-phenethyl alcohol, which yielded *sec*-phenethyl *O*-lactoyllactate (**2**, Scheme 2), as reported by Nederberg et al.[17] This compound was converted quantitatively into the linear dimer of lactic acid, lactoyl lactate (**3**). Cyclization of lactoyl lactate was attempted with two different cyclization reagents: dipyridyl disulfide/PPh_3[13−15] and cyanuric chloride/Et_3N[16] (Scheme 3). The cyclization reaction with dipyridyl disulfide and with PPh_3 in THF was not driven to completion even after 24 h at reflux, but when cyanuric chloride was used in acetone in the presence of Et_3N the reaction showed almost complete conversion at room temperature in less than one hour. This cyclization method was therefore used for other linear dimers as well.



Scheme 2



Scheme 3

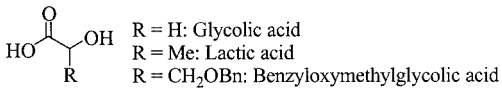
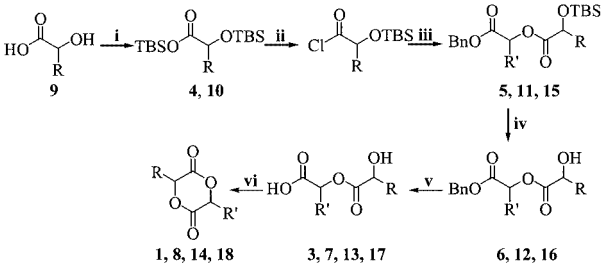


Figure 1. α-Hydroxy acids used in this study

To demonstrate the versatility of this route we attempted to synthesize a number of heterodimers based on the combinations of three different α-hydroxy acids: glycolic acid, lactic acid, and benzyloxymethylglycolic acid (Figure 1). This last compound was prepared from commercially available *O*-benzyl protected L-serine by diazotization;[18] the general route is depicted in Scheme 4. The hydroxyl and acid functionalities of one α-hydroxy acid were first simultaneously protected by silylation with TBSCl. The resulting compound could be converted into the acid chloride by addition of oxalyl chloride and a catalytic amount of DMF.[19] These conditions leave the silyl ether unaffected because no HCl is generated under these reaction conditions. Condensation with an α-hydroxy ester gave the fully protected linear dimer. It is very important that these protecting groups are selected on the basis of orthogonality, to provide selective deprotection.

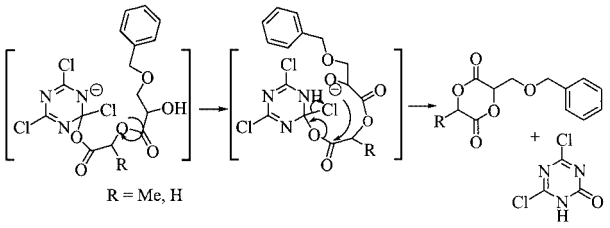


	1, 3	4	5–8	9–10	11–14	15–18
R	Me	H	H	CH_2OBn	CH_2OBn	CH_2OBn
R'	Me	-	Me	-	Me	H

Scheme 4. i) 2.1 equiv. TBSCl, imidazole, DMF. ii) $(COCl)_2$, cat DMF, DCM. iii) benzyl (*S*)-lactate/benzyl glycolate, pyridine, Et_2O. iv) TBAF/HOAc, EtOAc. v) 1 equiv. w/w Pd/C, 1,4-cyclohexadiene, EtOH. vi) cyanuric chloride, acetone, Et_3N

The TBS ether was cleaved selectively in EtOAc containing TBAF and acetic acid. Several methods to remove the silyl group were tried (TBAF/THF, camphorsulfonic acid, HCl/EtOH), but the buffered TBAF solution proved to be universally applicable. Secondary TBS ethers **11** and **15** were cleaved at elevated temperatures, whereas the primary TBS ether **5** could be cleaved at room temperature. Subsequently, the benzyl ester had to be removed. When the mild hydride donor 1,4-cyclohexadiene was used with Pd/C as a catalyst the benzyl ester could be cleaved selectively, keeping the benzyl ether intact.[20] This reaction took several hours to complete when a fresh batch of Pd/C was used, contradictory to earlier reports.[20] After both the carboxylic acid and the hydroxyl group had been deprotected, addition of cyanuric chloride yielded the (functionalized) six-membered dilactone. The optical rotation of the product lactide **1** showed that the ring-closure occurred with reten-

