Supplementary Information for

Ternary thiol-ene systems as high-performance bone adhesives for potential clinical use

Lisa Sinawehl,[a,b,d]‡ *Patrick Steinbauer,*[a,b,d]‡ *Danijela Kojic,*[a,b,d] *Paul Slezak,*[a,c,d] *Heinz Redl*[a,c,d] *and Stefan Baudis*[a,b,d*]

a) Christian Doppler Laboratory for Advanced Polymers for Biomaterials and 3D Printing, Getreidemarkt 9, 1060 Vienna, Austria

b) Institute of Applied Synthetic Chemistry, TU Wien, Getreidemarkt 9/163 MC, 1060 Vienna, Austria

c) LBG Ludwig Boltzmann Institute for Traumatology, The Research Center in Cooperation with AUVA, Donaueschingenstr 13, 1200 Vienna, Austria

d) Austrian Cluster for Tissue Regeneration, 1200 Vienna, Austria

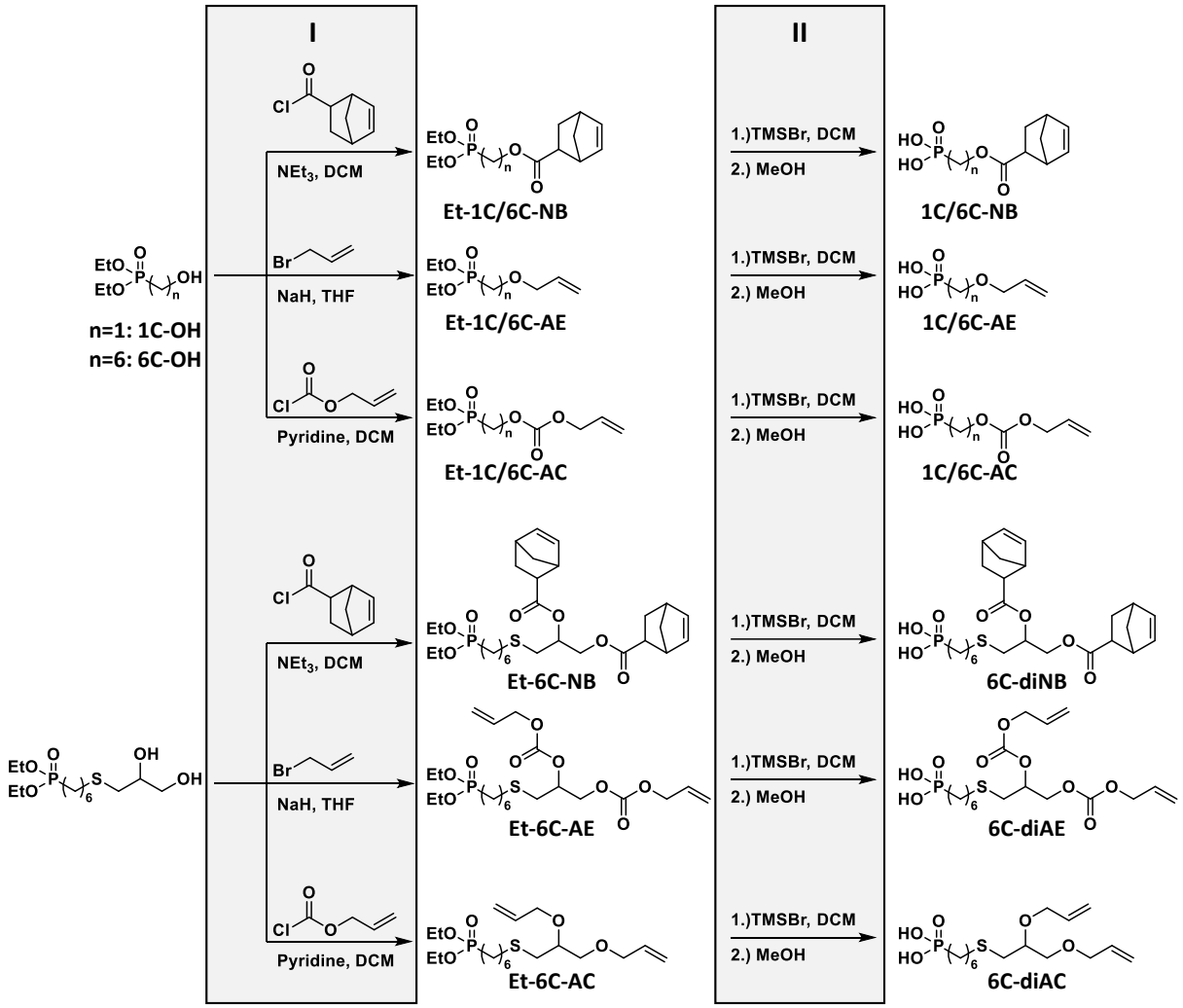
***Email:** stefan.baudis@tuwien.ac.at

‡ Both authors contributed equally

TABLE OF CONTENTS

1 Primer Synthesis

All primers were synthesized according to Scheme S1 from different building blocks.

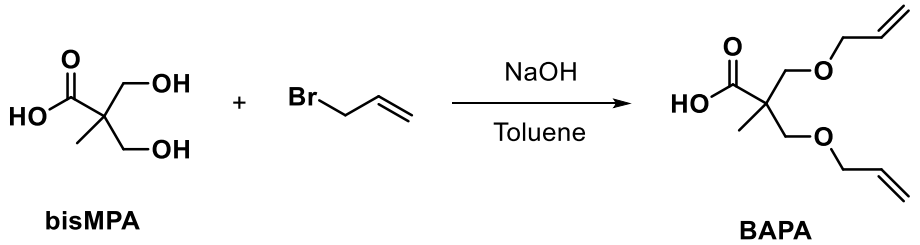


Scheme S1. Synthetic pathways for the preparation of the different self-etching primer molecules; I: Functionalization step to introduce the different polymerizable groups; II: Deprotection step to obtain the unprotected phosphonic acid adhesion motif.

1.1 Synthesis of the reference primer ((3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanamido) methyl)phosphonic acid (REF)

1.1.1 *Synthesis of 3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanoic acid (BAPA)*

The first step of the synthesis of the reference primer (REF) was done from 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) according to Antoni *et al.*[1]



Scheme 1. Synthesis pathway towards the compound BAPA.

In a round bottom flask bis-MPA (1 eq., 20.1 g, 150 mmol), sodium hydroxide (10 eq., 60 g, 1500 mmol), and allyl bromide (7.2 eq., 93.3 mL, 1080 mmol) were dissolved in 320 mL dry toluene under argon. The reaction mixture was refluxed overnight. After evaporation of the solvent, concentrated HCl was added to obtain a pH of 1. The organic layer was washed with distilled water (3x100 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified via silica flash column chromatography (PE:EE 9:1 → 1:1) to obtain the 24.1 g (75% of theory) of the desired product BAPA as a slightly yellow, viscous liquid.

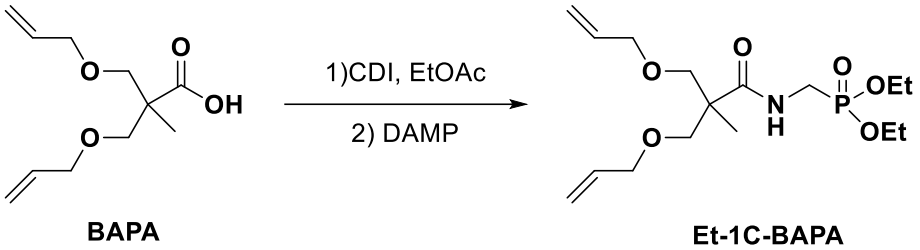
Yield: 24.1 g (75% theoretical yield, 94% literature yield[1])

RI $n_D^{20°C}$: 1.4566

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 6.00 – 5.77 (m, 2H, 2x C<u>H</u>=CH_2), 5.22 (dd, 4H, 2x CH=C<u>H_2</u>), 4.01 (d, $^3J_{HH}$ = 5.5, 1.5 Hz, 4H, 2x OC<u>H_2</u>CH), 3.58 (s, 4H, 2x CC<u>H_2</u>O), 1.25 (s, 3H, CC<u>H_3</u>)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 180.14 (s, COOH), 136.7 (s, CH=CH_2), 117.08 (s, CH=CH_2), 72.55 (s, CCH_2O), 72.01 (s, OCH_2CH), 48.24 (s, C_q), 17.97 (s, CCH_3)

1.1.2 *Synthesis of diethyl ((3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanamido) methyl)phosphonate (Et-1C-BAPA)*



Scheme 2. Synthesis pathway towards the compound Et-1C-BAPA.

