

Preparation of Free and of Specifically Protected Oligo[β -Malic Acids] for Enzymatic Degradation Studies

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The polyanionic poly[β -(S)-malic acids] (β -PMA) occur in slime molds (myxomycetes), black yeasts and other fungi and are involved in DNA replication. In order to be able to study the cleavage mechanism of β -PMA hydrolases, we have synthesized cyclic and linear oligomers of malic acid (β -OMA) consisting of up to eight residues. To this end, fragments with three different protecting groups were prepared, with allyl ester groups on the C-terminus, TBDPS groups at the O-terminus, and benzyl ester groups at the side chains (Schemes 2, 3, 7). Selective deprotection and fragment coupling ($\text{COCl}_2/\text{C}_5\text{H}_5\text{N}/\text{CH}_2\text{Cl}_2/-75^\circ\text{C}$) gave dimers, tetramers, and

octamers, either fully protected or specifically protected at the O- or C-terminus or at the side chain acid groups, and also fully deprotected oligoacids (Schemes 3–7). The new compounds were fully characterized (R_f , IR, ^1H - and ^{13}C -NMR spectroscopy, mass spectrometry and elemental analysis or high-resolution electrospray mass spectrometry). Enzymatic degradation experiments with the previously prepared cyclo-tetramer, the unprotected, and the O- or C-terminally protected samples of linear β -OMAs show that the enzyme from *Physarum polycephalum* is an *exo*-hydrolase cleaving the chain from the O-terminus.

Introduction

Polyhydroxyalkanoates (PHA) represent a class of biopolymers whose importance for living organisms was only recognized in the last decades.^[1,2] The most prominent member is poly[(*R*)-3-hydroxybutyric acid] (PHB), an apolar, water-insoluble material of high molecular weight, which was discovered in bacteria, where it accumulates as a carbon and energy storage substance (sPHB) in the form of inclusion bodies.^[3] Initially, PHB and related PHAs have attracted much interest, both, as chiral synthetic starting materials^[4] and as biocompatible and biodegradable materials.^[1,5] However, in the last fifteen years PHB was also detected in many eukaryotic organisms, and its low-molecular-weight form cPHB (complexing PHB) was found to be involved in calcium ion transport across membranes.^[6,7] Furthermore, low-molecular-weight PHB has proven to be a valuable material for investigating the role of any kind of PHB in nature. Well-defined synthetic oligomers of 3-hydroxybutanoic (OHBs) and higher alkanolic acids (OHAs) have been most useful in the study of ion transport and enzyme stereoselectivity, as they permit the unambiguous identification of the (in some cases critical) size of an oligomer/polymer fragment.^[2,7,8]

In contrast to PHB, the structurally related poly[β -(S)-malic acid] (β -PMA) is an acidic, highly water-soluble polyester which was artificially prepared before it was discovered in nature.^[9] The potential application of this material as drug carrier or part of a prodrug was extensively studied due to the non-toxicity of malic acid, a constituent of the citric acid cycle.^[10] In this context it has been shown that

β -PMA hydrolyzes spontaneously at room temperature in a buffered aqueous solution of pH 7.5.^[11] However, when the side chain carboxyl groups are esterified, the material appears to be stable under these conditions.^[12]

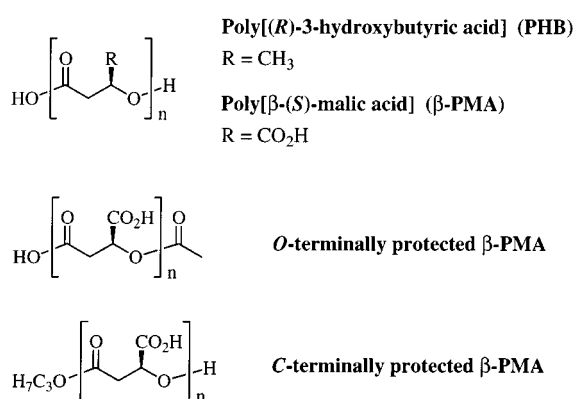
A natural polymer consisting of malic acid was first isolated from *Penicillium cyclopium*, thirty years ago.^[13] Although this substance is an inhibitor of acid proteases such as pepsin, it was not characterized with respect to its constitution. In 1989 Holler and co-workers reported that poly[(S)-malic acid], isolated from plasmodia of the slime mold *Physarum polycephalum*, acts as an endogenous inhibitor of DNA polymerase α .^[14] Its constitution corresponds to β -PMA.^[15] The biopolyester of molecular mass 4–50 kDa was found in the cytoplasm and in nuclei, and is secreted into the culture medium.^[16] However, highest concentrations were measured in the nuclei, (100 mg/mL) as the polyanion strongly interacts with the cationic nuclear proteins. It was proposed that β -PMA has the function of a storage and carrier molecule (e.g. for DNA polymerases) and is therefore assumed to be involved in DNA replication.^[17] The organisms most efficient in producing β -PMA are the black yeasts *Aureobasidium* sp.^[18] and *A. pullulans*,^[19] from which up to 61 g/l and 9.8 g/l culture medium were isolated, respectively. The polymer from these species was reported to be branched, and its molecular mass is 5–9 kDa. Recently, more β -PMA producing fungi and myxomycetes were discovered, among them *Cladosporium cladosporioides* and *Corollospora fusca*.^[20] Until now, all known β -PMA producing organisms are eukaryotes.

Unlike the PHAs, the enzymatic degradation of which has been studied thoroughly,^[5] not much is known about depolymerases that degrade β -PMA. Two enzymes have been isolated and characterized up to now. The first hydrolase, a 68 kDa glycoprotein, was found in the cytoplasm and culture medium of *P. polycephalum*.^[21] It hydrolyzes β -PMA specifically by cleaving single (S)-malic acid units in

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an exolytic manner (pH optimum 3.5). Studies on a synthetic polymer derivative suggested that hydrolysis starts at the *O*-terminus.^[22] Only recently, Steinbüchel and co-workers reported on a specific bacterial β -PMA hydrolase (43 kDa, pH optimum 8.1) isolated from the outer membrane of *Comamonas acidovorans*.^[23] It was shown that both enzymes are neither metallo nor serine esterases, and that they are distinct from PHB depolymerases.

All the dissimilarities between β -PMA and the PHAs make this highly functionalized biopolymer appealing for further investigations. We have described the preparation of cyclic oligomers of (*S*)-malic acid as model compounds for β -PMA.^[24] For structural and enzymatic studies, we have now developed a synthetic route providing access to pure, specifically modifiable and protected, linear oligomers of the type shown in Scheme 1.



Scheme 1. Linear oligomers of 3-hydroxyalkanoic acids and of malic acid

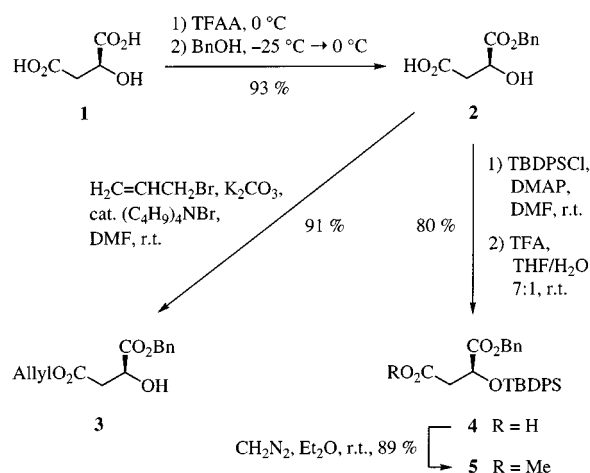
Results and Discussion

Synthesis of Fully Deprotected Oligomers of Malic Acid

Bearing in mind β -PMA's sensitivity to water as well as its hygroscopic nature, a synthetic strategy was devised, which involves the liberation of the side chain carboxyl groups under non-aqueous conditions as the final step. Furthermore, the strategy involves orthogonal protection of both terminal functionalities, enabling both efficient chain elongation by segment coupling, and specific modification of the termini. The protecting group chosen for the side chain is the cleanly cleavable benzyl (Bn) ester. The allyl ester^[25] was selected as second carboxylic acid protecting group and the *tert*-butyldiphenylsilyl (TBDPS) group^[26] was chosen to mask the *O*-terminus in a manner that permits acid chloride coupling as method for the backbone ester formation.

Following known procedures,^[27] malic acid **1** was converted into the trifluoroacetate of its cyclic anhydride which was subsequently treated with benzyl alcohol to give the monobenzyl ester **2** as the main regio isomer in high yield (Scheme 2). In contrast to the published procedures, the ring-opening was not carried out at room temperature, but between $-25\text{ }^{\circ}\text{C}$ and $0\text{ }^{\circ}\text{C}$ in CH_2Cl_2 , conditions under which the intermediate anhydride forms a suspension. The

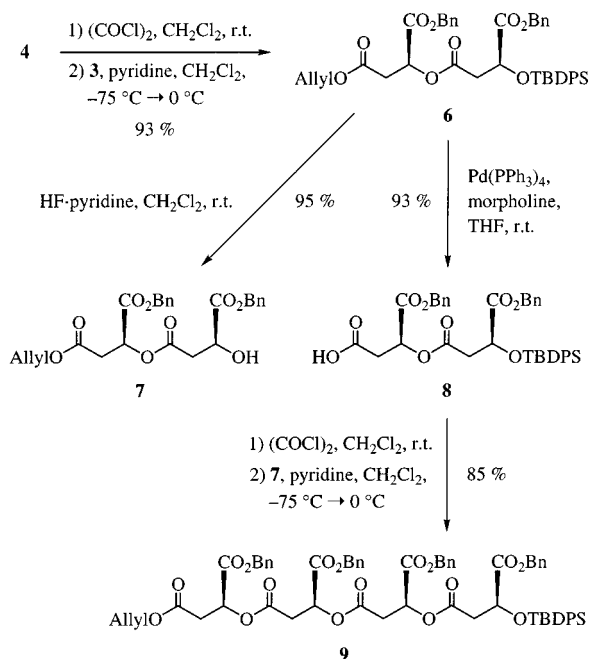
formation of previously unreported isomeric monobenzyl ester could thus be reduced from 5% to 3%, but not completely suppressed. This isomer shows a singlet at $\delta = 5.16$ in the ^1H -NMR spectrum as the only distinct signal. In view of the synthesis of long oligomer chains, the isomeric purity of the starting material is of great importance. However, the removal of the remaining impurity by recrystallization of the low-melting solid **2** (all previous reports^[27] describe the compound as an oil) failed, and final purification was therefore performed in the following steps.



Scheme 2. Preparation of the monomers **3** and **4** by specific protection of malic acid (**1**)

Hydroxy acid **2** was further protected by alkylation of its carboxylate group with allyl bromide in the presence of 10 mol-% of tetrabutylammonium bromide, giving alcohol **3** in 91% yield after a reaction time of only 4 h. Using standard DCC/DMAP esterification^[28] with five equivalents of allyl alcohol, a yield of only 40% of **3** was obtained, accompanied by a considerable amount of dimeric material. On the other hand, a short route, other than silylation of **3** followed by allyl ester cleavage, was desirable for the preparation of acid **4**. Hence, **2** was allowed to react with 1.3 equivalents of *tert*-butylchlorodiphenylsilane, giving a 3:2 mixture of the desired acid **4** and its TBDPS ester derivative (doubly silylated product). As the TBDPS ester does not decompose during aqueous workup,^[29] the crude mixture was treated with aqueous TFA for 2 h, affording acid **4** in 80% yield after column chromatography. A small amount of this product was converted into methyl ester **5**. Comparison by HPLC with a sample of *rac*-**5** (the enantiomers of which were separated on a Chiralcel OD column; for details see the Experimental Section) confirmed acid **4** to be enantiomerically pure.