tion of chirality ($[\alpha]_D^{20} = -278$); this has not been investigated for the heterodimers. The reaction times for the lactonization ranged from one hour (for lactide) to one night (for **14** and **18**). These different reaction times may be due to steric hindrance, occurring when the transition state complex between cyanuric chloride and the linear compound is formed. Scheme 5 shows a reaction mechanism that illustrates this possible steric hindrance and it also demonstrates that the intermediate has to rotate around the ester C−O bond to adapt the right conformation for cyclization. Esters have the tendency to exist almost exclusively in the *s-trans* geometry, which is primarily due to dipole repulsion.[21−24] Normally the barrier of rotation is quite low (≤ ca. 10 kcal/mol), but this extra contribution to the activation free energy makes cyclization difficult. Both factors explain the need for prolonged reaction times and elevated temperatures to give the desired dilactone.



Scheme 5

Conclusion

A number of differently substituted dilactones have been synthesized by the general procedure as described in this paper. The desired dilactones were obtained relatively easily, in reasonable overall yields and with good purities. It is likely that our procedure is not limited to the compounds synthesized here, but may be applicable to a wide variety of α-hydroxy acids. Work along these lines is currently in progress in our laboratory. With this route to hand, a wide variety of different functionalized dilactones may be synthesized with the goal of preparing a range of different poly(α-hydroxy) acids with tailored properties.

Experimental Section

General Information: All reagents and solvents were used without purification, unless stated otherwise. DMF was dried and stored over 4 Å molecular sieves. Peptide grade dichloromethane was used. Reagents were purchased from Aldrich unless stated otherwise. (*S*)-Benzyl lactate was purchased from Purac Biochem. Reactions were monitored by TLC. R_f values were obtained on silica coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated eluent. The compounds were analyzed by use of UV light (254 nm), I_2, or a 5% solution of ammonium molybdate in 2 M sulfuric acid followed by heating. Flash column chromatography was carried out with Acros silica gel (0.030−0.075 mm) and the indicated eluent. Optical rotation was measured on a Jasco P-1010 polarimeter. NMR measurements were performed at 298 K on a Varian Gemini-300 NMR machine, at 300 MHz (^{1}H) or 75 MHz (^{13}C). Chemical shifts (δ) are reported in ppm relative to TMS with the solvent peak as an internal reference. Mass spectra (ES) were recorded on a Micromass Quatro Ultima spectrometer. Melting points were measured on a DSC Q1000 DSC machine.

***sec*-Phenethyl *O*-Lactoyllactate (2):** DMAP (25.4 g, 0.21 mol) was dissolved in *sec*-phenethyl alcohol (250 mL, 2.02 mol) and heated to 40 °C. L-Lactide (30.0 g, 0.21 mol) was added, and the mixture was stirred for 20 min. After the mixture had cooled to room temp., EtOAc (300 mL) was added. Excess DMAP was removed by filtration through a silica filter. The filter was washed with EtOAc. Concentration in vacuo yielded **2** as an oil. Vacuum distillation yielded *sec*-phenethyl-*O*-lactoyl lactate (30.0 g) as a mixture of diastereoisomers (67%, Bp. (0.6 mbar) = 105−110 °C). ^{1}H NMR ($CDCl_3$): δ = 1.40−1.60 (m, 9 H), 4.34 (q, *J* = 7 Hz, 1 H), 5.16 (q, *J* = 7 Hz, 1 H), 5.18 (q, *J* = 7 Hz, 1 H), 5.87 (q, *J* = 7 Hz, 1 H), 5.90 (q, *J* = 7 Hz, 1 H), 7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.6; 16.8; 20.4; 20.4; 21.8; 21.9; 66.6; 69.3; 69.4; 73.6; 73.8; 125.9; 126.0; 128.1; 128.5; 140.6; 169.3; 175.0 ppm. MS (ES): calculated [M + Na]: 289.1, measured [M + Na]: 289.2.