The reference primer REF was synthesized according to a procedure of Granskog et al.[2] N,N'-Carbonyl diimidazole (CDI, 1 eq., 3.7 g, 23 mmol) was suspended in 20 mL dry ethyl acetate under argon atmosphere. Then, BAPA (1 eq., 4.9 g, 23 mmol) was slowly added and the mixture was stirred for 2 h at 50 °C. Afterwards, diethyl(aminomethyl)phosphonate (DAMP, 0.83 eq., 3.2 g, 19 mmol) was added dropwise. The reaction mixture was stirred overnight at 50 °C. After completion, the reaction was quenched with 50 mL distilled water and stirred for another 2 h at room temperature. 50 mL ethyl acetate were added and the solution was washed with saturated $NaHCO_3$ (3x50 mL) and brine (2x50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash column chromatography (PE:EE 1:9) to afford 5.87 g (85% of theory) of the desired product as a slightly yellow, viscous liquid.

Yield: 5.87 g (85% theoretical yield, 98% literature yield[2])

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 7.39 (s, 1H, NH), 6.03 – 5.74 (m, 2H, 2x CH=CH_2), 5.36 – 5.10 (m, 4H, 2x CH=CH_2), 4.21 – 4.06 (m, 4H, 2x OC$H_2$$CH_3$), 4.04 – 3.94

(m, 4H, 2x C$\underline{H_2}$CH=CH$_2$), 3.71 (dd, $^3J_{NH}$ = 12.1, 5.7 Hz, 2H, NHC$\underline{H_2}$P), 3.54 (s, 4H, 2x CC$\underline{H_2}$O), 1.31 (t, $^3J_{HH}$ = 7.1 Hz, 6H, 2x OCH$_2$C$\underline{H_3}$), 1.18 (s, 3H, CC$\underline{H_3}$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 134.75 (s, $\underline{C}$H=CH$_2$), 117.24 (s, CH=$\underline{C}$H$_2$), 73.28 (s, C$\underline{C}$H$_2$O), 72.62 (s, 2x $\underline{C}$H$_2$CH=CH$_2$), 62.52 (d, $^2J_{CP}$ = 6.3 Hz, 2x O$\underline{C}$H$_2$CH$_3$), 47.59 (s, $\underline{C_q}$), 34.56 (d, $^1J_{CP}$ = 155.2 Hz, NH$\underline{C}$H$_2$P), 18.56 (s, C$_q\underline{C}$H$_3$), 16.54 (d, $^3J_{CP}$ = 6.0 Hz, 2x OCH$_2\underline{C}$H$_3$)

^{31}P NMR (162 MHz, Chloroform-d) δ (ppm): 23.21

1.1.3 *Synthesis of ((3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanamido)methyl) phosphonic acid (REF)*

Et-1C-BAPA **REF**

Scheme 3. Synthesis pathway towards the compound REF.

REF was prepared from Et-1C-BAPA (1 eq., 1.4 g, 3.8 mmol) with TMSBr (3 eq., 1.5 mL, 11.4 mmol) according to General Procedure D with 5 mL MeOH and 5 mL DCM to afford the product in a yield of 1.1 g (94% theoretical yield).

Yield: 1.1 g (94% theoretical yield, 94% literature yield[2])

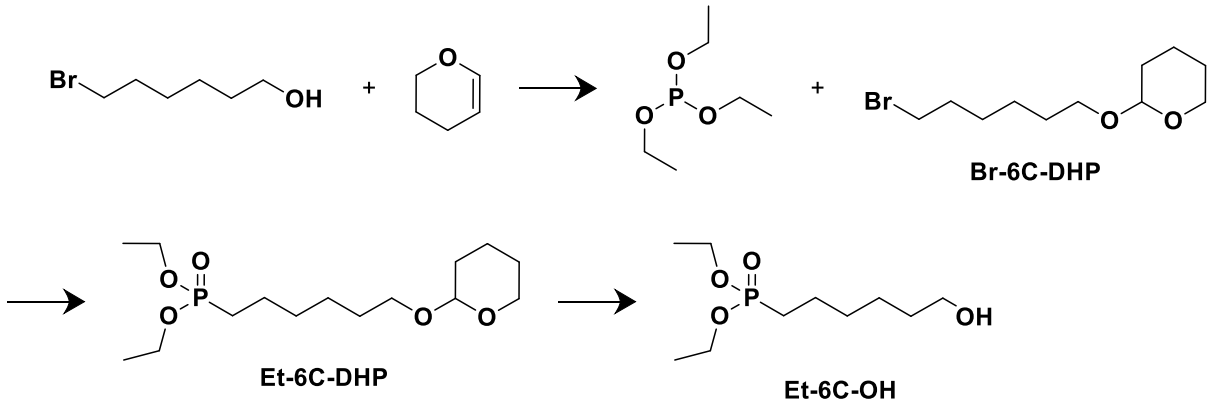
^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 6.02 – 5.73 (m, 2H, 2x C$\underline{H}$=CH$_2$), 5.35 – 5.08 (m, 4H, 2x CH=C$\underline{H_2}$), 4.01 (m, 4H, 2x C$\underline{H_2}$CH=CH$_2$), 3.72 – 3.64 (m, 2H, NHC$\underline{H_2}$P), 3.55 (s, 4H, 2x CC$\underline{H_2}$O), 1.19 (s, 3H, C$\underline{C}$H$_3$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 134.34 (s, $\underline{C}H=CH_2$), 117.70 (s, $CH=\underline{C}H_2$), 73.28 (s, $C\underline{C}H_2O$), 72.62 (s, 2x $\underline{C}H_2CH=CH_2$), 47.79 (s, $\underline{C}_q$), 34.56 (d, $^1J_{CP}$ = 155.3 Hz, $NH\underline{C}H_2P$), 18.38 (s, $C_q\underline{C}H_3$)

^{31}P NMR (162 MHz, Chloroform-d) δ (ppm): 19.22

1.2 Synthesis of the building block diethyl (6-hydroxyhexyl) phosphonate (6C-OH)

The synthesis of the building block Et-6C-OH was performed as shown in Scheme 4 following the procedure from Besse *et al*.[3]



Scheme 4. Synthesis pathway towards the compound Et-6C-OH.

1.2.1 *Synthesis of 2-((6-bromohexyl)oxy)tetrahydro-2H-pyran (Br-6C-DHP)*

The synthesis was performed based on the procedure given in Derbanne *et al*.[4] Pyridinium p-toluenesulfonate (PPTS) (0.021 eq., 0.2 g, 1.26 mmol) and 6-bromo-1-hexanol (1 eq., 7.3 mL, 60 mmol) were dissolved in 70 mL of degassed methylene chloride under argon in a light-protected three-necked round bottom flask. 3,4-dihydro-2H-pyran (2 eq., 10.1 g, 120 mmol) was added slowly to the reaction mixture at room temperature, which was afterwards stirred for 4 h. Afterwards, the reaction mixture was washed with $NaHCO_3$ (3 x 30 mL), distilled water (3 x 50 mL) and brine (3 x 30 mL). The combined organic layer was dried with $MgSO_4$ and

concentrated under reduced pressure. Purification of the crude product via silica flash column chromatography (PE:EE 9:1) yielded 13.91 g (87% of theory) Br-6C-DHP as colorless liquid.

Yield: 13.91 g (87% theoretical yield)

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 4.56 (t, $^{3}J_{HH}$ = 3.6 Hz, 1H, OC<u>H</u>O), 3.92 – 3.65 (m, 2H, OC<u>H</u>$_2$ pyran), 3.55 – 3.31 (m, 4H, C<u>H</u>$_2$Br, OC<u>H</u>$_2$), 1.94 – 1.33 (m, 14H, 3x C<u>H</u>$_2$ pyran, 4x C<u>H</u>$_2$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 99.08 (s, O<u>C</u>HO), 67.62 (s, O<u>C</u>H$_2$ pyran), 62.55 (s, O<u>C</u>H$_2$), 34.1 (s, <u>C</u>H$_2$Br), 32.9 (s, <u>C</u>H$_2$_CH$_2$Br), 30.90 (s, <u>C</u>H$_2$ pyran), 29.67 (s, OCH$_2$<u>C</u>H$_2$), 28.2 (s, <u>C</u>H$_2$ alkyl), 25.72 (s, <u>C</u>H$_2$ alkyl), 25.62 (s, <u>C</u>H$_2$ pyran), 19.85 (s, <u>C</u>H$_2$ pyran).

1.2.2 *Synthesis of diethyl (6-(tetrahydro-2H-pyran-2-yl)oxy)hexylphosphonate (Et-6C-DHP)*

DHP-6C-Br (1 eq., 10.9 g, 41 mmol) and triethyl phosphite (2 eq., 14.2 mL, 82 mmol) were placed in a round-bottom flask after which the mixture was heated at 150 °C for 20 h. The excess of triethyl phosphite and residues were evaporated. Afterwards, the obtained crude product was dissolved in 100 mL diethylether and washed with distilled water (3 x 30 mL) and 50 mL brine. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography providing 10.74 g (81% of theory) of the desired compound as slightly yellow viscous liquid.