For the preparation of the oligomers, acid chloride coupling was used under the conditions that were successful in the synthesis of OHBs containing up to 128 units.^[30] Treatment of acid **4** with oxalyl chloride gave the corresponding oily acid chloride, which (like all acid chlorides mentioned in this work) had to be dried thoroughly under high vacuum prior to its use, in order to completely remove excess

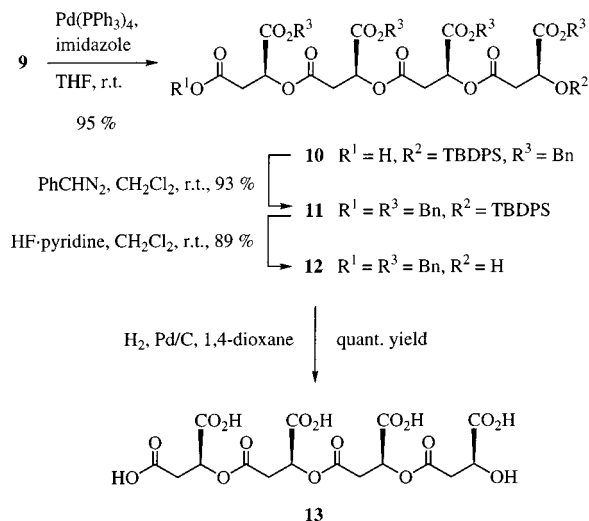


Scheme 3. Formation and selective deprotection of 6, followed by segment coupling of the dimer moieties 7 and 8

reagent (Scheme 3). Coupling with alcohol 3 at reduced temperature occurred upon addition of pyridine, yielding dimer 6, the first oligomer in the synthesis that bears all three different protecting groups.^[31]

Selective cleavage of the silyl ether 6 by HF-pyridine complex^[32] (which was chosen to prevent ester cleavage that would have occurred with the basic TBAF) gave alcohol 7 in high yield. Using the conditions of Kunz and co-workers,^[33] the C-terminal carboxylic acid group was liberated by Pd⁰-catalyzed allyl transfer to morpholine, furnishing acid 8 in reproducibly excellent yields. At least 3 mol-% of the purchased catalyst was necessary for the reaction to take place within a reasonable period of time. Having both moieties in hand, acid 8 was activated as before and coupled with the alcohol segment 7 under carefully defined conditions to obtain the fully protected tetramer 9. In the case of the OHBs, it had been shown that carboxylic acids carrying an acyloxy substituent in the 3-position are prone to β -elimination after activation.^[30] This destructive reaction, which not only gives rise to elimination products but also to oligomers containing one unit less, could be suppressed by keeping the temperature below -45°C .^[34]

On the way to a completely deprotected oligomer, tetramer 9 was first O- then C-terminally deprotected by means of the methods used before. However, we did not succeed in separating $\text{Ph}_3\text{P}=\text{O}$, formed from the Pd catalyst during workup, neither by silica gel nor by reversed-phase (RP) column chromatography. Debenzylation of the crude material would have made an RP-HPLC purification step inevitable, furnishing the product in a hydrous and thus unstable form (cf. introduction). In order to avoid this amphiphilic, resinous intermediate, it was intended to transform the allyl ester into a benzyl ester prior to silyl ether cleavage and debenzilation.



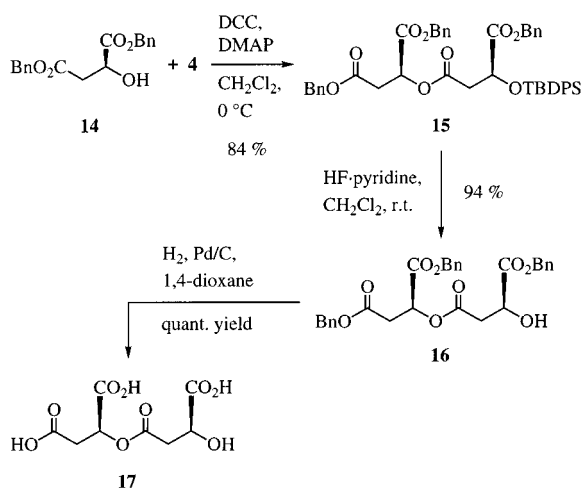
Scheme 4. Preparation of tetramer 13, involving transformation of the terminal allyl ester in 9 to a benzyl ester

Tetramer 9 was therefore subjected to the conditions used most successfully to cleave the allyl ester in dimer 6. However, the desired acid 10 (Scheme 4) was isolated in yields of only 12% to 16% due to fast decomposition under the basic reaction conditions, probably a result of intramolecular attack of backbone esters by the carboxylate anion. A study on a comparable model substrate, using neutral and weakly basic nucleophiles, revealed *N*-methylaniline and imidazole to be mild alternatives to morpholine. Indeed, when using 10 equivalents^[35] of imidazole in the presence of 8 mol-% of Pd catalyst, deprotection occurred cleanly in less than one hour, giving acid 10 in an excellent yield. The liberated carboxylic acid was then treated with a solution of phenyldiazomethane,^[36,37] yielding tetramer 11, which was O-terminally deprotected to afford alcohol 12. Hydrogenolysis of all five benzyl ester groups occurred smoothly, and gave tetramer 13 in an overall yield of 46% (initially 2.2%). A residual amount of 1.5 equivalents of 1,4-dioxane was detected after thorough drying under vacuum for several days^[38] (this is probably due to the product's highly polar nature).

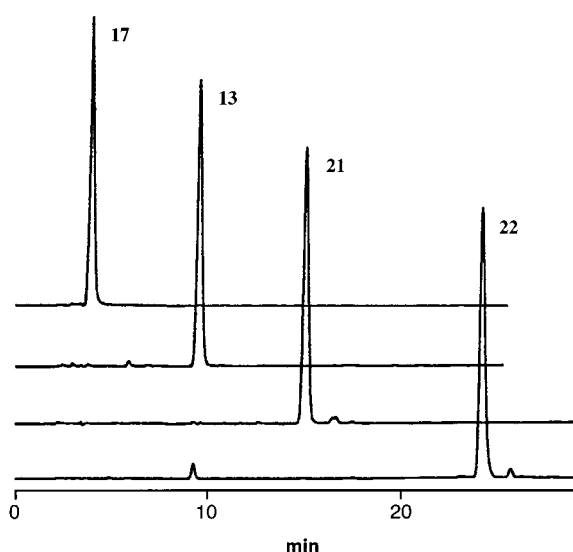
More straightforward was the preparation of the corresponding dimer 17 (Scheme 5). Dibenzyl malate 14^[39] was acylated with 4 by the DCC/DMAP method,^[28] giving dimer 15, which was deprotected as above to yield pure 17. The chromatograms of the hydroxypenta- and -triacids 13 and 17 are shown in Figure 1.

Preparation of Specifically Protected Oligomers

The substrates that had been used before to study the specificity of the β -PMA hydrolase were low-molecular-weight polymers carrying at one or the other terminus a fluorescent label or a positively charged triethylammonium group.^[22] In the course of this work, we intended to access enzyme substrates that are chemically and sterically as closely related to β -PMA as possible. Thus, the requirements were: (1) large enough molecular weight to be a "real" substrate, (2) monodisperse, (3) easy to identify and

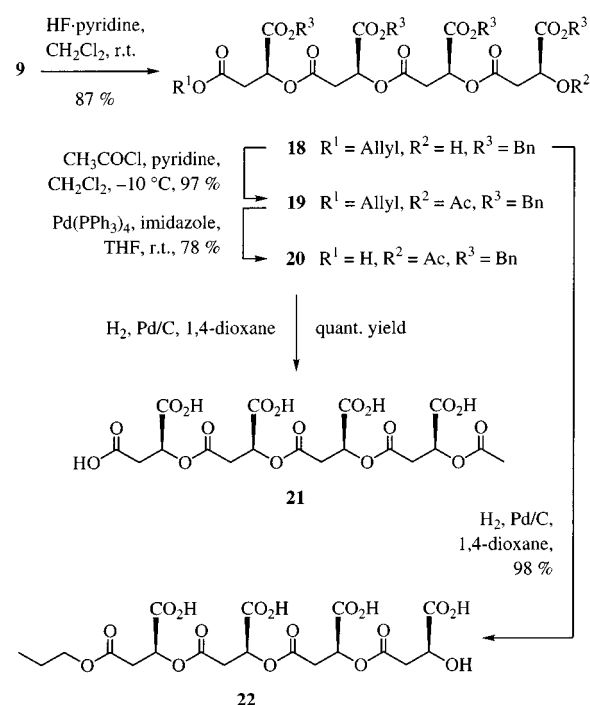


Scheme 5. Preparation of dimer 17

Figure 1. RP-HPLC traces of free (13 and 17) and terminally protected (21 and 22) acids (C₁₈ column; absorbance at 220 nm; linear gradient: cf. Experimental Section)

quantify, and (4) same polarity and solubility as β -PMA. Therefore, tetramers that are modified as shown in Scheme 1 were prepared.

The common precursor of the two products **21** and **22** with a free CO₂H and a free OH group, respectively, is alcohol **18**, which was obtained by cleavage of the silyl ether group in **9** (Scheme 6). In order to prepare the *O*-terminally protected substrate, **18** was first acetylated to yield **19**. Again, Pd⁰-catalyzed allyl ester cleavage using imidazole as allyl acceptor proceeded cleanly and afforded acid **20** in a yield of 78%.^[40] Finally, the five benzyl ester groups were cleaved hydrogenolytically to give **21**, the first of the two terminally modified substrates. Tetramer **21** was subjected to a p*K*_a determination procedure, in order to learn about the dependence of dissociation on the degree of deprotonation. However, only one value (p*K*_a = 3.46) could be measured as the other p*K*_a values are too close and therefore could not be distinguished. The measured p*K*_a value is in agreement with that determined for β -PMA from *A. sp.*

Scheme 6. Synthesis of terminally protected tetramers **21** and **22**

(p*K*_a = 3.6),^[18] and the first constant of malic acid (p*K*_a = 3.4).

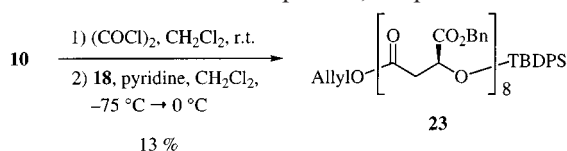
The *C*-terminally protected substrate **22** was directly prepared from **18** by simultaneous hydrogenation of the double bond and hydrogenolysis of the benzyl ester groups. Saturation of the allyl group was accompanied by 3.5% of hydrogenolytic ester cleavage, a known side reaction^[41] (the tetramer **13**, thereby formed, was detected and quantified by RP-HPLC, see below). Mass-spectrometric analysis of the protected tetramers **9–12** and **18–20** by the MALDI-TOF method was best suited to verify the monodispersity of the compounds. For the acids **13**, **21**, and **22**, electrospray mass spectrometry (ESI-MS; both ion modes) was appropriate.

In order to be able to determine kind and size of oligomers produced during enzymatic degradation of the substrates, as well as to check the uniform composition of the prepared compounds, RP-HPLC conditions were developed that permit the reproducible separation of the fully deprotected (**13** and **17**) and terminally protected (**21** and **22**) oligomers (Figure 1). For that purpose, a single linear gradient (phosphate buffer of pH = 2.4^[22]/MeCN) was used (cf. Experimental Section). The purities determined with this method were > 99% (dimer **17**), 99% (tetramer **13**), 97.5% (acetate **21**), and 93.5% (propyl ester **22**). In the case of ester **22**, we chose to keep the product in the relatively stable, water-free form and, therefore, no preparative purification was performed.

Preparation of an Octamer and Tests of Other Coupling Methods

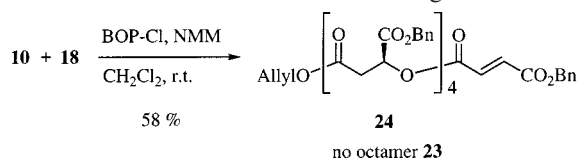
Undoubtedly, octamers or larger oligomers are interesting targets as their molecular weight approach that of the biopolyester more closely. Moreover, such compounds are

appealing for structural studies in solution and in the solid state. Thus, octamer **23** was prepared in the same manner as tetramer **9**, by coupling of acid **10** with alcohol **18** (Scheme 7). However, **10** did partially not survive the conditions of acid chloride formation, and as a result, by-products were formed that were separable only with great difficulty (see the low yield). Therefore, alternative coupling methods were tested on comparable, simpler substrates.