Lactoyl Lactate (3): Pd/C (250 mg, 10% w/w) was added to a solution of *sec*-phenethyl *O*-lactoyllactate **2** (2.50 g, 9.4 mmol) in EtOH (40 mL). The mixture was placed under a hydrogen atmosphere (balloon), and allowed to react overnight at room temp. Pd/C was removed by filtration through a Hyflo filter. The filter was washed extensively with EtOH, and the filtrate was concentrated in vacuo. This yielded **3** (1.56 g, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.47 (d, *J* = 7 Hz, 3 H), 1.56 (d, *J* = 7 Hz, 3 H), 4.30 (q, *J* = 7 Hz, 1 H), 5.21 (q, *J* = 7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.7; 20.2; 66.8; 69.2; 175.1 ppm. MS (ES): calculated [M + Na]: 185.1, measured [M + Na]: 185.0.

L-Lactide (1): Lactoyl lactate **3** (1.56 g, 9.40 mmol) was dissolved in dry acetone (100 mL). Cyanuric chloride (1.75 g, 9.40 mmol) was added and the mixture was stirred at room temp. until a clear solution was obtained. Et_3N (2.60 mL, 18.9 mmol) was added, and almost immediately a white precipitate appeared. The mixture was stirred for 1 h. The precipitate was removed by filtration through a Hyflo filter, the filter was washed extensively with acetone, and the filtrate was diluted with water (100 mL). The aqueous layer was extracted with three 80 mL portions of chloroform. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography with MTBE yielded L-lactide (1.07 g, 80%) as a white solid. (R_f = 0.3). Recrystallization from toluene gave L-lactide as colorless needle-like crystals. M.p. 97 °C. (ref.[25] 95 °C), $[\alpha]_D^{20} = -278$ (*c* = 1, chloroform).[26] ^{1}H NMR ($CDCl_3$): δ = 1.61 (d, *J* = 7 Hz, 6 H), 5.05 (q, *J* = 7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6; 72.4; 167.5 ppm. MS (ES): calculated [M + I]: 270.95, measured [M + I]: 270.94.

(*tert*-Butyldimethylsilanyl) (*tert*-Butyldimethylsilanyloxy)acetate (4): Glycolic acid (5.0 g, 65.7 mmol) was dissolved in DMF (60 mL). Imidazole (13.5 g, 197 mmol) and TBSCl (21.5 g, 138 mmol) were added successively. The mixture was allowed to react overnight at room temp. Water was added (100 mL) followed by extraction with four 80 mL portions of Et_2O. The combined organic layers were washed with 100 mL of water, dried ($MgSO_4$), filtered, and concentrated in vacuo to give **4** quantitatively as a white semi-solid (20.0 g). ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 6 H), 0.26 (s, 6 H), 0.81 −0.95 (m, 18 H), 4.17 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −5.5; −4.8; −3.6; 25.5; 25.7; 62.3; 171.9 ppm. MS (ES): calculated [M + Na]: 327.2, measured [M + Na]: 327.0.

Benzyl 2-[2-(*tert*-Butyldimethylsilanyloxy)acetoxy]propionate (5): Oxalyl chloride (1.7 mL, 19 mmol) was added carefully to an ice-

cooled solution of compound **4** (5.0 g, 16.5 mmol) in dichloromethane (20 mL) containing 10 drops of DMF. The reaction was performed under a dry nitrogen atmosphere, by use of standard Schlenk techniques. After the vigorous evolution of gas had ceased, the mixture was allowed to warm to room temp. After 2 hours, dichloromethane and TBSCl were removed in vacuo. A solution of Et_2O (10 mL), pyridine (10 mL), and (*S*)-benzyl lactate (12.0 g, 66.5 mmol) was added to the residue, and this mixture was stirred at room temp. for an additional 1.5 h. The white precipitate was removed by filtration and the filtrate was concentrated in vacuo. Flash column chromatography with MTBE/hexane (1:5) yielded benzyl ester **5** as a colorless oil. R_f = 0.5. Yield: 2.0 g (35% over two steps). ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 6 H), 0.91 (s, 9 H), 1.48 (d, *J* = 7 Hz, 3 H), 4.32 (s, 2 H), 5.10 (s, 2 H), 5.21 (q, *J* = 7 Hz, 1 H), 7.30−7.52 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −5.6; 16.8; 18.3; 25.6; 61.4; 66.9; 68.5; 128.0; 128.3; 128.5; 135.2; 170.2; 171.1 ppm. MS (ES): calculated [M + Na]: 375.2, measured [M + Na]: 375.2.