Yield: 10.74 g (81% theoretical yield)

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 4.55 (t, $^{3}J_{HH}$ = 3.6 Hz, 1H, OC<u>H</u>O), 4.16 – 3.99 (m, 4H, O<u>C</u>H$_2$CH$_3$), 3.91 – 3.65 (m, 2H, OC<u>H$_2$</u> pyran), 3.54 – 3.31 (m, 4H, OC<u>H$_2$</u>CH$_3$) 1.88 – 1.35 (m, 16H, 3x C<u>H$_2$</u> pyran, 5x C<u>H$_2$</u>), 1.31 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, OCH$_2$C<u>H$_3$</u>)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 99.06 (s, O<u>C</u>HO C$_7$), 67.60 (s, O<u>C</u>H$_2$ pyran C$_8$), 62.51 (s, O<u>C</u>H$_2$ C$_6$), 61.50 (d, $^{2}J_{CP}$ = 6.6 Hz, O<u>C</u>H$_2$CH$_3$), 30.90 (s, <u>C</u>H$_2$ pyran C$_{11}$), 30.58 (d, $^{3}J_{CP}$ = 17.0 Hz, PCH$_2$CH$_2$<u>C</u>H$_2$), 29.64 (s, <u>C</u>H$_2$ pyran C$_9$), 25.92 (d, $^{1}J_{CP}$ = 140.6 Hz, P<u>C</u>H$_2$ C$_1$), 25.62 (s, <u>C</u>H$_2$OCH), 25.10 (s, <u>C</u>H$_2$ C$_4$), 22.53 (d, $^{2}J_{CP}$ = 5.2 Hz, PCH$_2$<u>C</u>H$_2$), 19.83 (s, <u>C</u>H$_2$ pyran C$_{10}$), 16.56 (d, $^{3}J_{CP}$ = 6.1 Hz, OCH$_2$<u>C</u>H$_3$)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 32.45.

1.2.3 *Synthesis of diethyl (6-hydroxyhexyl) phosphonate (6C-OH)*

The starting material Et-6C-DHP (1 eq., 10.6 g, 33 mmol) was dissolved in 150 mL dry methanol. 75 g Amberlite 120 IR were added thereto and the reaction mixture was heated at 45 °C for 20 h. After filtration of the exchange resin and concentration under reduced pressure, 7.78 g (99% of theory) of diethyl (6-hydroxyhexyl) phosphonate were obtained as colorless viscous liquid.

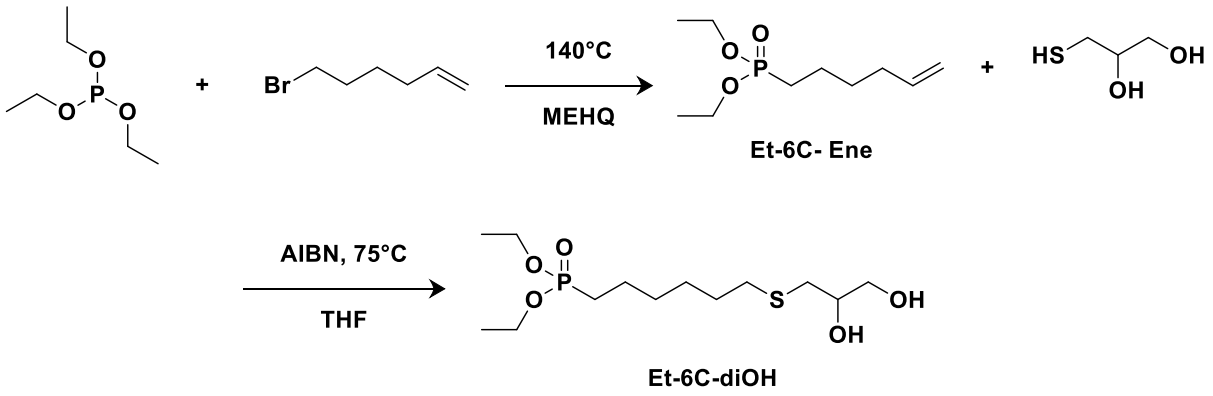
^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 4.15 – 3.99 (m, 4H, OC<u>H$_2$</u>CH$_3$), 3.61 (t, $^{3}J_{HH}$ = 6.6 Hz, 2H, C<u>H$_2$</u>OH), 2.49 (s, 1H, O<u>H</u>), 1.79 – 1.49 (m, 6H, C<u>H$_2$</u>P, C<u>H$_2$</u>CH$_2$OH, C<u>H$_2$</u>), 1.45 – 1.33 (m, 4H, C<u>H$_2$</u> CH$_2$CH$_2$P, C<u>H$_2$</u>CH$_2$P), 1.31 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, OCH$_2$C<u>H$_3$</u>)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 62.78 (d, $^{2}J_{CP}$ = 2.7 Hz, <u>C</u>H$_2$OH), 61.55 (d, $^{2}J_{CP}$ = 6.6 Hz, O<u>C</u>H$_2$CH$_3$), 32.56 (s, <u>C</u>H$_2$CH$_2$OH), 30.34 (d, $^{3}J_{CP}$ = 16.5 Hz, <u>C</u>H$_2$CH$_2$CH$_2$P), 25.49 (d, $^{1}J_{CP}$ = 140.6 Hz, <u>C</u>H$_2$P C$_1$), 25.18 (d, $^{4}J_{CP}$ = 1.2 Hz, <u>C</u>H$_2$ C$_4$), 22.47 (d, $^{2}J_{CP}$ = 5.2 Hz, <u>C</u>H$_2$CH$_2$P C$_2$), 16.64 (d, $^{3}J_{CP}$ = 6.0 Hz, OCH$_2$<u>C</u>H$_3$)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 32.60.

1.3 Synthesis of the building block diethyl (6-((2,3-dihydroxypropyl)thio)hexyl)-phosphonate (Et-6C-diOH)

Et-6C-diOH was synthesized according to Scheme 5 and an optimized procedure from Pelaprat *et al*[5]. and Catel *et al*[6]. The precursor molecule Et-6C-Ene was prepared in accordance to Boutevin *et al*.[7] and Putvinski *et al*[8].



Scheme 5. Synthesis pathway towards the building block 6C-diOH

1.3.1 *Synthesis of hex-5-en-1-yl phosphonate (Et-6C-Ene)*

6-Bromohex-1-enyl (9.8 g, 1 eq., 60 mmol) and triethyl phosphite (12.0 g, 1.2 eq., 72 mmol) and 11 mg of MEHQ were placed under argon in a distillation apparatus with a vigreux column. The reaction mixture was heated up to 140°C for 24 h, whereby the resulting side product ethyl bromide (bp 38 °C) was directly distilled off during reaction. Reaction progress was monitored via ^{31}P-NMR. After completion, the product was distilled fractionally under high vacuum (0.011 mbar) at 75 °C to yield 8.99 g (68% of theory) of the desired product as colorless liquid.

Yield: 8.99 g (68% theoretical yield, 98% literature yield[5])

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 5.84 – 5.69 (m, 1H, C<u>H</u>=CH_2), 5.04 – 4.89 (m, 2H, CH=C<u>H_2</u>), 4.16 – 4.00 (m, 4H, OC<u>H_2</u>CH_3), 2.11 – 2.00 (m, 2H, C<u>H_2</u>CH), 1.78 – 1.53 (m, 4H, C<u>H_2</u>), 1.51 – 1.41 (m, 2H, PC<u>H_2</u>), 1.30 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, OCH_2C<u>H_3</u>)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 138.31 (s, <u>C</u>H=CH_2), 114.92 (s, CH=<u>C</u>H_2), 61.50 (d, J = 6.5 Hz, O<u>C</u>H_2CH_3), 33.31 (d, $^{4}J_{CP}$ = 1.4 Hz, <u>C</u>H_2CH), 29.88 (d, $^{3}J_{CP}$ = 17.0 Hz, PCH_2 CH_2<u>C</u>H_2), 26.72 – 24.62 (d, $^{1}J_{CP}$ = 140.6 Hz, P<u>C</u>H_2, 22.03 (d, $^{2}J_{CP}$ = 5.2 Hz, PCH_2<u>C</u>H_2), 16.62 (d, $^{3}J_{CP}$ = 6.1 Hz, OCH_2<u>C</u>H_3)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 32.31

1.3.2 *Synthesis of (6-((2,3-dihydroxypropyl)thio)hexyl)phosphonate (Et-6C-diOH)*

Et-6C-Ene (10.1 g, 1 eq., 46 mmol) and thioglycerol (10.0 g, 2 eq., 92 mmol) were dissolved in dry THF under argon. The mixture was degassed with argon for about 45 min. Afterwards AIBN (0.2 g, 0.02 eq., 0.92 mmol) were added. The reaction mixture was stirred for about 24 h at 75 °C. The reaction progress was monitored via TLC and ^{31}P-NMR. The solution was concentrated under reduced pressure. The crude product was purified by silica flash column chromatography (EE → EE:MeOH 95:5) to afford 11.78 g (78% of theory) of Et-6C-diOH as slightly yellow, viscous liquid.