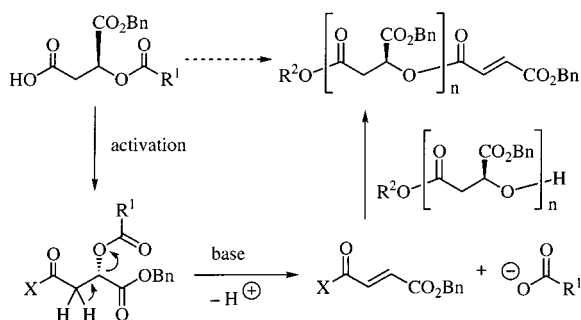


Scheme 7. Preparation of the octamer **23** by acid chloride coupling

Whereas DCC/DMAP esterification^[28] led to decomposition, no conversion of the starting material was observed with the 2,2'-dipyridyl disulfide method^[42] in the presence of CuBr_2 ,^[43] not even in boiling MeCN. More promising were attempts with the BOP-Cl reagent,^[44] after replacing Et_3N by NMM. However, when the tetramer segments **10** and **18** were allowed to react under these conditions, the fumaric acid ester **24** was isolated as the main product, and no octamer **23** was detected. The formation of **24** may be rationalized in the following way (see Scheme 8): As a result of carboxylic acid activation, the acidity of the protons in α -position is increased to an extent which causes elimination to be much faster than coupling; subsequently, the activated fumaric acid intermediate acylates the free hydroxy group of the oligoester to form a product such as **24**. Replacement of NMM by pyridine resulted in no conversion. These observations suggest that a procedure that permits the preparation of larger oligomers of this type in good yields has to work in the absence of stronger bases.



Proposed mechanism:

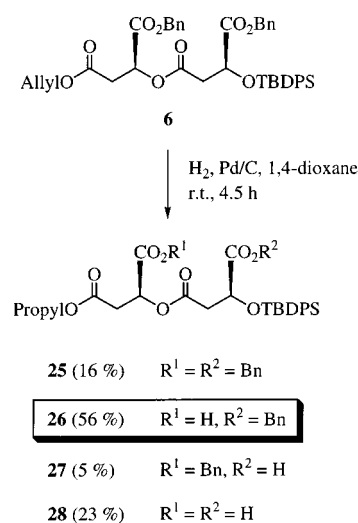


Scheme 8. β -Elimination prior to acylation in the case of carboxylic acid activation in the presence of a base

Selective Hydrogenolysis of Benzyl Esters near the C- and the TBDPS-Protected O-Terminus

During hydrogenolytic debenzoylation of the TBDPS-protected tetramer **9** (not described here), it was observed that

the benzyl ester next to the silyl protecting group is cleaved more slowly than the others. In order to explore the synthetic usefulness of this rate difference, dimer **6** was hydrogenated, with careful monitoring of the progress of the reaction (Scheme 9). After 4.5 h, the reaction was stopped and the components of the product mixture were separated by column chromatography. Acid **26** was isolated in analytically pure form in 56% yield. Obviously, the carboxylate group near the C-terminus and next to an acyloxy group is a better "leaving group" (more acidic) than the one near the O-terminus and next to the OTBDPS group. It is known that oxygen-bound benzyl groups are hydrogenolized faster the better negative charge is stabilized in the "leaving group".^[45] However, the bulky TBDPS group might also influence the reaction by rendering access to the catalyst surface more difficult.



Scheme 9. Preferred cleavage of one of the benzyl ester groups in **6**

Enzymatic Degradation Studies

The oligomers **13**, **17**, **21**, and **22**, and the cyclo-tetramer (see ref.^[24]) shown in Figure 2 were subjected to enzymatic degradation by the extracellular β -PMA hydrolase from *P. polyccephalum* by Holler and Gasslmaier.^[46] The C-terminally protected tetramer **22** was thus readily hydrolyzed to give fragments that were detected by RP-HPLC. In contrast, neither the acetate **21** nor the cyclic oligomer was degraded at all. This is compatible with the proposal^[22] that enzymatic hydrolysis starts at the O-terminus and that the enzyme is an *exo*-hydrolase.^[21] Another observation is, that not only tetramer **13** but also dimer **17** is degraded. Obviously, two monomer units are sufficient for substrate recognition. The quantitative investigation of the degradation rate, which allows for determination of K_M and V_{max} , is in progress. Complete and detailed results will be published elsewhere.^[46]

Conclusion

Starting from (*S*)-malic acid, differently protected monomers (**3** and **4**) were prepared in such a manner that con-

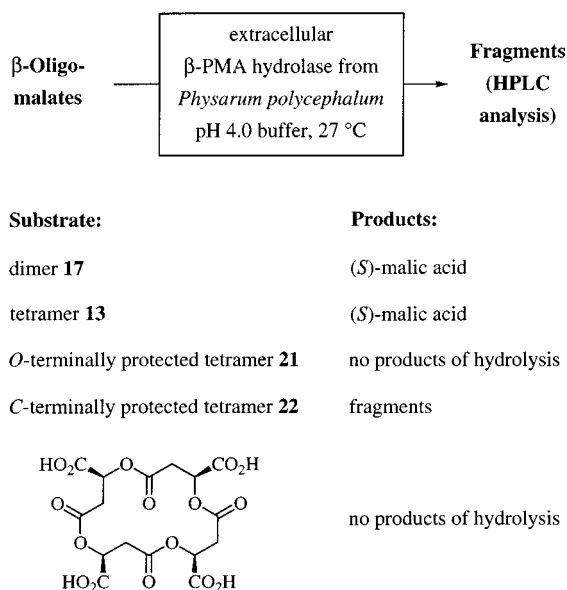


Figure 2. Enzymatic degradation of oligomers **13**, **17**, **21**, and **22**, and of a cyclic tetramer (an X-ray crystal structure of the tetra-benzyl ester^[24] of this tetramer was determined; the coordinates can be provided at request to the correspondence author)

struction of oligomers of up to eight units (**24**) was possible by segment coupling. Acid chloride coupling proved to be the most reliable method for backbone ester formation and can, so far, be replaced by a condensation reagent only in the case of the dimer. In order to avoid destruction of the larger oligomers during Pd⁰-catalyzed allyl ester cleavage, milder deprotection conditions had to be elaborated, and were found by replacing the widely used allyl acceptor morpholine by imidazole. It was shown that simultaneous hydrogenolytic cleavage of up to five benzyl ester groups permits the final deprotection of the water-sensitive products under non-aqueous conditions. By choosing orthogonal protecting groups for the termini, specific modification of the oligomers was possible. The compounds prepared in this way (**21** and **22**) proved to be useful for the determination of the substrate specificity of the extracellular β -PMA hydrolase of *P. polycephalum*, confirming that the enzyme hydrolyzes in an exolytic manner, starting from the *O*-terminus. Furthermore, it was shown that the oligomers can be cleanly separated by RP-HPLC, which may be advantageous for the study of β -PMA hydrolysis and detection.

Experimental Section

General: BnOH = benzyl alcohol, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, NMM = *N*-methylmorpholine, TBDPSCI = *tert*-butylchlorodiphenylsilane, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride. – All reactions, requiring water-free conditions, were carried out under Ar in oven-dried glassware (140 °C, for at least 12 h), which was allowed to cool in a desiccator. Solvents for reactions were of reagent-grade quality and stored over activated 4-Å molecular sieves. THF used for Pd-catalyzed reactions was freshly distilled (Na/benzophenone; under Ar). Samples for analytical purposes were thoroughly dried

under vacuum (0.1–0.01 mbar) at 45 °C (oligomers containing four monomeric units during t10 d) and/or under h.v. (high vacuum: 5×10^{-6} mbar; Balzers TPG 251; oligomers with free carboxyl groups). Solvent content of the oligoacids was determined by ¹H NMR. – Reagents: TFA and TFAA (Solvay), TBDPSCI (FMC and ABCR), Pd(PPh₃)₄ (Aldrich), imidazole (BASF). All other reagents were purchased from Fluka. CH₂N₂^[47] and PhCHN₂^[36] were prepared according to the literature. – Thin layer chromatography (TLC): Merck silica gel 60 F₂₅₄ (0.25 mm on glass). Detection by UV light or dipping into a solution of phosphomolybdic acid hydrate (2.5 g), cerium(IV) sulfate tetrahydrate (1 g) and conc. H₂SO₄ (6 mL) in water (94 mL), followed by heating. – Flash chromatography (FC): Fluka silica gel 60 (40–63 µm); at ca. 0.3 bar. – Normal-phase HPLC: Knauer HPLC system (pump 64), Daicel Chiralcel OD (250 × 4.6 mm) column, detection at 254 nm. Eluent: *t*BuOMe/hexane 1:6, flow rate of 2 mL/min. – RP-HPLC: Knauer HPLC system (pump WellChrom K-1000 Maxi-Star), Macherey–Nagel Nucleosil 100–5 C₁₈ (250 × 4 mm) column, detection at 220 nm. Linear gradient of *A* (10 mM sodium phosphate buffer, pH = 2.4) and *B* (MeCN) at a flow rate of 1 mL/min. 2 to 10% *B* in 12 min, 10 to 20% *B* in 13 min. *t*₀ = 2.3 min. – M.p.: Büchi 510; uncorrected values. – Optical rotations: Perkin–Elmer 241 polarimeter (10-cm, 1-mL cell). – IR: Perkin–Elmer 1600 (FT). – NMR: Varian Gemini 300 (¹H: 300 MHz, ¹³C: 75 MHz), Bruker AMX 400 (¹H: 400 MHz, ¹³C: 100 MHz), AMX 500 and DRX 500 (¹H: 500 MHz, ¹³C: 125 MHz); chemical shifts (δ) in ppm, relative to Me₄Si as internal standard. Carbon multiplicities were assigned by DEPT techniques. – MS: VG TRIBRID (EI; 70 eV), VG ZAB2-SEQ (FAB; 3-nitrobenzyl alcohol), Finnigan MAT TSQ 7000 (ESI; MeOH solutions), Bruker REFLEX (MALDI-TOF). – HRMS: VG ZAB2-SEQ (FAB), Finnigan New Star Dual Cell FT/MS (ESI; ICR, 7 T), Bruker APEX II FTMS (ESI; ICR, 4.7 T) – Elemental analyses and p*K*_a determination: Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

General Procedure for the Preparation of Acid Chlorides (GP 1):

The acid (1 equiv.) was dissolved in CH₂Cl₂ (0.25 M solution) in a flask, equipped with a bubble trap, and oxalyl chloride (1.5 equiv.) was added at room temp. After 30 min, DMF (0.5–1 drop/mmol acid) was added, and the mixture was stirred at room temp. over night. The volatile components were removed under reduced pressure (30 °C), and the resulting yellowish oil was dried under h.v. for 2–3 d. The acid chlorides were used for couplings without further purification. Compared with the corresponding carboxylic acid, the signals of the CH₂COCl protons exhibit a downfield shift of ca. 0.5 ppm in the ¹H-NMR spectrum.

General Procedure for the Coupling of Acid Chlorides with the Corresponding Alcohols (GP 2):

A solution of the thoroughly dried, crude acid chloride (1 equiv.) in CH₂Cl₂ was cooled to –78 °C, and a solution of the alcohol (1 equiv.) in CH₂Cl₂ was added. After 10 min, pyridine (1.5 equiv.), diluted with the same volume of CH₂Cl₂, was added dropwise to the stirred solution over the given time period. The mixture was allowed to reach room temp. within 14–20 h. After that, no more starting material could be detected by TLC, in general. The mixture was diluted with Et₂O (double the volume of CH₂Cl₂) and washed with 1 N HCl (2 ×), sat. NaHCO₃, and sat. NaCl solutions, dried (MgSO₄), and the solvent evaporated. The crude oligomer was purified by FC and dried under vacuum.