Benzyl 2-(2-Hydroxyacetoxy)propionate (6): A solution of compound **5** (7.15 g, 20.3 mmol) in EtOAc (100 mL) was added to a solution of TBAF (6.4 g, 24.4 mmol) and HOAc (101.5 mmol, 5.8 mL) in EtOAc (100 mL). The reaction mixture was stirred for 3 h at room temp. Water (200 mL) was added, followed by extractive workup with three 150 mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (EtOAc/hexane, 2:3) yielded compound **6** (3.65 g) as a colorless oil. R_f = 0.18. Yield: 75%. 20% of starting material could be recovered. ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, *J* = 7 Hz, 3 H), 4.2 (d, *J* = 17 Hz, 1 H), 4.25 (d, *J* = 17 Hz, 1 H), 5.17 (s, 2 H), 5.22 (q, *J* = 7 Hz, 1 H), 7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.7; 60.3; 67.1; 69.1; 128.0; 128.3; 128.5; 134.9; 170.1; 172.5 ppm. MS (ES): calculated [M + H]: 239.1, measured [M + H]: 239.0.

2-(2-Hydroxyacetoxy)propionic Acid (7): Benzyl ester **6** (3.64 g, 15.3 mmol) was dissolved in EtOH (250 mL). Pd/C (365 mg, 10% w/w) was added, and the reaction flask was placed under a hydrogen atmosphere (balloon). The reaction mixture was stirred vigorously and left to react overnight at room temp. The catalyst was removed by filtration through a Hyflo filter. The filter was washed extensively with EtOH and the filtrate was concentrated under reduced pressure. This yielded carboxylic acid **7** (2.46 g, 100%) as a colorless oil. No further purification was needed. ^{1}H NMR ($CDCl_3$): δ = 1.56 (d, *J* = 7 Hz, 3 H), 4.24 (d, *J* = 17 Hz, 1 H), 4.27 (d, *J* = 17 Hz, 1 H), 5.21 (q, *J* = 7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.7; 60.4; 69.1; 172.8; 173.2 ppm. MS (ES): calculated [M + Na]: 171.0, measured [M + Na]: 170.7.

3-Methyl-1,4-dioxane-2,5-dione (8): Carboxylic acid **7** (2.40 g, 16.2 mmol) was dissolved in acetone (150 mL). Cyanuric chloride (2.90 g, 16.2 mmol) was added, and the mixture was stirred at room temp. until a clear solution was obtained. After addition of Et_3N (4.4 mL, 32 mmol) a pale yellow precipitate appeared. The mixture was stirred overnight at room temp. The precipitate was removed by filtration through a Hyflo filter. The yellow filtrate was diluted with 100 mL of water, and extracted with three 100 mL portions of chloroform. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography (EtOAc/hexane, 1:3) yielded compound **8** (1.53 g) as a yellow oil. R_f = 0.14, yield: 72%. ^{1}H NMR ($CDCl_3$): δ = 1.67 (d, *J* = 7 Hz, 3 H), 4.93 (d, *J* = 17 Hz, 1 H), 4.99 (d, *J* = 17 Hz, 1 H), 5.04 (q, *J* = 7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.3; 65.6; 72.0 ppm. MS (ES): calculated [M + I]: 256.931, measured [M + I]: 256.933.

3-Benzyloxy-2-hydroxypropionic Acid (9): $NaNO_2$ (10.6 g, 153.6 mmol) was added slowly to an ice-cooled solution of *O*-benzyl-L-serine (20.0 g, 102.4 mmol) in sulfuric acid (0.6 M, 500 mL). Instantly a brown gas evolved. The reaction mixture was heated at reflux overnight, vigorous nitrogen gas evolution being observed when the reaction had reached reflux temperature. After cooling to room temperature the aqueous layer was extracted with four 150 mL portions of chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. α-Hydroxy acid **9** was obtained as a yellow oil in a 70% yield (14.0 g). No further purification was necessary. ^{1}H NMR ($CDCl_3$): δ = 3.74 (dd, *J* = 4, *J* = 15 Hz, 1 H), 3.79 (dd, *J* = 4, *J* = 15 Hz, 1 H), 4.36 (t, *J* = 4 Hz, 1 H), 4.57 (s, 2 H), 7.26−7.35 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 70.3; 70.8; 73.5; 127.7; 127.9; 128.9; 137.1; 176.2 ppm. MS (ES): calculated [M + Na]: 219.1, measured [M + Na]: 219.0.