Yield: 11.78 g (78% theoretical yield)

RI $n_D^{20°C}$: 1.4880

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 4.17 – 4.00 (m, 4H, OC<u>H_2</u>CH_3), 3.83 – 3.68 (m, 2H, C<u>H</u>OH, C<u>H_2</u>OH), 3.63 – 3.54 (m, 1H, C<u>H_2</u>OH), 2.71 (dd, $^{2}J_{HH}$ = 13.7, $^{3}J_{HH}$ = 5.0 Hz, 1H, SC<u>H_2</u>CH), 2.62 (dd, $^{2}J_{HH}$ = 13.7, $^{3}J_{HH}$ = 7.8 Hz, 1H, SC<u>H_2</u>CH), 2.56 (t, $^{3}J_{HH}$ = 7.4 Hz, 2H,

$CH_2C\underline{H_2}S$), 1.81 – 1.68 (m, 2H, $PC\underline{H_2}$), 1.68 – 1.54 (m, 4H, $PCH_2C\underline{H_2}$, $C\underline{H_2}CH_2CH_2S$), 1.48 – 1.39 (m, 4H, $PCH_2CH_2CH_2$, CH_2CH_2S), 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 6H, $OCH_2C\underline{H_3}$)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 70.32 (s, $\underline{C}HOH$), 65.54 (s, $\underline{C}H_2OH$), 61.75 (d, $^3J_{CP}$ = 6.7 Hz, $O\underline{C}H_2CH_3$), 35.78 (s, $S\underline{C}H_2CH$), 32.30 (s, $CH_2\underline{C}H_2S$), 29.95 (d, $^3J_{CP}$ = 16.8 Hz, $PCH_2CH_2\underline{C}H_2$), 29.30 (s, $\underline{C}H_2CH_2CH_2S$), 28.11 (s, $\underline{C}H_2CH_2S$), 26.64 – 24.44 (d, $^1J_{CP}$ = 140.8 Hz, $P\underline{C}H_2$), 22.21 (d, $^2J_{CP}$ = 5.1 Hz, $PCH_2\underline{C}H_2$), 16.51 (d, $^3J_{CP}$ = 6.1 Hz, $OCH_2\underline{C}H_3$)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 32.60

1.4 Synthesis of the norbornene (NB)-primers

1.4.1 *Synthesis of 5-norbornene-2-carbonyl chloride (NB-Cl)*

The synthesis of 5-norbornene-2-carbonyl chloride (NB-Cl) was performed following a literature procedure.[9] Oxalyl chloride (24 mL, 280 mmol, 4 eq.), 10 mL methylene chloride and 0.1 mL dimethyl formamide were placed under argon atmosphere in a three-necked round bottom flask equipped with a dropping funnel. The dropping funnel was charged with 5-norbornene-2-carboxylic acid (6.5 mL, 70 mmol, 1 eq.) and 40 mL methylene chloride (DCM). After stirring for 15 min under ice cooling, the solution in the dropping funnel was slowly added to the reaction mixture. Afterwards, the ice bath was removed and the reaction mixture was stirred at RT for 24 h. Evaporation of methylene chloride and oxalyl chloride followed *in vacuo*. The obtained residual was finally distilled at 6 mbar and 47 °C to afford 8.5 g (78% of theory) NB-Cl as colorless liquid.

Yield: 8.5 g (78% theoretical yield, 104% literature yield[9])

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.32 – 6.17 (m, 1H, C<u>H</u>=CH endo/exo), 6.17 – 5.99 (m, 1H, C<u>H</u>=CH exo/endo), 3.49 – 2.71 (m, 3H, C<u>H</u>), 2.07 – 1.87 (m, 1H, C<u>H$_2$</u>, C<u>H$_2$</u> bridge), 1.57 – 1.38 (m, 2H, C<u>H$_2$</u>, C<u>H$_2$</u> bridge), 1.37 – 1.28 (m, 1H, C<u>H$_2$</u>, C<u>H$_2$</u> bridge)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 175.19 (s, C=O), 139.17 (s, <u>C</u>H=CH exo), 138.83 (s, <u>C</u>H=CH endo), 135.02 (s, CH=<u>C</u>H exo), 131.75 (s, CH=<u>C</u>H endo), 56.56 (s, <u>C</u>HC=O endo), 56.45 (s, <u>C</u>HC=O exo), 49.36 (s, <u>C</u>H$_2$ bridge), 47.29 (s, <u>C</u>H endo), 47.03 (s, <u>C</u>H exo), 46.43 (s, <u>C</u>H$_2$ bridge), 43.00 (s, <u>C</u>H endo), 42.00 (s, <u>C</u>H exo), 31.29 (s, <u>C</u>H$_2$ exo), 30.21 (s, <u>C</u>H$_2$ endo)

1.4.2 *Synthesis of (((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy)methyl) phosphonic acid (1C-NB)*

1.4.2.1 Synthesis of (((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy)methyl) phosphonate (Et-1C-NB)

Et-1C-NB was prepared from diethyl hydroxymethyl phosphonate (1C-OH, 1 eq., 2.2 mL, 15 mmol) and NB-Cl (1.5 eq., 3.5 g, 22.5 mmol) in 50 mL dry DCM and TEA (1.8 eq., 3.7 mL, 27 mmol) according to General Procedure A to afford the product in a yield of 4.3 g (99% of theory) as a brown viscous liquid.

Yield: 4.3 g (99% theoretical yield)

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 6.26 – 5.90 (m, 2H, C<u>H</u>=C<u>H</u>), 4.47 – 4.23 (m, 2H, PC<u>H$_2$</u>O), 4.22 – 4.10 (m, 4H, O<u>C</u>H$_2$CH$_3$), 3.27 – 2.84 (m, 3H, 2x C<u>H</u> norb, C<u>H</u>C=O), 2.00 – 1.87 (m, 1H, C<u>H$_2$</u> norb), 1.57 – 1.23 (m, 9H, C<u>H$_2$</u> norb, C<u>H$_2$</u> bridge, 2x OCH$_2$C<u>H$_3$</u>)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 175.47 (s, exo C=O), 173.89 (s, endo C=O), 138.34 (s, exo <u>C</u>H=CH), 137.99 (s, endo <u>C</u>H=CH), 135.69 (s, exo CH=<u>C</u>H), 132.42 (s, endo CH=<u>C</u>H), 62.89 – 62.73 (m, O<u>C</u>H$_2$CH$_3$), 56.85 (d, $^{1}J_{CP}$ = 168.5 Hz, <u>C</u>H$_2$P C_1 endo), 56.61 (d,

$^{1}J_{CP}$ = 168.7 Hz, $\underline{C}H_2P$ C_1 exo), 49.73 (s, $\underline{C}H_2$ bridge), 46.75 (s, exo $\underline{C}H$ norb), 46.44 (s, $\underline{C}H_2$ bridge), 45.89 (s, endo $\underline{C}H$ norb), 43.15 (s, endo $\underline{C}H$ norb), 42.93 (s, exo $\underline{C}H$ norb), 42.63 (s, endo $\underline{C}H$ norb), 41.77 (s, exo $\underline{C}H$ norb), 30.57 (s, exo $\underline{C}H_2$ norb), 29.51 (s, endo $\underline{C}H_2$ norb), 16.53 (d, $^{3}J_{CP}$ = 5.9 Hz, $OCH_2\underline{C}H_3$)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 19.47

1.4.2.2 Synthesis of (((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy)methyl) phosphonic acid (1C-NB)

1C-NB was prepared from Et-1C-NB (1 eq., 5.2 g, 18 mmol) with TMSBr (3 eq., 6 mL, 45 mmol) according to General Procedure D with 50 mL DCM and MeOH to afford the product in a yield of 4.17 g (99% of theory) as brown viscous liquid.

Yield: 4.17 g (99% theoretical yield)

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 8.17 (s, 2H), 6.23 – 5.87 (m, 2H, C$\underline{H}$=C$\underline{H}$), 4.51 – 4.27 (m, 2H, PC$\underline{H_2}$O), 3.30 – 3.14 (m, 1H, C$\underline{H}$ norb), 3.12 – 2.99 (m, 1H, C$\underline{H}$ norb), 2.97 – 2.87 (m, 1H, C$\underline{H}$C=O), 2.01 – 1.86 (m, 1H, C$\underline{H_2}$ norb), 1.62 – 1.19 (m, 3H, C$\underline{H_2}$ norb, C$\underline{H_2}$ bridge)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 176.13 (s, exo C=O), 174.86 (s, endo C=O), 138.34 (s, exo $\underline{C}$H=CH), 137.99 (s, endo $\underline{C}$H=CH), 135.69 (s, exo CH=$\underline{C}$H), 132.42 (s, endo CH=$\underline{C}$H), 57.63 (d, $^{1}J_{CP}$ = 169.3 Hz, $\underline{C}H_2P$ C_1 exo), 56.96 (d, $^{1}J_{CP}$ = 169.2 Hz, $\underline{C}H_2P$ C_1 endo), 49.78 (s, $\underline{C}H_2$ bridge), 46.80 (s, exo $\underline{C}$H norb), 46.48 (s, $\underline{C}H_2$ bridge), 46.03 (s, endo $\underline{C}$H norb), 43.20 (s, endo $\underline{C}$H norb), 42.99 (s, exo $\underline{C}$H norb), 42.72 (s, endo $\underline{C}$H norb), 41.79 (s, exo $\underline{C}$H norb), 30.61 (s, exo $\underline{C}H_2$ norb), 29.51 (s, endo $\underline{C}H_2$ norb)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 20.93

HR-MS (MeOH, ESI, m/z): calc. 288.28, found 288.28 [M]

1.4.3 *Synthesis of 6C-NB*

1.4.3.1 Synthesis of (6-((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy)hexyl) phosphonate (Et-6C-NB)

Et-6C-NB was prepared from 6C-OH (1 eq., 2.9 g, 12 mmol) and NB-Cl (2.5 eq., 4.7 g, 30 mmol) in 100 mL dry DCM and TEA (2.8 eq., 4.7 mL, 33 mmol) according to General Procedure A to afford the product in a yield of 3.0 g (70% of theory) as a brown viscous liquid, which was used without further purification.