General Procedure for the Cleavage of *t*BuPh₂Si Ethers (GP 3):

A solution of the *t*BuPh₂Si ether (1 equiv.) in CH₂Cl₂ in a polyethylene bottle was cooled to 0 °C and a solution of 70% HF in pyridine (10–20 equiv. HF) was added. The mixture was vigorously stirred

for 15 min (emulsion) and afterwards was allowed to warm to room temp. Stirring was continued for 12–22 h, and the progress of the reaction was monitored by TLC. The reaction time was kept minimal. The mixture was poured into water and Et₂O or CH₂Cl₂ was added. The organic layer was separated, washed with water (3 $\times$), sat. NaHCO₃, and sat. NaCl solutions, dried (MgSO₄) and concentrated. The resulting oil was purified by FC and dried under vacuum.

General Procedure for Hydrogenations (GP 4): Glassware intended for use in hydrogenation reactions was carefully rinsed with 2 N HCl solution, deionized water, acetone, and CH₂Cl₂ and subsequently oven-dried. The benzyl ester was dissolved in the solvent and a catalytic amount of 10% Pd/C was added. The apparatus was evacuated and flushed with H₂ (3 $\times$), and the mixture was stirred under H₂ (balloon) for 12–22 h. The suspension was filtered through Celite and the filtrate concentrated under reduced pressure followed by thorough drying (up to three weeks) under vacuum and under h.v. However, the solvent never could be completely removed from the oligoacids.

(3S)-4-Benzoyloxy-3-hydroxy-4-oxobutanoic Acid (2): (S)-Malic acid (40.2 g, 0.30 mol; pre-dried under vacuum for 12 h) was cooled to 0 °C and TFAA (101 mL, 0.72 mol) was added in portions over 10 min. The suspension was stirred at 0 °C for 3 h. After 90 min, it had turned into a colorless solution which again became cloudy at the end. The volatile components were removed under reduced pressure at 0 °C. The resulting white solid was thoroughly dried under vacuum and CH₂Cl₂ (150 mL) was added. The stirred suspension was cooled to –25 °C and BnOH (77.7 mL, 0.75 mol; distilled over CaO) was added over 15 min. The mixture was allowed to warm slowly to 0 °C, and stirring was continued at this temperature. After 18 h, the colorless solution was concentrated by rotary evaporation. The resulting residue was dissolved in Et₂O (100 mL), stirred and sat. NaHCO₃ solution (300 mL) was added. The mixture was diluted with Et₂O (300 mL) and the aqueous phase separated. The ether phase was extracted with sat. NaHCO₃ solution (2 $\times$ 300 mL). The combined aqueous extracts were washed with Et₂O (5 $\times$ 300 mL), cooled to 0 °C, acidified to pH = 2 with 6N HCl solution and extracted with Et₂O (6 $\times$ 300 mL). After washing the combined organic layers with sat. NaCl solution and drying (MgSO₄), the solvent was evaporated and **2** (62.4 g, 93%) was obtained as a colorless oil which solidified upon standing at 5 °C. Isomeric purity according to ¹H NMR: 97%. – M.p. 39.5–41.0 °C. – [α]_D²⁰ = –15.9 (*c* = 1.0, CHCl₃). – IR (CHCl₃): 3526w, 1739s, 1498w, 1456w, 1409w, 1263m, 1105m, 1039w, 954w, 908w. – ¹H NMR (300 MHz, CDCl₃): δ = 2.84 and 2.91 [*AB* of *ABX*, *J*_{AB} = 16.8, *J*_{AX} = 6.5, *J*_{BX} = 4.1 Hz, 2 H, C(O)CH₂], 4.54 (*X* of *ABX*, 1 H, HOCH), 5.23 (s, 2 H, PhCH₂), 7.31–7.39 (m, 5 H, arom. H). The spectrum of the other isomer differs as follows: δ = 5.16 (s, 2 H, PhCH₂). – ¹³C NMR (75 MHz, CDCl₃): δ = 38.27 (t), 67.03 (d), 67.86 (t), 128.51 (d), 128.75 (d), 134.92 (s), 173.19 (s), 176.11 (s). – MS (FAB): *m/z* (%) = 449 (8) [2 M + H]⁺, 247 (8) [M + Na]⁺, 225 (40) [M + H]⁺, 107 (19), 91 (100).

4-Allyl 1-Benzyl (2S)-2-Hydroxybutanedioate (3): Ground K₂CO₃ (12.3 g, 89.2 mmol) and tetrabutyl ammonium bromide (2.40 g, 7.43 mmol) were suspended in DMF (150 mL), and acid **2** (16.7 g, 74.3 mmol) and allyl bromide (7.55 mL, 89.2 mmol) were added. The mixture was stirred at room temp. After 4 h, it was concentrated (at ca. 1 mbar; 35 °C) to a quarter of its initial volume and Et₂O (250 mL), 5% aq. citric acid solution (150 mL) and water (50 mL) were added. The aqueous phase was separated and extracted with Et₂O. The combined organic phases were washed with 5% NaHCO₃ and sat. NaCl solutions, dried (MgSO₄), and concen-

trated. Purification by FC (Et₂O/pentane 1:1) gave **3** (18.0 g, 92%) as a colorless, oily liquid. – *R*_f (Et₂O/pentane 1:1) = 0.28. – [α]_D²⁰ = –20.0 (*c* = 1.0, CHCl₃). – IR (CHCl₃): 3538w, 1738s, 1498w, 1456w, 1423w, 1378m, 1177s, 1104m, 1039w, 986m, 938w. – ¹H NMR (300 MHz, CDCl₃): δ = 2.83 and 2.88 [*AB* of *ABX*, *J*_{AB} = 16.5, *J*_{AX} = 6.2, *J*_{BX} = 4.4 Hz, 2 H, C(O)CH₂], 3.19 (d, *J* = 5.3 Hz, 1 H, OH), 4.53 (*X* of *ABX*, 1 H, HOCH), 4.55–4.58 (m, 2 H, CH₂CH=CH₂), 5.20–5.33 (m, 2 H, CH=CH₂), 5.22 (s, 2 H, PhCH₂), 5.79–5.92 (m, 1 H, CH=CH₂), 7.32–7.38 (m, 5 H, arom. H). – ¹³C NMR (75 MHz, CDCl₃): δ = 38.50 (t), 65.58 (t), 67.26 (d), 67.68 (t), 118.71 (t), 128.49 (s), 128.69 (s), 128.72 (d), 131.75 (d), 135.05 (s), 170.22 (s), 173.32 (s). – MS (EI): *m/z* (%) = 264 (4) M⁺, 140 (2), 129 (46), 107 (25), 91 (100), 87 (15). – C₁₄H₁₆O₅ (264.28): calcd. C 63.63, H 6.10; found C 63.61, H 6.30.

(3S)-4-Benzoyloxy-3-(tert-butyldiphenylsilyloxy)-4-oxobutanoic Acid (4): Acid **2** (897 mg, 4.0 mmol) and DMAP (1.22 g, 10 mmol) were dissolved in DMF (12 mL) and TBDPSCI (1.33 mL, 5.2 mmol) was added over 15 min. After stirring the mixture at room temp. for 28 h, it was concentrated (at ca. 1 mbar; 35 °C) to a quarter of its initial volume. The residue was dissolved in Et₂O (60 mL), washed with 10% aq. citric acid solution (2 $\times$ 10 mL), 5% NaHCO₃ solution (8 mL), water, and sat. NaCl solution. Evaporation of the solvent gave an oil which was dissolved in THF/H₂O 7:1 (16 mL). The solution was cooled to 0 °C, treated with TFA (0.77 mL, 10 mmol), and stirred at room temp. for 2 h before Et₂O (60 mL) and water (10 mL) were added. The aqueous phase was separated and discarded. The organic phase was washed as described above, dried (MgSO₄) and concentrated. Purification by FC (Et₂O/pentane 1:2) gave **4** (1.47 g, 80%) as a colorless oil which solidified upon standing at 5 °C. – M.p. 70.5–71.5 °C. – *R*_f (Et₂O/pentane 1:2) = 0.08. – [α]_D²⁰ = –49.8 (*c* = 1.0, CHCl₃). – IR (CHCl₃): 2933m, 2860m, 1730s, 1472w, 1427m, 1392w, 1362w, 1287m, 1175m, 1113s, 998w, 956w. – ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (s, 9 H, Me₃C), 2.77 and 2.79 [*AB* of *ABX*, *J*_{AB} = 16.2, *J*_{AX} = 5.2, *J*_{BX} = 6.3 Hz, 2 H, C(O)CH₂], 4.56 (*X* of *ABX*, 1 H, SiOCH), 4.92 and 5.00 [*AB*, *J*_{AB} = 12.1 Hz, 2 H, PhCH₂], 7.14–7.44 (m, 11 H, arom. H), 7.59–7.67 (m, 4 H, arom. H). – ¹³C NMR (75 MHz, CDCl₃): δ = 19.20 (s), 26.64 (q), 39.50 (t), 66.86 (t), 69.35 (d), 127.62 (d), 127.75 (d), 128.37 (d), 128.53 (d), 129.93 (d), 130.03 (d), 132.67 (s), 132.73 (s), 135.26 (s), 135.99 (d), 136.05 (d), 171.48 (s), 175.85 (s). – MS (FAB): *m/z* (%) = 485 (100) [M + Na]⁺, 475 (14), 455 (12), 405 (95), 385 (98), 199 (11), 197 (16), 135 (14), 91 (55). – C₂₇H₃₀O₅Si (462.62): calcd. C 70.10, H 6.54; found C 70.16, H 6.41.

1-Benzyl 4-Methyl (2S)-2-(tert-Butyldiphenylsilyloxy)butanedioate (5): Acid **4** (140 mg, 0.30 mmol) was dissolved in Et₂O (4 mL) and treated with an ethereal solution of diazomethane until the color of the solution remained yellow. After 12 h, the solvent was evaporated and the residue purified by FC (Et₂O/pentane 1:4) to give **5** (129 mg, 89%) as a colorless oil. – *R*_f (Et₂O/pentane 1:4) = 0.28. – HPLC: *t*_r = 14.2 min. – [α]_D²⁰ = –51.6 (*c* = 1.0, CHCl₃). – IR (CHCl₃): 2955w, 1738s, 1428w, 1364w, 1167m, 1113s. – ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (s, 9 H, Me₃C), 2.74 and 2.78 [*AB* of *ABX*, *J*_{AB} = 15.6, *J*_{AX} = 5.4, *J*_{BX} = 6.4 Hz, 2 H, C(O)CH₂], 3.56 (s, 3 H, Me), 4.59 (*X* of *ABX*, 1 H, SiOCH), 4.92 and 4.99 [*AB*, *J*_{AB} = 12.1 Hz, 2 H, PhCH₂], 7.14–7.44 (m, 11 H, arom. H), 7.59–7.68 (m, 4 H, arom. H). – ¹³C NMR (75 MHz, CDCl₃): δ = 19.31 (s), 26.70 (q), 39.86 (t), 51.66 (q), 66.71 (t), 69.67 (d), 127.49 (d), 127.58 (d), 128.21 (d), 128.38 (d), 128.42 (d), 129.77 (d), 129.85 (d), 132.70 (s), 132.74 (s), 135.25 (s), 135.83 (d), 135.91 (d), 170.37 (s), 171.46 (s). – MS (FAB): *m/z* (%) = 476 (< 1) M⁺, 419 (100), 399 (47), 391 (14), 341 (20), 283 (11), 251 (11), 199 (11), 197 (18), 135

(24), 91 (62). – $C_{28}H_{32}O_5Si$ (476.64): calcd. C 70.56, H 6.77; found C 70.49, H 6.72.

1-Benzyl 4-Methyl 2-(tert-Butyldiphenylsilyloxy)butanedioate (rac-5): Prepared, starting from *rac*-malic acid, in a similar manner as **5**. White solid. – M.p. 46.5–48.5 °C. – HPLC: $t_R(R)$ = 10.3 min, $t_R(S)$ = 14.2 min. – The spectroscopic data were in accordance with those of **5**.