***tert*-Butyldimethylsilanyl 3-Benzyloxy-2-(*tert*-butyldimethylsilanyloxy)propionate (10):** α-Hydroxy acid **9** (6.20 g, 31.6 mmol) was dissolved in DMF (70 mL). Imidazole (6.45 g, 94.8 mmol) was added, followed by addition of TBSCl (10.3 g, 66.4 mmol). The mixture was left to react overnight at room temp. Water (100 mL) was added, followed by extractive workup with four 80 mL portions of Et_2O. The combined organic layers were washed with an additional 100 mL of water and dried with $MgSO_4$. Filtration and concentration yielded **10** (13.0 g, 97%) as a yellow oil. No further purification was necessary. ^{1}H NMR ($CDCl_3$): δ = 0.02 (m, 6 H), 0.21 (m, 6 H), 0.85 (m, 18 H), 3.65 (m, 2 H), 4.29 (t, *J* = 4 Hz, 1 H), 4.51 (d, *J* = 17 Hz, 1 H), 4.55 (d, *J* = 17 Hz, 1 H), 7.24 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −5.4; −4.9; −4.8; −3.7; 17.5; 18.3; 25.6; 25.7; 72.6; 73.3; 73.4; 127.4; 127.5; 128.3; 138.0; 171.7 ppm. MS (ES): calculated [M + Na]: 447.2, measured [M + Na]: 447.3.

1-(Benzyloxycarbonyl)ethyl 3-Benzyloxy-2-(*tert*-butyldimethylsilanyloxy)propionate (11): Oxalyl chloride (0.57 mL, 6.5 mmol) was carefully added to an ice-cooled solution of compound **10** (2.5 g, 5.9 mmol) in dichloromethane (8 mL) containing DMF (10 drops), by the same procedure as used for compound **5**. After the vigorous evolution of gas had ceased, the mixture was allowed to warm to room temp. and left to react overnight. Dichloromethane and TBSCl were removed in vacuo. A solution of Et_2O (8 mL), pyridine (2 mL), and (*S*)-benzyl lactate (3.2 g, 17.6 mmol) was added to the residue, and this mixture was stirred at room temp. for an additional 1.5 h. The resulting white precipitate was removed by filtration through a Hyflo/silica filter. The filter was washed extensively with Et_2O and the filtrate was concentrated in vacuo. Flash column chromatography with MTBE/hexane (1:5) yielded benzyl ester **11** as a colorless oil. R_f = 0.48. Yield: 1.2 g (43%) over two steps. ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.49 (d, *J* = 7 Hz, 3 H), 3.62 (dd, *J* = 7, *J* = 10 Hz, 1 H), 3.76 (dd, *J* = 7, *J* = 10 Hz, 1 H), 4.45 (dd, *J* = 3, *J* = 7 Hz, 1 H), 4.53 (s, 2 H), 5.12 (s, 2 H), 5.19 (q, *J* = 7 Hz, 1 H), 7.25−7.36 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −5.2; 16.9; 25.6; 67.0; 69.1; 72.4; 72.5; 73.4; 127.5; 128.3; 128.4; 128.6; 170.2 ppm. MS (ES): calculated [M + Na]: 495.2, measured [M + Na]: 495.1.

1-Benzyloxycarbonylethyl 3-Benzyloxy-2-hydroxypropionate (12): A solution of benzyl ester **11** (500 mg, 1.06 mmol) in EtOAc (10 mL) was added to a solution of TBAF (290 mg, 1.11 mmol) and acetic acid (0.3 mL, 5.6 mmol) in EtOAc (10 mL) and the mixture was heated at reflux. After 1.5 h the reaction mixture was allowed to cool to room temp., followed by addition of 10 mL of saturated $NaHCO_3$ and 15 mL of water. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

Flash column chromatography with MTBE/hexane (1:1) yielded benzyl ester **12** (325 mg, 86%) as a pale yellow oil. R_f = 0.28. 10% of starting material could be recovered. ^{1}H NMR ($CDCl_3$): δ = 1.5 (d, J = 7 Hz, 3 H), 3.72 (dd, J = 5, J = 10 Hz, 1 H), 3.79 (dd, J = 5, J = 10 Hz, 1 H), 4.40 (m, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.55 (d, J = 12 Hz, 1 H), 5.14 (s, 2 H), 5.25 (q, J = 7 Hz, 1 H), 7.25−7.36 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.9; 67.1; 69.4; 70.6; 71.3; 73.4; 127.6; 127.7; 128.1; 128.3; 128.4; 128.6; 135.0; 137.6; 169.9; 171.8 ppm. MS (ES): calculated [M + Na]: 381.1, measured [M + Na]: 381.2.