Yield: 4.17 g (99% theoretical yield)

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 8.17 (s, 2H), 6.23 – 5.87 (m, 2H, C<u>H</u>=C<u>H</u>), 4.51 – 4.27 (m, 2H, PC<u>H$_2$</u>O), 3.30 – 3.14 (m, 1H, C<u>H</u> norb), 3.12 – 2.99 (m, 1H, C<u>H</u> norb), 2.97 – 2.87 (m, 1H, C<u>H</u>C=O), 2.01 – 1.86 (m, 1H, C<u>H$_2$</u> norb), 1.62 – 1.19 (m, 3H, C<u>H$_2$</u> norb, C<u>H$_2$</u> bridge)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 176.13 (s, exo C=O), 174.86 (s, endo C=O), 138.34 (s, exo <u>C</u>H=CH), 137.99 (s, endo <u>C</u>H=CH), 135.69 (s, exo CH=<u>C</u>H), 132.42 (s, endo CH=<u>C</u>H), 57.63 (d, $^{1}J_{CP}$ = 169.3 Hz, <u>C</u>H$_2$P C$_1$ exo), 56.96 (d, $^{1}J_{CP}$ = 169.2 Hz, <u>C</u>H$_2$P C$_1$ endo), 49.78 (s, <u>C</u>H$_2$ bridge), 46.80 (s, exo <u>C</u>H norb), 46.48 (s, <u>C</u>H$_2$ bridge), 46.03 (s, endo <u>C</u>H norb), 43.20 (s, endo <u>C</u>H norb), 42.99 (s, exo <u>C</u>H norb), 42.72 (s, endo <u>C</u>H norb), 41.79 (s, exo <u>C</u>H norb), 30.61 (s, exo <u>C</u>H$_2$ norb), 29.51 (s, endo <u>C</u>H$_2$ norb)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 20.93

HR-MS (MeOH, ESI, m/z): calc. 288.28, found 288.28 [M]

1.4.3.2 Synthesis of (6-((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy)hexyl) phosphonic acid (6C-NB)

6C-NB was prepared from Et-6C-NB (1 eq., 2.9 g, 8 mmol) with TMSBr (2 eq., 2.1 mL, 16 mmol) according to General Procedure D with 25 mL DCM and MeOH to afford the product in a yield of 2.37 g (99% of theory) as brown viscous liquid, which was used without further purification.

Yield: 2.37 g (99% theoretical yield)

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 8.27 (s, 2H, O<u>H</u>), 6.24 – 5.84 (m, 2H, C<u>H</u>=C<u>H</u>), 4.12 – 3.95 (m, 2H, C<u>H$_2$</u>OC=O alkyl), 3.24 – 3.14 (m, 1H, C<u>H</u> norb), 3.07 – 2.84 (m, 2H, C<u>H</u> norb, C<u>H</u>C=O), 2.25 – 2.15 (m, 1H, C<u>H$_2$</u> norb), 1.95 – 1.11 (m, 13H, C<u>H$_2$</u> norb, C<u>H$_2$</u> bridge, C<u>H$_2$</u>P, 4x C<u>H$_2$</u> alkyl)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 176.60 (s, exo C=O), 175.15 (s, endo C=O), 138.17 (s, exo <u>C</u>H=CH), 137.92 (s, endo <u>C</u>H=CH), 135.90 (s, exo CH=<u>C</u>H), 132.46 (s, endo CH=<u>C</u>H), 64.39 (d, J = 24.3 Hz, <u>C</u>H$_2$OC=O), 49.77 (s, <u>C</u>H$_2$ bridge), 46.75 (s, exo <u>C</u>H norb), 46.51 (s, <u>C</u>H$_2$ bridge), 45.87 (s, endo <u>C</u>H norb), 43.52 (s, endo <u>C</u>H norb), 43.35 (s, exo <u>C</u>H norb), 42.67 (s, endo <u>C</u>H norb), 41.77 (s, exo <u>C</u>H norb), 30.48 (s, exo <u>C</u>H$_2$ norb), 30.04 (d, $^{3}J_{CP}$ = 17.0 Hz, <u>C</u>H$_2$CH$_2$CH$_2$P), 29.36 (s, <u>C</u>H$_2$CH$_2$O C$_5$), 28.51 (s, endo <u>C</u>H$_2$ norb), 25.54 (s, <u>C</u>H$_2$ C$_4$), 25.43 (d, $^{1}J_{CP}$ = 141 Hz, <u>C</u>H$_2$P C$_1$), 22.07 (d, $^{2}J_{CP}$ = 5.0 Hz, PCH$_2$<u>C</u>H$_2$ C$_2$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 36.87

HR-MS (MeOH, ESI, m/z): calc. 302.31, found 302.35 [M]

1.4.4 *Synthesis of (6-((2,3-bis((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy) propyl) thio)hexyl) phosphonic acid (Phn-6C-bisNorb) (6C-diNB)*

1.4.4.1 Synthesis of 6-((2,3-bis((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy) propyl)thio) hexyl) phosphonate (Et-6C-diNB)

Et-6C-diNB was prepared from 6C-diOH (1 eq., 3.3 g, 10 mmol) and NB-Cl (2.3 eq., 4 3.6 g, 23 mmol) in 100 mL dry DCM and TEA (2.5 eq., 3.5 mL, 25 mmol) according to General Procedure A. After silica flash column chromatography (100% EE), 3 g (73% of theory) of the compound were isolated as red viscous liquid.

Yield: 3 g (73% theoretical yield)

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.24 – 5.87 (m, 4H, 2x C<u>H</u>=C<u>H</u>), 5.23 – 4.98 (m, 1H, C<u>H</u>O), 4.46 – 4.15 (m, 2H, C<u>H$_2$</u>O), 4.09 (m, 4H, OC<u>H$_2$</u>CH$_3$), 3.25 – 3.16 (m, 2H, 2x C<u>H</u> norb), 3.12 – 2.87 (m, 4H, 2x C<u>H</u> norb, SC<u>H$_2$</u>CH), 2.74 – 2.62 (m, 2H, C<u>H$_2$</u>SCH$_2$ C$_6$), 2.60 – 2.49 (m, 2H, C<u>H</u>C=O), 1.99 – 1.84 (m, 2H, C<u>H$_2$</u> norb), 1.79 – 1.22 (m, 22H, 2x C<u>H$_2$</u> bridge, 5x C<u>H$_2$</u> C$_1$-C$_5$, C<u>H$_2$</u> norb, 2x OCH$_2$C<u>H$_3$</u>)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 174.14 (m, 2x <u>C</u>=O), 138.14 (s, <u>C</u>H=CH), 137.80 (s, CH=<u>C</u>H), 135.67 (s, <u>C</u>H=CH), 132.39 (s, CH=<u>C</u>H), 70.55-70.34 (m, <u>C</u>HO), 64.48 – 62.74 (m, CH<u>C</u>H$_2$O), 61.42 (d, J = 6.5 Hz, O<u>C</u>H$_2$CH$_3$), 49.64 (s, <u>C</u>H$_2$ bridge), 46.35 (s, CH$_2$ norb), 45.82 – 45.70 (m, <u>C</u>H norb), 43.42 – 43.25 (m, <u>C</u>HC=O), 42.59 – 42.49 (m, <u>C</u>H norb), 32.58 (s, S<u>C</u>H$_2$CH), 32.34 (s, <u>C</u>H$_2$SCH$_2$), 30.18 (d, $^{3}J_{CP}$ = 17.0 Hz, PCH$_2$CH$_2$<u>C</u>H$_2$), 29.24 (s, <u>C</u>H$_2$CH$_2$CH$_2$S), 28.26 (s, <u>C</u>H$_2$CH$_2$S), 25.65 (d, $^{1}J_{CP}$ = 140.7 Hz, P<u>C</u>H$_2$), 22.36 (d, $^{2}J_{CP}$ = 5.2 Hz, PCH$_2$<u>C</u>H$_2$), 16.52 (d, $^{3}J_{CP}$ = 6.0 Hz, OCH$_2$<u>C</u>H$_3$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 32.34

HR-MS (MeOH, ESI, m/z): calc. 568.71, found 568.75 [M]

1.4.4.2 Synthesis of (6-((2,3-bis((bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxy) propyl) thio)hexyl) phosphonic acid (6C-diNB)

6C-diNB was prepared from Et-6C-diNB (1 eq., 2.3 g, 4 mmol) with TMSBr (2.3 eq., 1.2 mL, 9.2 mmol) according to General Procedure D with 25 mL DCM and MeOH to afford the product in a yield of 1.86 g (91% of theory) as brown viscous liquid, which was used without further purification.