4-Allyl 1-Benzyl (2S)-2-[(3S)-3-Benzyloxycarbonyl-3-(tert-butyldiphenylsilyloxy)propanoyloxy]butanedioate (6): According to GP 1, acid **4** (4.16 g, 9.0 mmol) was converted into the acid chloride which was dissolved in CH_2Cl_2 (25 mL) and coupled according to GP 2 with **3** (2.38 g, 9.0 mmol) in CH_2Cl_2 (25 mL) upon addition of the pyridine solution within 45 min. FC (Et_2O /pentane 2:5) yielded **6** (5.96 g, 93%) as a colorless, viscous oil. – R_f (Et_2O /pentane 2:5) = 0.25. – $[\alpha]_D^{25}$ = –38.5 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 2954w, 2859w, 1746s, 1602w, 1456w, 1428w, 1380w, 1278m, 1161s, 1114m, 986w. – 1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, Me_3C), 2.78–2.92 (m, 4 H, $C(O)CH_2$), 4.50–4.58 (m, 3 H, $CH_2CH=CH_2$, SiOCH), 4.90 and 4.96 (AB, J_{AB} = 12.1 Hz, 2 H, $PhCH_2$), 5.15 (d, J = 1.5 Hz, 2 H, $PhCH_2$), 5.18–5.31 (m, 2 H, $CH=CH_2$), 5.46–5.51 (m, 1 H, $OCHCH_2$), 5.78–5.91 (m, 1 H, $CH=CH_2$), 7.12–7.44 (m, 16 H, arom. H), 7.59–7.67 (m, 4 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.31 (s), 26.74 (q), 35.96 (t), 39.43 (t), 65.71 (t), 66.76 (t), 67.39 (t), 68.46 (d), 69.22 (d), 118.62 (t), 127.50 (d), 127.63 (d), 128.20 (d), 128.39 (d), 128.42 (d), 128.55 (d), 129.75 (d), 129.88 (d), 131.64 (d), 132.65 (s), 132.70 (s), 135.04 (s), 135.27 (s), 135.88 (d), 135.93 (d), 168.30 (s), 168.48 (s), 168.88 (s), 171.13 (s). – MS (FAB): m/z (%) = 731 (2) [$M + Na$]⁺, 651 (49), 631 (33), 309 (100), 297 (64), 277 (68), 197 (33), 181 (56), 135 (41). – $C_{41}H_{44}O_9Si$ (708.88): calcd. C 69.47, H 6.26; found C 69.47, H 6.22.

4-Allyl 1-Benzyl (2S)-2-[(3S)-3-Benzyloxycarbonyl-3-hydroxypropanoyloxy]butanedioate (7): According to GP 3, dimer **6** (2.71 g, 3.83 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with 70% HF in pyridine (0.99 mL, 38.3 mmol) for 14 h. FC (Et_2O /pentane 1:1) yielded **7** (1.71 g, 95%) as a colorless oil. – R_f (Et_2O /pentane 1:1) = 0.13. – $[\alpha]_D^{25}$ = –26.2 (c = 1.2, $CHCl_3$). – IR ($CHCl_3$): 3541w, 3011w, 2953w, 1744s, 1498w, 1456w, 1379m, 1273s, 1166s, 1106m, 1058w, 986m. – 1H NMR (300 MHz, $CDCl_3$): δ = 2.84–3.01 [m, 4 H, $C(O)CH_2$], 3.28 (d, J = 5.9 Hz, 1 H, OH), 4.52–4.56 (m, 1 H, HOCH), 4.56–4.59 (m, 2 H, $CH_2CH=CH_2$), 5.13–5.24 (m, 4 H, $PhCH_2$), 5.24–5.33 (m, 2 H, $CH=CH_2$), 5.53–5.57 (m, 1 H, $OCHCH_2$), 5.80–5.93 (m, 1 H, $CH=CH_2$), 7.30–7.40 (m, 10 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.70 (t), 38.55 (t), 65.82 (t), 67.20 (d), 67.62 (t), 67.71 (t), 68.52 (d), 118.87 (t), 128.40 (d), 128.58 (d), 128.66 (d), 128.74 (d), 131.67 (d), 134.97 (s), 135.08 (s), 168.49 (s), 168.79 (s), 169.36 (s), 172.94 (s). – MS (EI): m/z (%) = 471 (3) [$M + H$]⁺, 273 (19), 245 (52), 181 (22), 175 (12), 131 (12), 129 (22), 107 (11), 91 (100). – $C_{25}H_{26}O_9$ (470.47): calcd. C 63.82, H 5.57; found C 63.67, H 5.53.

(3S)-4-Benzyloxy-3-[(3S)-3-benzyloxycarbonyl-3-(tert-butyldiphenylsilyloxy)propanoyloxy]butanoic Acid (8): Dimer **6** (2.45 g, 3.45 mmol) was dissolved in THF (35 mL) and $Pd(PPh_3)_4$ (225 mg, 0.195 mmol) and morpholine (3.0 mL, 34.5 mmol) were added. After stirring the solution at room temp. for 2 h, the THF was removed under reduced pressure (35 °C). The residue was dissolved in CH_2Cl_2 , washed with 1 N HCl solution (3 ×), dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in Et_2O (5 mL), filtered through Celite and the solution concentrated. Purification by FC (Et_2O /pentane 4:1) yielded acid **8** (2.15 g, 93%) as a highly viscous, yellow oil. – R_f (Et_2O /pentane 4:1) = 0.16. – $[\alpha]_D^{25}$ = –

40.6 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3036w, 2934w, 2859w, 1749s, 1602w, 1456w, 1428w, 1362w, 1281m, 1162s, 1114m, 956w. 1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, Me_3C), 2.77–2.92 [m, 4 H, $C(O)CH_2$], 4.54–4.58 (m, 1 H, SiOCH), 4.91 and 4.96 (AB, J_{AB} = 12.1 Hz, 2 H, $PhCH_2$), 5.15 (s, 2 H, $PhCH_2$), 5.45–5.49 (m, 1 H, $OCHCH_2$), 7.12–7.44 (m, 16 H, arom. H), 7.59–7.67 (m, 4 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.18 (s), 26.62 (q), 35.49 (t), 39.34 (t), 66.79 (t), 67.47 (t), 68.14 (d), 69.20 (d), 127.60 (d), 127.75 (d), 128.28 (d), 128.32 (d), 128.51 (d), 128.56 (d), 128.69 (d), 129.89 (d), 130.02 (d), 132.72 (s), 132.78 (s), 135.06 (s), 135.34 (s), 136.00 (d), 136.03 (d), 168.36 (s), 169.05 (s), 171.40 (s), 174.02 (s). – MS (FAB): m/z (%) = 692 (9) [$M + Na$]⁺, 197 (14), 181 (19), 135 (8), 133 (38), 105 (15), 91 (100). – $C_{38}H_{40}O_9Si$ (668.81): calcd. C 68.24, H 6.03; found C 68.05, H 5.91.

Protected Tetramer 9: According to GP 1, acid **8** (1.90 g, 2.84 mmol) was converted into the acid chloride which was dissolved in CH_2Cl_2 (7.5 mL) and coupled according to GP 2 with **7** (1.34 g, 2.84 mmol) in CH_2Cl_2 (7.5 mL) upon addition of the pyridine solution within 30 min. FC (Et_2O /pentane 3:4) yielded **9** (2.71 g, 85%) as a colorless, highly viscous glass. – R_f (Et_2O /pentane 1:1) = 0.27. – $[\alpha]_D^{25}$ = –31.8 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3038w, 2950w, 2860w, 1751s, 1602w, 1498w, 1456w, 1380w, 1278m, 1161s, 1113m, 984w. – 1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, Me_3C), 2.80–2.98 [m, 8 H, $C(O)CH_2$], 4.52–4.55 (m, 2 H, $CH_2CH=CH_2$), 4.56–4.59 (m, 1 H, SiOCH), 4.89 and 4.95 (AB, J_{AB} = 12.2 Hz, 2 H, $PhCH_2$), 5.09–5.18 (m, 6 H, $PhCH_2$), 5.18–5.29 (m, 2 H, $CH=CH_2$), 5.46–5.53 (m, 3 H, $OCHCH_2$), 5.78–5.88 (m, 1 H, $CH=CH_2$), 7.11–7.41 (m, 26 H, arom. H), 7.59–7.67 (m, 4 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.34 (s), 26.77 (q), 35.47 (t), 35.49 (t), 35.81 (t), 39.29 (t), 65.78 (t), 66.73 (t), 67.40 (t), 67.57 (t), 68.16 (d), 68.40 (d), 68.74 (d), 69.27 (d), 118.74 (t), 127.51 (d), 127.64 (d), 128.16 (d), 128.25 (d), 128.26 (d), 128.30 (d), 128.40 (d), 128.42 (d), 128.54 (d), 128.58 (d), 128.64 (d), 129.74 (d), 129.87 (d), 131.61 (d), 132.75 (s), 132.83 (s), 134.95 (s), 135.13 (s), 135.39 (s), 135.94 (d), 135.98 (d), 167.82 (s), 167.90 (s), 167.91 (s), 168.09 (s), 168.12 (s), 168.45 (s), 169.00 (s), 171.21 (s). – MS (MALDI): m/z = 1144 [$M + Na$]⁺. – $C_{63}H_{64}O_{17}Si$ (1121.27): calcd. C 67.49, H 5.75; found C 67.49, H 5.71.

Tetramer Acid 10: Allyl ester **9** (4.25 g, 3.79 mmol) was dissolved in THF (38 mL) and $Pd(PPh_3)_4$ (350 mg, 0.303 mmol) and imidazole (2.58 g, 37.9 mmol) were added. The pale yellow solution was stirred at room temp. for 1 h and then concentrated under reduced pressure (30 °C) to half of the initial volume. The solution was diluted with CH_2Cl_2 (200 mL), washed with 0.5 N HCl (3 ×) and half-sat. NaCl solutions, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in Et_2O (10 mL), filtered through Celite and purified by FC (Et_2O /hexane 1:1, 2% AcOH) to yield acid **10** (3.87 g, 95%) as a yellowish, highly viscous glass. – R_f (Et_2O /hexane 1:1, 2% AcOH) = 0.14. – $[\alpha]_D^{25}$ = –33.1 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3036w, 2950w, 1752s, 1456w, 1428w, 1381w, 1278w, 1163m, 1113w, 960w. – 1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 9 H, Me_3C), 2.77–2.96 [m, 8 H, $C(O)CH_2$], 4.54–4.57 (m, 1 H, SiOCH), 4.91 and 4.96 (AB, J_{AB} = 12.1 Hz, 2 H, $PhCH_2$), 5.08–5.23 (m, 6 H, $PhCH_2$), 5.43–5.50 (m, 2 H, $OCHCH_2$), 5.52–5.56 (m, 1 H, $OCHCH_2$), 7.11–7.41 (m, 26 H, arom. H), 7.58–7.65 (m, 4 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.31 (s), 26.75 (q), 35.36 (t), 35.58 (t), 35.62 (t), 39.28 (t), 66.98 (t), 67.61 (t), 68.39 (d), 68.59 (d), 68.67 (d), 69.24 (d), 127.54 (d), 127.68 (d), 128.24 (d), 128.29 (d), 128.31 (d), 128.42 (d), 128.46 (d), 128.55 (d), 128.59 (d), 128.65 (d), 128.66 (d), 129.05 (d), 129.80 (d), 129.93 (d), 132.65 (s), 132.71 (s), 134.89 (s), 134.91 (s), 134.98 (s), 135.21 (s), 135.92 (d), 135.95 (d), 167.78 (s), 167.80 (s), 167.82 (s), 168.01 (s), 168.54

(s), 169.16 (s), 171.38 (s), 171.63 (s). – MS (MALDI): m/z = 1126 $[M - H + 2 Na]^+$, 1120 $[M + K]^+$, 1104 $[M + Na]^+$. – $C_{60}H_{60}O_{17}Si$ (1081.21): calcd. C 66.65, H 5.59; found C 66.81, H 5.82.