2-(3-Benzyloxy-2-hydroxypropoxy)propionic Acid (13): Pd/C (10%, 1.5 g, 1:1 w/w) was added to a solution of benzyl ester **12** (1.5 g, 4.2 mmol) in EtOH (50 mL). Five equivalents of 1,4-cyclohexadiene (1.7 g, 2 mL) were added and the mixture was stirred vigorously at room temp. under a nitrogen atmosphere. After 4 h the catalyst was removed by filtration through a Hyflo filter. The filter was washed extensively with EtOH, and the filtrate was concentrated under reduced pressure to yield compound **13** (985 mg, 90%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, J = 7 Hz, 3 H), 3.80−3.85 (m, 2 H), 4.42 (t, J = 3.5 Hz, 1 H), 4.59 (s, 2 H), 5.30 (q, J = 7 Hz, 1 H), 7.25−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.7; 17.7; 58.1; 69.4; 70.5; 71.3; 73.4; 127.7; 128.3; 137.4; 171.8 ppm. MS (ES): calculated [M + Na]: 291.1, measured [M + Na]: 291.0.

3-Benzyloxymethyl-6-methyl-1,4-dioxane-2,5-dione (14): Cyanuric chloride (700 mg; 3.8 mmol) was added to a solution of compound **13** (984 mg, 3.7 mmol) in dry acetone (40 mL). After a clear solution was obtained, Et_3N (1.6 mL, 7.6 mmol) was added. A white precipitate instantly appeared. The mixture was heated at 40 °C for 1 hour, and was subsequently stirred at room temp. overnight. The precipitate was removed by filtration through a Hyflo filter, the filter was washed extensively with acetone, and the filtrate was diluted with water (50 mL). The aqueous layer was extracted with three 40 mL portions of chloroform. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography with EtOAc/hexane (1:2) yielded compound **14** (550 mg, 60%) as a white solid. (R_f = 0.35) Recrystallization from toluene gave **14** as white, needle-like crystals. M.p. 88 °C. ^{1}H NMR ($CDCl_3$): δ = 1.56 (d, J = 7 Hz, 3 H), 3.90 (d, J = 3 Hz, 2 H), 4.59 (s, 2 H), 5.11 (m, 2 H), 7.25−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.5; 68.5; 73.1; 73.9; 127.6; 127.9; 128.3 ppm. MS (ES): calculated [M + I]: 376.9886, measured [M + I]: 376.9904.

1-(Benzyloxycarbonyl)ethyl 2-*tert*-Butyldimethylsilanyloxypropionate (15): Oxalyl chloride (0.45 mL, 5.2 mmol) was added carefully to an ice-cooled solution of compound **10** (2.0 g, 4.7 mmol) in dichloromethane (8 mL) containing 10 drops of DMF by the same procedure as used for compound **5**. After the vigorous evolution of gas had ceased, the mixture was allowed to warm to room temp. and left to react for 2.5 h. Dichloromethane and TBSCl were removed in vacuo. A solution of Et_2O (8 mL), pyridine (2 mL), and benzyl glycolate (2.35 g, 14.2 mmol) was added to the residue, and this mixture was stirred overnight at room temp. The resulting precipitate was removed by filtration through a Hyflo/silica filter. The filter was washed extensively with Et_2O and the filtrate was concentrated in vacuo. Flash column chromatography with MTBE/hexane (1:5) yielded benzyl ester **15** as a colorless oil. R_f = 0.45. Yield: 1.7 g (78%) over two steps. ^{1}H NMR ($CDCl_3$): δ = 0.08 (m, 6 H), 0.9 (m, 9 H), 3.7 (m, 2 H), 4.5 (m, 1 H), 4.6 (d, J = 3 Hz, 2 H), 4.6 (d, J = 12 Hz, 1 H), 4.7 (d, J = 12 Hz, 1 H), 5.2 (s, 2 H), 7.3 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −5.1; 25.7; 60.9; 67.1; 72.3; 72.4; 73.5; 127.6; 127.6; 128.3; 128.4; 128.5; 128.6; 138.0; 171.1 ppm. MS (ES): calculated [M + Na]: 481.2, measured [M + Na]: 481.1.