Yield: 1.86 g (91% theoretical yield)

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.24 – 5.86 (m, 4H, 2x CH=CH), 5.25 – 4.98 (m, 1H, CHO), 4.46 – 4.08 (m, 2H, CH2O), 3.26 – 3.14 (m, 2H, 2x CH norb), 3.12 – 2.87 (m, 4H, 2x CH norb, SCH2CH), 2.77 – 2.63 (m, 2H, CH2SCH2 C6), 2.60 – 2.50 (m, 2H, CHC=O), CH2 norb), 1.99 – 1.21 (m, 18H, 2x CH2 bridge, 5x CH2 C1-C5, 2x CH2 norb)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 175.99 – 174.17 (m, 2x C=O), 138.28 (s, CH=CH), 137.99 (s, CH=CH), 135.79 (s, CH=CH), 132.47 (s, CH=CH), 70.80- 70.39 (m, CHO), 64.19 – 63.51 (m, CHCH2O), 50.78 (s, CH2 norb), 49.74 (s, CH2 bridge), 45.82 – 45.70 (m, CH norb), 43.42 – 43.25 (m, CHC=O), 42.59 – 42.49 (m, CH norb), 32.64 (s, SCH2CH), 32.41 (s, CH2SCH2), 30.18 (d, 3JCP = 17.0 Hz, PCH2CH2CH2), 29.34 (s, CH2CH2CH2S), 28.25 (s, CH2CH2S), 25.58 (s, 1JCP = 140.9 Hz, PCH2, 22.08 (d, 2JCP = 5.2 Hz, PCH2CH2)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 36.46

HR-MS (MeOH, ESI, m/z): calc. 512.60, found 512.62 [M]

1.5 Synthesis of the allyl ether (AE)-primers

1.5.1 *Synthesis of ((allyloxy)methyl)phosphonic acid (1C-AE)*

1.5.1.1 Synthesis of ((allyloxy)methyl)phosphonate (Et-1C-AE)

The Wiliamson ether synthesis of Et-1C-AE and allyl bromide was conducted according to General Procedure B from 1C-OH (1 eq., 2.2 mL, 15 mmol) with allyl bromide (1 1.3 eq., 1.7 mL, 19.5 mmol) and sodium hydride (1.9 eq., 0.7 g, 28.5 mmol) in 40 mL THF. After silica flash column chromatography (100% EE), 1.4 g (49% of theory) of the desired compound were isolated as colorless liquid.

Yield: 1.85 g (59% theoretical yield)

RI $n_D^{20°C}$: 1.4357

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.24 – 5.86 (m, 4H, 2x C<u>H</u>=C<u>H</u>), 5.25 – 4.98 (m, 1H, C<u>H</u>O), 4.46 – 4.08 (m, 2H, C<u>H$_2$</u>O), 3.26 – 3.14 (m, 2H, 2x C<u>H</u> norb), 3.12 – 2.87 (m, 4H, 2x C<u>H</u> norb, SC<u>H$_2$</u>CH), 2.77 – 2.63 (m, 2H, C<u>H$_2$</u>SCH$_2$ C$_6$), 2.60 – 2.50 (m, 2H, C<u>H</u>C=O), C<u>H$_2$</u> norb), 1.99 – 1.21 (m, 18H, 2x C<u>H$_2$</u> bridge, 5x C<u>H$_2$</u> C$_1$-C$_5$, 2x C<u>H$_2$</u> norb)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 175.99 – 174.17 (m, 2x <u>C</u>=O), 138.28 (s, <u>C</u>H=CH), 137.99 (s, CH=<u>C</u>H), 135.79 (s, <u>C</u>H=CH), 132.47 (s, CH=<u>C</u>H), 70.80-70.39 (m, <u>C</u>HO), 64.19 – 63.51 (m, CH<u>C</u>H$_2$O), 50.78 (s, CH$_2$ norb), 49.74 (s, <u>C</u>H$_2$ bridge), 45.82 – 45.70 (m, <u>C</u>H norb), 43.42 – 43.25 (m, <u>C</u>HC=O), 42.59 – 42.49 (m, <u>C</u>H norb), 32.64 (s, S<u>C</u>H$_2$CH), 32.41 (s, <u>C</u>H$_2$SCH$_2$), 30.18 (d, $^3J_{CP}$ = 17.0 Hz, PCH$_2$CH$_2$<u>C</u>H$_2$), 29.34 (s, <u>C</u>H$_2$CH$_2$CH$_2$S), 28.25 (s, <u>C</u>H$_2$CH$_2$S), 25.58 (s, $^1J_{CP}$ = 140.9 Hz, P<u>C</u>H$_2$, 22.08 (d, $^2J_{CP}$ = 5.2 Hz, PCH$_2$<u>C</u>H$_2$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 36.46

HR-MS (MeOH, ESI, m/z): calc. 512.60, found 512.62 [M]

1.5.1.2 Synthesis of ((allyloxy)methyl)phosphonic acid (1C-AE)

1C-AE was prepared from Et-6C-AE (1 eq., 1.1 g, 5 mmol)) with TMSBr (2.5 eq., 1.7 mL, 12.5 mmol) according to General Procedure D with 20 mL DCM and MeOH to afford the product in a yield of 0.75 g (99% of theory) as brown viscous liquid, which was used without further purification.

Yield: 0.75 g (99% theoretical yield)

RI $n_D^{20°C}$: 1.4773

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 9.78 (s, 2H, 2x O<u>H</u>), 5.97 – 5.78 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.41 – 5.21 (m, 2H, $CH_2CH=C\underline{H_2}$), 4.15 (d, J = 5.7 Hz, 2H, $C\underline{H_2}CH=CH_2$), 3.85 (d, J = 8.8 Hz, 2H, $PC\underline{H_2}O$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 133.19 (s, $OCH_2\underline{C}HCH_2$), 119.51 (s, $OCH_2CH\underline{C}H_2$), 74.44 (d, J = 12.5 Hz, $O\underline{C}H_2CHCH_2$), 63.81 (d, $^2J_{CP}$ = 167.9 Hz, $\underline{C}H_2P$ C_1)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 23.73

HR-MS (MeOH, ESI, m/z): calc. 152.09, found 152.07 [M]

1.5.2 *Synthesis of (6-(allyloxy)hexyl)phosphonic acid (6C-AE)*

1.5.2.1 Synthesis of (6-(allyloxy)hexyl)phosphonate (Et-6C-AE)

Et-6C-AE was prepared from 6C-OH (1 eq., 3.1 g, 13 mmol) with allyl bromide (1.5 eq., 1.7 mL, 19.5 mmol) and sodium hydride (1.9 eq., 0.6 g, 24.7 mmol) in 70 mL THF according to General Procedure B. After silica flash column chromatography (100% EE), 1.4 g (49% of theory) of the desired compound were isolated as colorless liquid.

Yield: 1.4 g (49% theoretical yield)

TLC (EE/MeOH 19:1) R_f = 0.47

RI $n_D^{20°C}$: 1.4461

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 5.98 – 5.81 (ddt, $^1J_{HH}$ = 17.3, $^2J_{HH}$ = 10.4, $^3J_{HH}$ = 5.6 Hz, 1H, C<u>H</u>=CH$_2$), 5.24 (dq, $^1J_{HH}$ = 17.2, $^2J_{HH}$ = 1.7 Hz, 1H, CH=C<u>H</u>$_2$), 5.15 (dq, $^1J_{HH}$ = 10.4, $^2J_{HH}$ = 1.4 Hz, 1H, CH=C<u>H</u>$_2$), 4.16 – 4.00 (m, 4H, 2x OC<u>H</u>$_2$CH$_3$), 3.94 (dt, $^1J_{HH}$ = 5.8, $^2J_{HH}$ = 1.4 Hz, 2H, OC<u>H</u>$_2$CH), 3.40 (t, $^2J_{HH}$ = 6.6 Hz, 2H, C<u>H</u>$_2$OCH$_2$CH), 1.77 – 1.48 (m, 6H, C<u>H</u>$_2$P C$_1$, C<u>H</u>$_2$CH$_2$O C$_5$, C<u>H</u>$_2$ C$_4$), 1.42 – 1.20 (m, 10H, 2x OCH$_2$C<u>H</u>$_3$, C<u>H</u>$_2$ C$_3$, C<u>H</u>$_2$CH$_2$P)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 135.17 (s, CH$_2$<u>C</u>H=CH$_2$), 116.83 (s, CH$_2$CH=<u>C</u>H$_2$), 71.92 (s, <u>C</u>H$_2$CH=CH$_2$), 70.37 (s, <u>C</u>H$_2$O), 61.49 (d, $^2J_{CP}$ = 6.6 Hz, O<u>C</u>H$_2$CH$_3$), 30.55 (d, $^3J_{CP}$ = 16.8 Hz, <u>C</u>H$_2$CH$_2$CH$_2$P), 29.63 (s, <u>C</u>H$_2$CH$_2$O C$_5$), 25.84 (s, $^4J_{CP}$ = 1.3 Hz, <u>C</u>H$_2$ C$_4$), 25.76 (d, $^1J_{CP}$ = 140.6 Hz, <u>C</u>H$_2$P C$_1$), 22.50 (d, $^2J_{CP}$ = 5.1 Hz, PCH$_2$<u>C</u>H$_2$), 16.62 (d, $^3J_{CP}$ = 6.0 Hz, OCH$_2$<u>C</u>H$_3$