Protected Tetramer 11: Acid **10** (1.10 g, 1.01 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with an ethereal solution of phenyldiazomethane (48 mL, ca. 0.03 M). After stirring the solution at room temp. for 14 h, it was diluted with CH_2Cl_2 , washed with 5% aq. citric acid and sat. NaCl solutions, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by FC (Et_2O /pentane 3:4) gave **11** (1.10 g, 93%) as a yellowish, viscous oil. – R_f (Et_2O /pentane 1:1) = 0.31. – $[\alpha]_D^{25}$ = –29.9 (c = 1.1, $CHCl_3$). – IR ($CHCl_3$): 3036w, 2956w, 1752s, 1498w, 1456w, 1381w, 1280m, 1161s, 1113m, 964w. – 1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, Me_3C), 2.80–2.94 [m, 8 H, $C(O)CH_2$], 4.56–4.58 (m, 1 H, $SiOCH$), 4.88 and 4.95 (AB , J_{AB} = 12.2 Hz, 2 H, $PhCH_2$), 5.05–5.15 (m, 8 H, $PhCH_2$), 5.46–5.53 (m, 3 H, $OCHCH_2$), 7.11–7.40 (m, 31 H, arom. H), 7.59–7.66 (m, 4 H, arom. H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.33 (s), 26.77 (q), 35.44 (t), 35.88 (t), 39.28 (t), 66.71 (t), 66.94 (t), 67.38 (t), 67.55 (t), 68.16 (d), 68.37 (d), 68.74 (d), 69.26 (d), 127.49 (d), 127.63 (d), 128.14 (d), 128.23 (d), 128.25 (d), 128.30 (d), 128.38 (d), 128.41 (d), 128.43 (d), 128.52 (d), 128.56 (d), 128.58 (d), 128.61 (d), 128.63 (d), 129.73 (d), 129.86 (d), 132.74 (s), 132.82 (s), 134.91 (s), 134.94 (s), 135.11 (s), 135.33 (s), 135.38 (s), 135.93 (d), 135.97 (d), 167.79 (s), 167.87 (s), 167.90 (s), 168.04 (s), 168.10 (s), 168.59 (s), 168.98 (s), 171.19 (s). – MS (MALDI): m/z = 1210 $[M + K]^+$, 1194 $[M + Na]^+$. – $C_{67}H_{66}O_{17}Si$ (1171.33): calcd. C 68.70, H 5.68; found C 68.85, H 5.80.

Tetramer Alcohol 12: According to GP 3, tetramer **11** (447 mg, 0.382 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with 70% HF in pyridine (0.20 mL, 7.63 mmol) for 17 h. FC (Et_2O / CH_2Cl_2 1:20) yielded **12** (314 mg, 89%) as a colorless oil. – R_f (Et_2O / CH_2Cl_2 1:20) = 0.10. – $[\alpha]_D^{25}$ = –20.6 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3541w, 2959w, 1750s, 1498w, 1456w, 1379w, 1358w, 1266m, 1164s, 1105w, 1052w, 961w. – 1H NMR (400 MHz, $CDCl_3$): δ = 2.82–2.98 [m, 8 H, $C(O)CH_2$], 3.37 (d, J = 6.0 Hz, 1 H, OH), 4.51–4.56 (m, 1 H, $HOCH$), 5.04–5.24 (m, 10 H, $PhCH_2$), 5.51–5.57 (m, 3 H, $OCHCH_2$), 7.24–7.38 (m, 25 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.41 (t), 35.87 (t), 38.67 (t), 66.98 (t), 67.28 (d), 67.60 (t), 67.66 (t), 67.69 (t), 68.27 (d), 68.44 (d), 68.78 (d), 128.27 (d), 128.35 (d), 128.40 (d), 128.46 (d), 128.53 (d), 128.56 (d), 128.60 (d), 128.63 (d), 128.67 (d), 134.86 (s), 134.89 (s), 134.90 (s), 135.12 (s), 135.31 (s), 167.87 (s), 167.94 (s), 168.01 (s), 168.09 (s), 168.17 (s), 168.67 (s), 169.23 (s), 172.76 (s). – MS (MALDI): m/z = 956 $[M + Na]^+$. – $C_{51}H_{48}O_{17}$ (932.93): calcd. C 65.66, H 5.19; found C 65.46, H 5.15.

Free Tetramer 13: Tetramer **12** (49 mg, 0.053 mmol) was deprotected in dioxane (2 mL) according to GP 4 in the presence of 10% Pd/C (5 mg) to yield the oligoacid **13** (38 mg, containing 1.5 equiv. dioxane, quant.) as a colorless, hygroscopic glass. – RP-HPLC: t_r = 9.6 min, purity 99%. – IR (neat): 3479m, 2960m, 2605w, 1959w, 1738s, 1641w, 1377m, 1234m, 1171s, 1048m, 955w. – 1H NMR (500 MHz, CD_3OD): δ = 2.75–3.08 [m, 8 H, $C(O)CH_2$], 4.52–4.55 (m, 1 H, $HOCH$), 4.88 (br. s, 6 H, $5 \times CO_2H$, $HOCH$), 5.44–5.49 (m, 3 H, $OCHCH_2$). – ^{13}C NMR (125 MHz, CD_3OD): δ = 36.68 (t), 36.70 (t), 36.73 (t), 39.96 (t), 68.15 (d), 69.72 (d), 69.95 (d), 70.38 (d), 170.05 (s), 170.07 (s), 171.20 (s), 171.58 (s), 171.94 (s), 171.97 (s), 172.76 (s), 176.14 (s). – MS (ESI $^-$): m/z (%) = 481 (100) $[M - H]^-$, 365 (18), 347 (17), 249 (39), 133 (22); (ESI $^+$): m/z (%) = 505 (100) $[M + Na]^+$. – HRMS (ESI $^-$, 7 T): m/z ($C_{16}H_{17}O_{17}$, $[M - H]^-$) calcd. 481.0471; found 481.0485.

Dibenzyl (2S)-2-[(3S)-3-Benzoyloxycarbonyl-3-(*tert*-butyldiphenylsilyloxy)propanoyloxy]butanedioate (15): A solution of acid **4**

(2.31 g, 5.0 mmol), dibenzyl (*S*)-malate (**14**) and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and DCC (1.14 g, 5.5 mmol) was added. The mixture was stirred at 0 °C for 6 h and was then filtered twice through Celite. The filtrate was diluted with Et_2O (100 mL), washed with 0.5 N HCl (3 $\times$), sat. $NaHCO_3$, and sat. NaCl solutions, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by FC (Et_2O /pentane 1:3) yielded dimer **15** (3.18 g, 84%) as a colorless oil. – R_f (Et_2O /pentane 1:3) = 0.20. – $[\alpha]_D^{25}$ = –34.5 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3040w, 2956w, 1747s, 1456w, 1428w, 1361w, 1281w, 1161m, 1114m. – 1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, Me_3C), 2.77–2.92 [m, 4 H, $C(O)CH_2$], 4.55–4.58 (m, 1 H, $SiOCH$), 4.90 and 4.96 (AB , J_{AB} = 12.1 Hz, 2 H, $PhCH_2$), 5.08 (s, 2 H, $PhCH_2$), 5.10 (s, 2 H, $PhCH_2$), 5.47–5.50 (m, 1 H, $OCHCH_2$), 7.12–7.42 (m, 21 H, arom. H), 7.58–7.67 (m, 4 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.34 (s), 26.77 (q), 36.06 (t), 39.45 (t), 66.78 (t), 66.89 (t), 67.39 (t), 68.48 (d), 69.26 (d), 127.53 (d), 127.66 (d), 128.22 (d), 128.37 (d), 128.42 (d), 128.45 (d), 128.56 (d), 128.57 (d), 128.79 (d), 129.91 (d), 132.71 (s), 132.73 (s), 135.06 (s), 135.32 (s), 135.41 (s), 135.91 (d), 135.97 (d), 168.30 (s), 168.68 (s), 168.90 (s), 171.15 (s). – MS (FAB): m/z (%) = 781 (14) $[M + Na]^+$, 771 (31), 701 (64), 681 (59), 567 (29), 547 (28), 309 (49), 297 (22), 277 (28), 271 (42), 197 (28), 181 (100), 135 (54), 105 (20). – $C_{45}H_{46}O_9Si$ (758.94): calcd. C 71.22, H 6.11; found C 71.27, H 6.30.

Dibenzyl (2S)-2-[(3S)-3-Benzoyloxycarbonyl-3-hydroxypropanoyloxy]butanedioate (16): According to GP 3, dimer **15** (2.13 g, 2.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with 70% HF in pyridine (0.73 mL, 28 mmol) for 15 h. FC (Et_2O /hexane 2:1) yielding **16** (1.37 g, 94%) as a colorless oil. – R_f (Et_2O /hexane 2:1) = 0.24. – $[\alpha]_D^{25}$ = –23.2 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 3536w, 1745s, 1498w, 1456w, 1379w, 1265m, 1165s, 1105w, 1056w, 965w. – 1H NMR (400 MHz, $CDCl_3$): δ = 2.80–2.96 [m, 4 H, $C(O)CH_2$], 3.28 (d, J = 5.5 Hz, 1 H, OH), 4.50–4.54 (m, 1 H, $HOCH$), 5.09–5.23 (m, 6 H, $PhCH_2$), 5.53–5.56 (m, 1 H, $OCHCH_2$), 7.25–7.38 (m, 15 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.89 (t), 38.63 (t), 67.03 (t), 67.22 (d), 67.64 (t), 67.72 (t), 68.57 (d), 128.32 (d), 128.44 (d), 128.46 (d), 128.51 (d), 128.57 (d), 128.59 (d), 128.61 (d), 128.63 (d), 128.65 (d), 134.86 (s), 135.02 (s), 135.30 (s), 168.31 (s), 168.79 (s), 169.18 (s), 172.76 (s). – MS (FAB): m/z (%) = 1041 (4) $[2 M + H]^+$, 543 (14) $[M + Na]^+$, 521 (36) $[M + H]^+$, 271 (36), 225 (24), 181 (100), 106 (12). – $C_{29}H_{28}O_9$ (520.53): calcd. C 66.92, H 5.42; found C 67.02, H 5.19.

(2S)-2-[(3S)-3-Carboxy-3-hydroxypropanoyloxy]butanedioic Acid (17): Dimer **16** (66 mg, 0.127 mmol) was deprotected in dioxane (2 mL) according to GP 4 in the presence of 10% Pd/C (7 mg) to yield the oligoacid **17** (42 mg, containing 0.9 equiv. dioxane, quant.) as a colorless, hygroscopic glass. – RP-HPLC: t_r = 4.1 min, purity > 99%. – $[\alpha]_D^{25}$ = –13.3 (c = 0.50, H_2O ; calcd. for solvent free compound). – IR (neat): 3415m, 3108m, 2969m, 2615w, 1737s, 1635w, 1404m, 1376m, 1173s, 1047m, 952w. – 1H NMR (400 MHz, CD_3OD): δ = 2.72–2.95 [m, 4 H, $C(O)CH_2$], 4.51–4.54 (m, 1 H, $HOCH$), 5.01 (br. s, 4 H, $3 \times CO_2H$, $HOCH$), 5.42–5.45 (m, 1 H, $OCHCH_2$). – ^{13}C NMR (100 MHz, CD_3OD): δ = 36.85 (t), 39.99 (t), 68.19 (d), 70.19 (d), 171.28 (s), 172.32 (s), 172.85 (s), 176.15 (s). – MS (FAB): m/z (%) = 501 (8) $[2 M + H]^+$, 273 (100) $[M + Na]^+$, 251 (48) $[M + H]^+$. – HRMS (FAB): m/z ($C_8H_{10}NaO_9$, $[M + Na]^+$) calcd. 273.0217; found 273.0219.