Benzyloxycarbonylmethyl 3-Benzyloxy-2-hydroxypropionate (16): A solution of benzyl ester **15** (1.6 g, 3.5 mmol) in EtOAc (15 mL) was added to a solution of TBAF (985 mg, 3.7 mmol) in EtOAc (15 mL) containing acetic acid (1.1 mL, 18.5 mmol). The mixture was heated at reflux. After 2.5 h the mixture was cooled to room temp. followed by addition of 10 mL of saturated $NaHCO_3$ and 40 mL of water. The aqueous layer was extracted with EtOAc (3 × 50 mL); the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography with MTBE/hexane (1:1) yielded benzyl ester **16** (746 mg, 62%) as a pale yellow oil. R_f = 0.15. 35% of starting material could be recovered. ^{1}H NMR ($CDCl_3$): δ = 3.78 (d, J = 3.5 Hz, 2 H), 4.16 (s, 1 H), 4.55−4.78 (m, 4 H), 5.17 (s, 2 H), 7.25−7.36 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 61.2; 67.2; 70.7; 71.0; 73.4; 127.6; 127.7; 128.3; 128.4; 128.5; 128.6; 137.5; 167.0; 171.9 ppm. MS (ES): calculated [M + Na]: 367.1, measured [M + Na]: 367.1.

2-(3-Benzyloxy-2-hydroxypropoxy)acetic Acid (17): Pd/C (10%, 740 mg) was added to a solution of benzyl ester **16** (740 mg, 1.61 mmol) in EtOH (15 mL). 1,4-Cyclohexadiene (0.76 mL, 8.06 mmol) was added and the mixture was stirred vigorously at room temp. After 1.5 h the catalyst was removed by filtration through a Hyflo filter. The filter was washed extensively with EtOH, and the filtrate was concentrated in vacuo to yield carboxylic acid **17** (380 mg, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.8 (s, 2 H), 4.4 (t, J = 3.5 Hz, 1 H), 4.6 (d, J = 3 Hz, 2 H), 4.7 (s, 2 H), 7.3 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 60.9; 70.5; 70.9; 73.4; 128.7; 127.7; 127.8; 128.3; 137.2; 170.7; 171.8 ppm. MS (ES): calculated [M + H]: 255.1, measured [M + H]: 255.0.

3-Benzyloxymethyl[1,4]dioxane-2,5-dione (18): Cyanuric chloride (572 mg, 3.1 mmol) was added to a solution of compound **17** (765 mg, 3.0 mmol) in dry acetone (35 mL). When a clear solution was obtained, Et_3N (0.85 mL, 6.2 mmol) was added. A yellow precipitate instantly appeared. The mixture was heated at 40 °C for 1 hour, and was subsequently stirred at room temp. overnight. The precipitate was removed by filtration through a Hyflo filter, the filter was washed extensively with acetone, and the filtrate was diluted with water (50 mL). The aqueous layer was extracted with three 40 mL portions of chloroform. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography with EtOAc/hexane (1:2) as an eluent yielded compound **18** (90 mg, 13%) as an off-white solid. (R_f = 0.25). Recrystallization from toluene gave **18** as white, needle-like crystals. M.p. 51 °C. ^{1}H NMR ($CDCl_3$): δ = 3.9 (dd, J = 2.5, J = 8 Hz, 1 H), 4.1 (dd, J = 2.5, J = 8 Hz, 1 H), 4.5 (s, 2 H), 4.8 (d, J = 17 Hz, 1 H), 5.0 (d, J = 17 Hz, 1 H), 5.1 (t, J = 2.5 Hz, 1 H), 7.3 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.3; 70.6; 73.7; 76.3; 127.6; 128.2; 128.5; 136.2; 163.6; 164.5 ppm. MS (ES): calculated [M + I]: 362.9730, measured [M + I]: 362.9723.

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[26] Measured for starting material supplied by Purac Biochem. (The Netherlands): $[\alpha]_D^{20} = -268$ ($c = 1$, chloroform).

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