^{31}P-NMR (Chloroform-*d*) δ (ppm): 32.55

HR-MS (MeOH, ESI, m/z): calc. 278.33, found 278.41 [M]

1.5.2.2 Synthesis of (6-(allyloxy)hexyl)phosphonic acid (6C-AE)

6C-AE was prepared from Et-6C-AE (1 eq., 1.4 g, 5 mmol) with TMSBr (2.5 eq., 1.7 mL, 12.5 mmol) according to General Procedure D with 20 mL DCM and MeOH to afford the product in a yield 0.95 g (99% of theory) as brown viscous liquid, which was used without further purification.

Yield: 0.95 g (99% theoretical yield)

RI $n_D^{20°C}$: 1.4775

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 9.03 – 8.47 (m, 2H, 2x O<u>H</u>), 5.91 (ddt, $^1J_{HH}$ = 17.2, $^2J_{HH}$ = 10.3, $^3J_{HH}$ = 5.7 Hz, 1H, C<u>H</u>=CH$_2$), 5.27 (dq, $^1J_{HH}$ = 17.2, $^2J_{HH}$ = 1.6 Hz, 1H, CH=C<u>H</u>$_2$), 5.18 (dq, $^1J_{HH}$ = 10.4, $^2J_{HH}$ = 1.4 Hz, 1H, CH=C<u>H</u>$_2$), 3.98 (dt, $^1J_{HH}$ = 5.7, $^2J_{HH}$ = 1.4 Hz, 2H, OC<u>H</u>$_2$CH), 3.45 (t, $^3J_{HH}$ = 6.6 Hz, 2H, C<u>H</u>$_2$OCH$_2$CH), 1.88 – 1.73 (m, 2H, PC<u>H</u>$_2$), 1.62 (m, 4H, C<u>H</u>$_2$CH$_2$O C$_5$, C<u>H</u>$_2$ C$_4$), 1.40 (m, 4H, PCH$_2$C<u>H</u>$_2$ C$_2$, PCH$_2$CH$_2$C<u>H</u>$_2$ C$_3$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 134.70 (s, CH$_2$<u>C</u>H=CH$_2$), 117.38 (s, CH$_2$CH=<u>C</u>H$_2$), 71.97 (s, <u>C</u>H$_2$CH=CH$_2$), 70.43 (s, <u>C</u>H$_2$O), 30.15 (d, $^3J_{CP}$ = 16.9 Hz, <u>C</u>H$_2$CH$_2$CH$_2$P), 29.35 (s, <u>C</u>H$_2$CH$_2$O C$_5$), 25.65 (s, <u>C</u>H$_2$ C$_4$), 25.53 (d, $^1J_{CP}$ = 141 Hz, <u>C</u>H$_2$P C$_1$), 21.96 (d, $^2J_{CP}$ = 5.1 Hz, PCH$_2$<u>C</u>H$_2$ C$_2$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 36.26

HR-MS (MeOH, ESI, m/z): calc. 222.22, found 222.20 [M]

1.5.3 *Synthesis of (6-((2,3-bis(allyloxy)propyl)thio)hexyl) phosphonic acid (6C-diAE)*

1.5.3.1 Synthesis of 6-((2,3-bis(allyloxy)propyl)thio)hexyl) phosphonate (Et-6C-diAE)

Et-6C-AE was prepared from 6C-diOH (1 eq., 3.3 g, 10 mmol) with allyl bromide (2.6 eq., 2.2 mL, 26 mmol) and sodium hydride (3.8 eq., 0.9 g, 38 mmol) according to General Procedure B in 120 mL THF. After silica flash column chromatography (EE:MeOH 9:1), 1.63 g (50% of theory) of the desired compound were isolated as colorless liquid.

Yield: 1.63 g (50% theoretical yield)

TLC (EE) R_f = 0.3

RI $n_D^{20°C}$: 1.4775

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 5.99 – 5.82 (m, 2H, C<u>H</u>=CH$_2$), 5.32 – 5.09 (m, 4H, CH=C<u>H$_2$</u>), 4.23 – 3.95 (m, 8H, OC<u>H$_2$</u>CH$_3$, OC<u>H$_2$</u>), 3.74 – 3.49 (m, 3H, C<u>H</u>O, C<u>H$_2$</u>O), 2.80 – 2.61 (m, 2H, alkyl-C<u>H$_2$</u>SCH$_2$), 2.59 – 2.47 (m, 2H, alkyl-CH$_2$SC<u>H$_2$</u>), 1.79 – 1.50 (m, 6H, PC<u>H$_2$</u>, PCH$_2$C<u>H$_2$</u>, C<u>H$_2$</u>CH$_2$CH$_2$S), 1.38 (m, 4H, PCH$_2$CH$_2$C<u>H$_2$</u>, CH$_2$CH$_2$S), 1.31 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, OCH$_2$C<u>H$_3$</u>)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 134.93 (s, 2x <u>C</u>H=CH$_2$), 117.00 (s, 2x CH=<u>C</u>H$_2$), 78.2 (s, <u>C</u>HO), 72.35 (s, <u>C</u>H$_2$O), 71.18 (d, $^{3}J_{CP}$ = 3.6 Hz, 2x O<u>C</u>H$_2$CH=CH$_2$), 61.42 (d, $^{3}J_{CP}$ = 6.5 Hz, O<u>C</u>H$_2$CH$_3$), 33.61 (s, CH$_2$S<u>C</u>H$_2$), 33.05 (s, alkyl-<u>C</u>H$_2$SCH$_2$), 30.22 (d, $^{3}J_{CP}$ = 16.8 Hz, PCH$_2$CH$_2$<u>C</u>H$_2$), 29.44 (s, <u>C</u>H$_2$CH$_2$CH$_2$S), 28.33 (s, <u>C</u>H$_2$CH$_2$S), 25.67 (d, $^{1}J_{CP}$ = 140.6 Hz, P<u>C</u>H$_2$), 22.36 (d, $^{2}J_{CP}$ = 5.2 Hz, PCH$_2$<u>C</u>H$_2$), 16.45 (d, $^{3}J_{CP}$ = 6.0 Hz, OCH$_2$<u>C</u>H$_3$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 32.40

HR-MS (MeOH, ESI, m/z): calc. 408.53, found 408.56 [M]

1.5.3.2 Synthesis of (6-((2,3-bis(allyloxy)propyl)thio)hexyl) phosphonic acid (6C-diAE)

6C-diAE was prepared from Et-6C-diAE (1 eq., 0.8 g, 1.9 mmol) with TMSBr (2.5 eq., 0.6 mL, 4.75 mmol) according to General Procedure D with 15 mL DCM and MeOH to afford the product in a yield 0.5 g (75% of theory) as brown viscous liquid, which was used without further purification.

Yield: 0.5 g (75% theoretical yield)

RI $n_D^{20°C}$: 1.5084

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.02 – 5.80 (m, 2H, C<u>H</u>=CH$_2$), 5.32 – 5.14 (m, 4H, CH=C<u>H$_2$</u>), 4.19 – 3.98 (m, 4H, OC<u>H$_2$</u>), 3.75 – 3.52 (m, 3H, C<u>H</u>O, C<u>H$_2$</u>O), 2.77 – 2.62

(m, 2H, alkyl-$CH_2SC\underline{H_2}$), 2.60 – 2.50 (m, 2H, alkyl-$C\underline{H_2}SCH_2$), 1.87 – 1.70 (m, 2H, $PC\underline{H_2}$), 1.70 – 1.49 (m, 4H, $PCH_2C\underline{H_2}$, $C\underline{H_2}CH_2CH_2S$), 1.45 – 1.33 (m, 4H, $PCH_2CH_2C\underline{H_2}$, CH_2CH_2S)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 135.12 (s, $\underline{C}H=CH_2$), 134.74 (s, $\underline{C}H=CH_2$), 117.20 (s, 2x $CH=\underline{C}H_2$), 78.10 (s, $\underline{C}HO$), 72.51 (s, $\underline{C}H_2O$), 71.30 (d, $^3J_{CP}$ = 3.7 Hz, 2x $O\underline{C}H_2CH=CH_2$), 33.67 (s, $CH_2S\underline{C}H_2$), 33.13 (s, alkyl-$\underline{C}H_2SCH_2$), 30.22 (d, $^3J_{CP}$ = 17.1 Hz, $PCH_2CH_2\underline{C}H_2$), 29.45 (s, $\underline{C}H_2CH_2CH_2S$), 28.27 (s, $\underline{C}H_2CH_2S$), 25.32 (d, $^1J_{CP}$ = 141 Hz, $P\underline{C}H_2$), 21.95 (d, $^2J_{CP}$ = 5.5 Hz, $PCH_2\underline{C}H_2$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 37.32