Tetramer Alcohol 18: According to GP 3, tetramer **9** (5.61 g, 5.0 mmol) was dissolved in CH_2Cl_2 (25 mL) and treated with 70% HF in pyridine (1.95 mL, 75 mmol) for 22 h. FC (Et_2O /hexane 2:1) yielded **18** (3.85 g, 87%) as a colorless oil. – R_f (Et_2O /hexane 2:1) = 0.15. – $[\alpha]_D^{25}$ = –21.7 (c = 1.1, $CHCl_3$). – IR ($CHCl_3$): 3530w,

3037w, 2954w, 1750s, 1602w, 1498w, 1456w, 1379w, 1275m, 1166s, 1105w, 1059w, 984w. – ^1H NMR (400 MHz, CDCl_3): δ = 2.82–2.99 [m, 8 H, $\text{C}(\text{O})\text{CH}_2$], 3.35 (d, J = 6.0 Hz, 1 H, OH), 4.52–4.56 (m, 3 H, HOCH , $\text{CH}_2\text{CH}=\text{CH}_2$), 5.08–5.29 (m, 10 H, $\text{CH}=\text{CH}_2$, $4 \times \text{PhCH}_2$), 5.52–5.58 (m, 3 H, OCHCH_2), 5.78–5.88 (m, 1 H, $\text{CH}=\text{CH}_2$) 7.26–7.36 (m, 20 H, arom. H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 35.44 (t), 35.47 (t), 35.80 (t), 38.68 (t), 65.80 (t), 67.30 (d), 67.59 (t), 67.65 (t), 67.68 (t), 68.28 (d), 68.47 (d), 68.79 (d), 118.75 (t), 128.26 (d), 128.33 (d), 128.45 (d), 128.52 (d), 128.55 (d), 128.58 (d), 128.64 (d), 128.66 (d), 131.61 (d), 134.88 (s), 134.93 (s), 135.15 (s), 167.87 (s), 167.94 (s), 167.99 (s), 168.11 (s), 168.17 (s), 168.49 (s), 169.21 (s), 172.75 (s). – MS (MALDI): m/z = 922 [$\text{M} + \text{K}$] $^+$, 906 [$\text{M} + \text{Na}$] $^+$. – $\text{C}_{47}\text{H}_{46}\text{O}_{17}$ (882.87): calcd. C 63.94, H 5.25; found C 63.97, H 5.39.

Tetramer Acetate 19: A solution of compound **18** (646 mg, 0.73 mmol) in CH_2Cl_2 (8 mL) was cooled to -10°C and pyridine (0.59 mL) was added. Acetyl chloride (0.078 mL, 1.1 mmol) was added over 10 min before the solution was stirred at -10°C for 45 min. The reaction mixture was poured on ice and extracted with CH_2Cl_2 (3 $\times$). The organic layer was washed with 5% aq. citric acid, sat. NaHCO_3 , and half sat. NaCl solutions, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by FC ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ 3:97) yielded acetate **19** (654 mg, 97%) as a colorless oil. – R_f ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ 3:97) = 0.23. – $[\alpha]_{\text{D}}^{25}$ = -19.1 (c = 1.0, CHCl_3). – IR (CHCl_3): 3032w, 2952w, 1751s, 1499w, 1456w, 1378w, 1281w, 1166m, 1053w, 986w. – ^1H NMR (500 MHz, CDCl_3): δ = 2.07 (s, 3 H, Me), 2.86–3.01 (m, 8 H, $\text{C}(\text{O})\text{CH}_2$), 4.53–4.55 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.10–5.18 (m, 8 H, PhCH_2), 5.19–5.29 (m, 2 H, $\text{CH}=\text{CH}_2$) 5.50–5.57 (m, 4 H, OCHCH_2), 5.79–5.87 (m, 1 H, $\text{CH}=\text{CH}_2$) 7.27–7.36 (m, 20 H, arom. H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 20.44 (q), 35.42 (t), 35.46 (t), 35.57 (t), 35.76 (t), 65.76 (t), 67.40 (t), 67.55 (t), 67.57 (t), 67.63 (t), 67.95 (d), 68.38 (d), 68.41 (d), 68.74 (d), 118.73 (t), 128.18 (d), 128.22 (d), 128.24 (d), 128.29 (d), 128.36 (d), 128.43 (d), 128.51 (d), 128.54 (d), 128.57 (d), 128.58 (d), 128.62 (d), 128.64 (d), 131.58 (d), 134.86 (s), 134.89 (s), 134.93 (s), 135.07 (s), 167.76 (s), 167.83 (s), 167.92 (s), 168.05 (s), 168.11 (s), 168.42 (s), 168.53 (s), 169.93 (s). – MS (MALDI): m/z = 948 [$\text{M} + \text{Na}$] $^+$. – $\text{C}_{49}\text{H}_{48}\text{O}_{18}$ (924.91): calcd. C 63.63, H 5.23; found C 63.61, H 5.13.

Tetramer Acid 20: Allyl ester **19** (651 mg, 0.704 mmol) was dissolved in THF (7 mL) and $\text{Pd}(\text{PPh}_3)_4$ (65 mg, 0.056 mmol) and imidazole (477 mg, 7.0 mmol) were added. The pale yellow solution was stirred at room temp. for 2 h and then concentrated under reduced pressure (30°C) to half of the initial volume. The solution was diluted with CH_2Cl_2 (30 mL), washed with 1 N HCl (3 $\times$) and half sat. NaCl solutions, dried (Na_2SO_4), and concentrated. The resulting residue was dissolved in Et_2O (5 mL), filtered through Celite and purified by two FC ($\text{Et}_2\text{O}/\text{hexane}$ 2:1, 2% AcOH ; $\text{Et}_2\text{O}/\text{toluene}$ 1:5, 2% AcOH) to yield acid **20** (488 mg, 78%) as a yellowish, highly viscous glass. – R_f ($\text{Et}_2\text{O}/\text{hexane}$ 2:1, 2% AcOH) = 0.15; R_f ($\text{Et}_2\text{O}/\text{toluene}$ 1:5, 2% AcOH) = 0.17. – $[\alpha]_{\text{D}}^{25}$ = -21.4 (c = 1.0, CHCl_3). – IR (CHCl_3): 3032w, 1752s, 1600w, 1498w, 1456w, 1377w, 1280w, 1161m, 1112w, 1059w. – ^1H NMR (500 MHz, CDCl_3): δ = 1.02 (s, 9 H, Me_3C), 2.79–2.97 [m, 16 H, $\text{C}(\text{O})\text{CH}_2$], 4.52–4.53 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$) 4.55–4.57 (m, 1 H, SiOCH), 4.87 and 4.94 (AB , J_{AB} = 12.2 Hz, 2 H, PhCH_2), 5.08–5.17 (m, 14 H, PhCH_2), 5.18–5.28 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.45–5.47 (m, 1 H, OCHCH_2), 5.49–5.53 (m, 6 H, OCHCH_2), 5.78–5.86 (m, 1 H, $\text{CH}=\text{CH}_2$), 7.11–7.13 (m, 2 H, arom. H), 7.24–7.40 (m, 44 H, arom. H), 7.59–7.66 (m, 4 H, arom. H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 19.34 (s), 26.78 (q), 35.37 (t), 35.42 (t), 35.47 (t), 35.78 (t), 39.28 (t), 65.78 (t), 66.71 (t), 67.35 (t), 67.47 (t), 67.53 (t), 67.54 (t), 67.59 (t), 67.64 (t), 68.21 (d), 68.42 (d), 68.76 (d), 69.28 (d), 118.76 (t), 127.50 (d), 127.64 (d), 128.14 (d), 128.22 (d), 128.24 (d), 128.27 (d), 128.31 (d), 128.36 (d), 128.39 (d), 128.43 (d), 128.44 (d), 128.48 (d), 128.49 (d), 128.53 (d), 128.57 (d), 128.59 (d), 128.61 (d), 128.62 (d), 128.64 (d), 128.66 (d), 129.73 (d), 129.86 (d), 131.61 (d), 132.77 (s), 132.86 (s), 134.89 (s), 134.92 (s), 134.95 (s), 134.99 (s), 135.01 (s), 135.05 (s), 135.18 (s), 135.42 (s), 135.94 (d), 135.99 (d), 167.81 (s), 167.84 (s), 167.86 (s), 167.91 (s), 167.94 (s), 167.95 (s), 168.00 (s), 168.07 (s), 168.16

O-Terminally Protected Tetramer 21: Acid **20** (308 mg, 0.348 mmol) was deprotected in dioxane (8 mL) according to GP 4 in the presence of 10% Pd/C (30 mg) to yield the oligoacid **21** (249 mg, containing 1.9 equiv. dioxane, quant.) as a colorless, hygroscopic glass. – RP-HPLC: t_r = 15.1 min, purity 97.5%. – pK_a (25°C): 3.46. – $[\alpha]_{\text{D}}^{25}$ = -17.3 (c = 0.49, H_2O ; calcd. for solvent free compound). – IR (neat): 3479m, 2940m, 2595w, 1959w, 1740s, 1641w, 1377m, 1236m, 1169s, 1051m, 949w. – ^1H NMR (400 MHz, CD_3OD): δ = 2.09 (s, 3 H, Me), 2.80–3.13 [m, 8 H, $\text{C}(\text{O})\text{CH}_2$], 4.95 (br. s, 5 H, CO_2H), 5.41–5.51 (m, 4 H, OCHCH_2) – ^{13}C NMR (100 MHz, CD_3OD): δ = 20.58 (q), 36.72 (t), 36.75 (t), 36.84 (t), 69.59 (d), 69.93 (d), 69.97 (d), 70.41 (d), 170.04 (s), 170.06 (s), 170.17 (s), 171.55 (s), 171.64 (s), 171.91 (s), 171.98 (s), 172.19 (s), 172.78 (s). – MS (ESI^-): m/z (%) = 523 (100) [$\text{M} - \text{H}$] $^-$, 365 (21), 249 (14); (ESI^+): m/z (%) = 547 (100) [$\text{M} + \text{Na}$] $^+$. – HRMS (ESI^- , 4.7 T): m/z ($\text{C}_{18}\text{H}_{19}\text{O}_{18}^-$, [$\text{M} - \text{H}$] $^-$) calcd. 523.0577; found 523.0573.

C-Terminally Protected Tetramer 22: Tetramer **18** (2.22 g, 2.51 mmol) was deprotected in dioxane (60 mL) according to GP 4 in the presence of 10% Pd/C (200 mg) to yield the oligoacid **22** (1.61 g, containing 1.5 equiv. dioxane, 98%) as a colorless, hygroscopic glass. – RP-HPLC: t_r = 24.2 min, purity 93.5% (3.5% of tetramer **13**). – IR (neat): 3468m, 2967w, 2600w, 1738s, 1639w, 1381w, 1173s, 1056m. – ^1H NMR (400 MHz, CD_3OD): δ = 0.95 (t, J = 7.4 Hz, 3 H, MeCH_2), 1.66 (tq, J = 6.6, 7.4 Hz, 2 H, MeCH_2), 2.74–3.08 [m, 8 H, $\text{C}(\text{O})\text{CH}_2$], 4.09 (t, J = 6.6 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{O}$) 4.52–4.55 (m, 1 H, HOCH), 4.88 (br. s, 5 H, $4 \times \text{CO}_2\text{H}$, HOCH), 5.44–5.51 (m, 3 H, OCHCH_2) – ^{13}C NMR (100 MHz, CD_3OD): δ = 10.72 (q), 22.99 (t), 36.73 (t), 36.77 (t), 37.01 (t), 39.99 (t), 67.86 (t), 68.17 (d), 69.74 (d), 69.97 (d), 70.25 (d), 169.99 (s), 170.05 (s), 171.12 (s), 171.21 (s), 171.56 (s), 171.76 (s), 171.95 (s), 176.17 (s). – MS (ESI^-): m/z (%) = 523 (100) [$\text{M} - \text{H}$] $^-$, 407 (14), 389 (10), 291 (38), 249 (11); (ESI^+): m/z (%) = 547 [$\text{M} + \text{Na}$] $^+$. – HRMS (ESI^- , 4.7 T): m/z ($\text{C}_{16}\text{H}_{17}\text{O}_{17}^-$, [$\text{M} - \text{H}$] $^-$) calcd. 523.0941; found 523.0932.

Octamer 23: According to GP 1, acid **10** (162 mg, 0.150 mmol) was converted into the acid chloride which was dissolved in CH_2Cl_2 (1.1 mL) and coupled according to GP 2 with **18** (132 mg, 0.150 mmol) in CH_2Cl_2 (0.5 mL) upon addition of the pyridine solution within 40 min. Two FC ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ 1:30; first $\text{Et}_2\text{O}/\text{hexane}$ 2:1, then $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ 1:1) and recrystallization from boiling ($i\text{Pr}_2\text{O}$) yielded **23** (39 mg, 13%) as a white solid. – M.p. $79.5\text{--}80.0^\circ\text{C}$. – R_f ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ 1:30) = 0.19. – $[\alpha]_{\text{D}}^{25}$ = -20.2 (c = 0.20, CHCl_3). – IR (CHCl_3): 3036w, 1752s, 1602w, 1498w, 1456w, 1377w, 1280w, 1161m, 1112w, 1059w. – ^1H NMR (500 MHz, CDCl_3): δ = 1.02 (s, 9 H, Me_3C), 2.79–2.97 [m, 16 H, $\text{C}(\text{O})\text{CH}_2$], 4.52–4.53 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$) 4.55–4.57 (m, 1 H, SiOCH), 4.87 and 4.94 (AB , J_{AB} = 12.2 Hz, 2 H, PhCH_2), 5.08–5.17 (m, 14 H, PhCH_2), 5.18–5.28 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.45–5.47 (m, 1 H, OCHCH_2), 5.49–5.53 (m, 6 H, OCHCH_2), 5.78–5.86 (m, 1 H, $\text{CH}=\text{CH}_2$), 7.11–7.13 (m, 2 H, arom. H), 7.24–7.40 (m, 44 H, arom. H), 7.59–7.66 (m, 4 H, arom. H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 19.34 (s), 26.78 (q), 35.37 (t), 35.42 (t), 35.47 (t), 35.78 (t), 39.28 (t), 65.78 (t), 66.71 (t), 67.35 (t), 67.47 (t), 67.53 (t), 67.54 (t), 67.59 (t), 67.64 (t), 68.21 (d), 68.42 (d), 68.76 (d), 69.28 (d), 118.76 (t), 127.50 (d), 127.64 (d), 128.14 (d), 128.22 (d), 128.24 (d), 128.27 (d), 128.31 (d), 128.36 (d), 128.39 (d), 128.43 (d), 128.44 (d), 128.48 (d), 128.49 (d), 128.53 (d), 128.57 (d), 128.59 (d), 128.61 (d), 128.62 (d), 128.64 (d), 128.66 (d), 129.73 (d), 129.86 (d), 131.61 (d), 132.77 (s), 132.86 (s), 134.89 (s), 134.92 (s), 134.95 (s), 134.99 (s), 135.01 (s), 135.05 (s), 135.18 (s), 135.42 (s), 135.94 (d), 135.99 (d), 167.81 (s), 167.84 (s), 167.86 (s), 167.91 (s), 167.94 (s), 167.95 (s), 168.00 (s), 168.07 (s), 168.16

(s), 168.44 (s), 169.03 (s), 171.21 (s). – MS (MALDI): m/z = 1969 $[M + Na]^+$. – $C_{107}H_{104}O_{33}Si$ (1946.06): calcd. C 66.04, H 5.39; found C 65.59, H 5.27.

Tetramer 24: Acid **10** (216 mg, 0.20 mmol) and alcohol **18** (185 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (1 mL) and NMM (42 mg, 0.42 mmol) and BOP-Cl (53 mg, 0.21 mmol) were added. The suspension was stirred at room temp. for 27 h and a 5% $NaHCO_3$ solution (10 mL) and CH_2Cl_2 were added. The organic layer was separated, washed with 0.5 N HCl (2 $\times$), 5% $NaHCO_3$ (2 $\times$), and half-sat. NaCl solutions, dried ($MgSO_4$) and concentrated. FC (Et_2O/CH_2Cl_2 1:50) yielded **24** (125 mg, 58%) as a colorless oil. – R_f (Et_2O/CH_2Cl_2 1:50) = 0.13. – $[\alpha]_D^{25}$ = -16.7 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 2954 w , 1751 s , 1498 w , 1455 w , 1379 w , 1262 m , 1166 s , 1057 w , 979 w . – 1H NMR (400 MHz, $CDCl_3$): δ = 2.82–3.07 [m, 8 H, $C(O)CH_2$], 4.52–4.54 (m, 2 H, $CH_2CH=CH_2$), 5.07–5.29 (m, 12 H, $CH=CH_2$, 4 $\times$ $PhCH_2$), 5.50–5.57 (m, 3 H, $OCHCH_2$), 5.61–5.65 (m, 1 H, $OCHCH_2$), 5.76–5.88 (m, 1 H, $CH=CH_2$), 6.90 and 6.94 (AB , J_{AB} = 15.8 Hz, 2 H, $C(O)CH=CH$), 7.25–7.39 (m, 25 H, arom. H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.44 (t), 35.76 (t), 65.78 (t), 67.08 (t), 67.57 (t), 67.59 (t), 67.63 (t), 67.64 (t), 68.40 (d), 68.49 (d), 68.74 (d), 118.74 (t), 128.25 (d), 128.27 (d), 128.31 (d), 128.34 (d), 128.50 (d), 128.52 (d), 128.53 (d), 128.56 (d), 128.58 (d), 128.62 (d), 128.65 (d), 131.59 (d), 132.65 (d), 134.57 (d), 134.87 (s), 134.90 (s), 135.20 (s), 163.76 (s), 164.49 (s), 167.80 (s), 167.81 (s), 167.84 (s), 167.86 (s), 167.94 (s), 167.96 (s), 168.07 (s), 168.45 (s). – MS (MALDI): m/z = 1110 $[M + K]^+$, 1094 $[M + Na]^+$. – $C_{58}H_{54}O_{20}$ (1071.05): calcd. C 65.04, H 5.08; found C 65.10, H 4.88.

Hydrogenation of the Fully Protected Dimer 6: Dimer **6** (213 mg, 0.30 mmol) was dissolved in dioxane (5 mL) and 10% Pd/C (21 mg) was added. The apparatus was evacuated and flushed with H_2 (3 $\times$), and the mixture was stirred under H_2 (balloon) while following the progress of the reaction by TLC. The reaction was stopped after 4.5 h and the suspension was filtered through Celite. The filtrate was concentrated under reduced pressure and the components separated by FC ($tBuOMe$ /hexane 3:1 to 5:1, 2% AcOH) yielding **25** (33 mg, 16%), **26** (105 mg, 56%), **27** (10 mg, 5%) and **28** (36 mg, 23%).

1-Benzyl 4-Propyl (2S)-2-[(3S)-3-Benzylloxycarbonyl-3-(tert-butylidiphenylsilyloxy)propanoyloxy]butanedioate (25): Colorless oil. – R_f ($tBuOMe$ /hexane 4:1) = 0.73. – 1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.5 Hz, 3 H, $MeCH_2$), 1.04 (s, 9 H, Me_3C), 1.52–1.62 (m, 2 H, $MeCH_2$), 2.80–2.86 [m, 4 H, $C(O)CH_2$], 3.98–4.03 (m, 2 H, CH_2CH_2O), 4.56–4.59 (m, 1 H, $SiOCH$), 4.90 and 4.96 (AB , J_{AB} = 12.2 Hz, 2 H, $PhCH_2$), 5.15 (s, 2 H, $PhCH_2$), 5.48–5.50 (m, 1 H, $OCHCH_2$), 7.13–7.43 (m, 16 H, arom. H), 7.60–7.67 (m, 4 H, arom. H). – MS (FAB): m/z (%) = 734 (9) $[M + Na]^+$, 654 (21), 634 (12), 309 (93), 297 (67), 277 (65), 269 (28), 227 (23), 225 (34), 197 (100), 181 (100), 135 (76), 105 (24).

(2S)-2-[(3S)-3-Benzylloxycarbonyl-3-(tert-butylidiphenylsilyloxy)propanoyloxy]-3-(propoxycarbonyl)propanoic Acid (26): Colorless oil. – R_f ($tBuOMe$ /hexane 4:1) = 0.14. – $[\alpha]_D^{25}$ = -36.9 (c = 1.0, $CHCl_3$). – IR ($CHCl_3$): 2960 w , 1740 s , 1604 w , 1428 w , 1275 m , 1162 m , 1114 m . – 1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.3 Hz, 3 H, $MeCH_2$), 1.02 (s, 9 H, Me_3C), 1.54–1.66 (m, 2 H, $MeCH_2$), 2.76–2.85 [m, 4 H, $C(O)CH_2$], 4.03 (t, J = 6.7 Hz, 2 H, CH_2CH_2O), 4.53–4.57 (m, 1 H, $SiOCH$), 4.90 and 4.95 (AB , J_{AB} = 12.1 Hz, 2 H, $PhCH_2$), 5.38–5.42 (m, 1 H, $OCHCH_2$), 6.4–6.8 (br. s, 1 H, CO_2H), 7.11–7.42 (m, 11 H, arom. H), 7.58–7.65 (m, 4 H, arom. H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.25 (q), 19.26 (s), 21.77 (t), 26.70 (q), 35.96 (t), 39.35 (t), 66.79 (t), 66.92 (t), 68.55 (d), 69.28

(d), 127.49 (d), 127.63 (d), 128.20 (d), 128.38 (d), 128.47 (d), 129.74 (d), 129.90 (d), 132.55 (s), 132.66 (s), 135.14 (s), 135.87 (d), 135.90 (d), 169.05 (s), 169.43 (s), 171.41 (s), 173.80 (s). – MS (FAB): m/z (%) = 659 (2) $[M + K]^+$, 643 (12) $[M + Na]^+$, 225 (12), 197 (100), 195 (14), 183 (33), 181 (50), 165 (13), 137 (10), 135 (25), 104 (20). – $C_{34}H_{40}O_9Si$ (620.77): calcd. C 65.79, H 6.49; found C 65.65, H 6.63.

(2S)-4-[(1S)-1-Benzylloxycarbonyl-2-propoxycarbonylethoxy]-2-(tert-butylidiphenylsilyloxy)-4-oxobutanoic Acid (27): Colorless oil. – R_f ($tBuOMe$ /hexane 4:1) = 0.48. – 1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.5 Hz, 3 H, $MeCH_2$), 1.10 (s, 9 H, Me_3C), 1.54–1.64 (m, 2 H, $MeCH_2$), 2.74–2.95 [m, 4 H, $C(O)CH_2$], 4.03 (t, J = 6.7 Hz, 2 H, CH_2CH_2O), 4.43–4.47 (m, 1 H, $SiOCH$), 5.15–5.20 (m, 2 H, $PhCH_2$), 5.47–5.51 (m, 1 H, $OCHCH_2$), 7.30–7.50 (m, 11 H, arom. H), 7.62–7.70 (m, 4 H, arom. H). – MS (FAB): m/z (%) = 643 (100) $[M + Na]^+$, 563 (32), 543 (24), 309 (41), 297 (32), 277 (54), 269 (20), 199 (76), 197 (79), 183 (23), 181 (27), 165 (21), 139 (22), 135 (95), 105 (25).

(2S)-2-(tert-Butylidiphenylsilyloxy)-4-[(1S)-1-carboxy-2-propoxycarbonylethoxy]-4-oxobutanoic Acid (28): Colorless oil. – R_f ($tBuOMe$ /hexane 4:1) = 0.03. – 1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.2 Hz, 3 H, $MeCH_2$), 1.08 (s, 9 H, Me_3C), 1.60–1.67 (m, 2 H, $MeCH_2$), 2.73–2.96 [m, 4 H, $C(O)CH_2$], 4.07 (t, J = 6.7 Hz, 2 H, CH_2CH_2O), 4.48–4.52 (m, 1 H, $SiOCH$), 5.45–5.49 (m, 1 H, $OCHCH_2$), 7.35–7.48 (m, 6 H, arom. H), 7.64–7.68 (m, 4 H, arom. H). – MS (FAB): m/z (%) = 530 (3) M^+ , 352 (45), 332 (12), 289 (12), 257 (16), 239 (19), 199 (100), 197 (30), 177 (10), 165 (13).

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