HR-MS (MeOH, ESI, m/z): calc. 352.43, found 352.47 [M]

1.6 Synthesis of the allyl carbonate (AC)-primers

1.6.1 *Synthesis of ((((allyloxy)carbonyl)oxy)methyl)phosphonic acid (1C-AC)*

1.6.1.1 Synthesis of ((((allyloxy)carbonyl)oxy)methyl)phosphonate (Et-1C-AC)

The synthesis of Et-1C-AC was conducted according to General Procedure C from 1C-OH (1 eq., 2.2 mL, 15 mmol) with allyl chloroformate (1.3 eq., 2.1 mL, 19.5 mmol) and pyridine (4 eq., 4.8 mL, 60 mmol) in 40 mL THF. After precipitating the pyridinium salts from cold ethyl acetate and evaporation of the solvent, 2.9 g (77% of theory) of the desired compound were isolated as a colorless liquid.

Yield: 2.9 g (77% theoretical yield)

TLC (EE) R_f = 0.5

RI $n_D^{20°C}$: 1.4460

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 6.00 – 5.85 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.43 – 5.22 (m, 2H, $CH_2CH=C\underline{H_2}$), 4.69 – 4.61 (m, 2H, $C\underline{H_2}CH=CH_2$), 4.43 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, $PC\underline{H_2}O$), 4.25 – 4.10 (m, 4H, $OC\underline{H_2}CH_3$), 1.35 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, $OCH_2C\underline{H_3}$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 154.71 (d, $^{3}J_{CP}$ = 9.5 Hz, OC=OO), 131.26 (s, $OCH_2\underline{C}HCH_2$), 119.42 (s, $OCH_2CH\underline{C}H_2$), 69.31 (s, $O\underline{C}H_2CHCH_2$), 63.07 (d, $^{2}J_{CP}$ = 6.5 Hz, $O\underline{C}H_2CH_3$), 60.32 (d, $^{1}J_{CP}$ = 168.5 Hz, $\underline{C}H_2P$ C_1), 16.49 (d, $^{3}J_{CP}$ = 6.0 Hz, $OCH_2\underline{C}H_3$)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 17.74

HR-MS (MeOH, ESI, m/z): calc. 252.20, found 252.23 [M]

1.6.1.2 Synthesis of ((((allyloxy)carbonyl)oxy)methyl)phosphonic acid (1C-AC)

1C-AC was prepared from Et-1C-AC (1 eq., 2.5 g, 10 mmol) with TMSBr (2.5 eq., 3.3 mL, 25 mmol) according to General Procedure D with 20 mL DCM and MeOH to afford the product in a yield of 1.76 g (99% of theory) as a colorless liquid, which was used without further purification.

Yield: 1.76 g (99% theoretical yield)

RI $n_D^{20°C}$: 1.4566

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 9.52 (s, 2H, $O\underline{H}$), 6.00 – 5.81 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.43 – 5.22 (m, 2H, $CH_2CH=C\underline{H_2}$), 4.65 (d, $^{3}J_{HH}$ = 5.7 Hz, 2H, $C\underline{H_2}CH=CH_2$), 4.46 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, $PC\underline{H_2}O$)

^{13}C NMR (101 MHz, Chloroform-d) δ (ppm): 154.87 (d, $^{3}J_{CP}$ = 9.5 Hz, O<u>C</u>=OO), 131.19 (s, $OCH_2\underline{C}HCH_2$), 119.58 (s, $OCH_2CH\underline{C}H_2$), 69.64 (s, $O\underline{C}H_2CHCH_2$), 61.19 (d, $^{1}J_{CP}$ = 169.5 Hz, <u>C</u>H_2P C_1)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 19.11

HR-MS (MeOH, ESI, m/z): calc. 196.09, found 196.06 [M]

1.6.2 *Synthesis of (6-(((allyloxy)carbonyl)oxy)hexyl)phosphonic acid (6C-AC)*

1.6.2.1 Synthesis of (6-(((allyloxy)carbonyl)oxy)hexyl)phosphonate (Et-6C-AC)

The synthesis of Et-6C-AC was conducted according to General Procedure C from 6C-OH (1 eq., 2.4 g, 10 mmol) with allyl chloroformate (1.5 eq., 1.6 mL, 15 mmol) and pyridine (4 eq., 3.2 mL, 40 mmol) in 70 mL THF. After precipitating the pyridinium salts from cold ethyl acetate and evaporation of the solvent, 2.2 g (68% of theory) of the desired compound were isolated as a slightly yellow, viscous liquid.

Yield: 2.2 g (68% theoretical yield)

TLC (EE/MeOH 9:1) R_f = 0.51

RI $n_D^{20°C}$: 1.4463

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 5.98 – 5.82 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.39 – 5.20 (m, 2H, $CH_2CH=C\underline{H_2}$), 4.64 – 4.53 (m, 2H, $C\underline{H_2}CH=CH_2$), 4.15 – 3.94 (m, 6H, CH_2O C_6, $OC\underline{H_2}CH_3$), 1.83 – 1.47 (m, 4H, $C\underline{H_2}P$ C_1, CH_2CH_2O C_5), 1.44 – 1.19 (m, 12H, $C\underline{H_2}$ C_2-C_4 , $OCH_2C\underline{H_3}$)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 155.15 (s, OC=OO), 131.67 (s, $OCH_2\underline{C}HCH_2$), 118.93 (s, $OCH_2CH\underline{C}H_2$), 68.41 (s, $CH_2\underline{C}H_2O$ C_6), 68.05 (s, $O\underline{C}H_2CHCH_2$),

61.49 (d, $^{2}J_{CP}$ = 6.4 Hz, O<u>C</u>H_2CH_3), 32.54 (s, <u>C</u>H_2CH_2O C_5), 30.21 (d, $^{3}J_{CP}$ = 16.8 Hz, <u>C</u>$H_2CH_2CH_2P$ C_3), 25.68 (d, $^{1}J_{CP}$ = 140.7 Hz, <u>C</u>H_2P C_1), 25.32 (d, $^{4}J_{CP}$ = 1.2 Hz, <u>C</u>H_2 C_4), 22.40 (d, $^{2}J_{CP}$ = 5.1 Hz, <u>C</u>H_2CH_2P C_2), 16.55 (d, $^{3}J_{CP}$ = 6.0 Hz, OCH_2<u>C</u>H_3)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 32.23

HR-MS (MeOH, ESI, m/z): calc. 322.34, found 322.36 [M]

1.6.2.2 Synthesis of (6-(((allyloxy)carbonyl)oxy)hexyl)phosphonic acid (6C-AC)

6C-AC was prepared from Et-6C-AC (1 eq., 2.1 g, 6.5 mmol) with TMSBr (2.5 eq., 2.2 mL, 16.25 mmol) according to General Procedure D with 20 mL DCM and MeOH to afford the product in a yield of 1.5 g (87% of theory) as a brown viscous liquid without further purification.

Yield: 1.5 g (87% theoretical yield)

RI $n_D^{20°C}$: 1.4775

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.02 – 5.84 (m, 1H, CH_2<u>C</u>H=CH_2), 5.40 – 5.21 (m, 2H, CH_2CH=C<u>H</u>$_2$), 4.67 – 4.53 (m, 2H, C<u>H</u>$_2CH$=CH_2), 4.13 (t, J = 6.6 Hz, 2H, C<u>H</u>$_2$O), 1.94 – 1.56 (m, 6H, C<u>H</u>$_2$P C_1, C<u>H</u>$_2CH_2O$ C_5, C<u>H</u>$_2$ C_4), 1.49 – 1.35 (m, 4H, C<u>H</u>$_2CH_2P$ C_2, C<u>H</u>$_2$ C_3)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 155.13 (s, O<u>C</u>=OO), 131.61 (s, OCH_2<u>C</u>HCH_2), 118.92 (s, OCH_2CH<u>C</u>H_2), 68.40 (s, <u>C</u>H_2O C_6), 68.01 (s, O<u>C</u>H_2CHCH_2), 30.02 (d, $^{3}J_{CP}$ = 17.0 Hz, <u>C</u>$H_2CH_2CH_2P$ C_3), 28.52 (s, <u>C</u>H_2CH_2O C_5), 25.45 (d, $^{1}J_{CP}$ = 141 Hz, <u>C</u>H_2P C_1), 25.31 (s, <u>C</u>H_2 C_4), 21.93 (d, $^{2}J_{CP}$ = 5.0 Hz, PCH_2<u>C</u>H_2 C_2)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 36.31

HR-MS (MeOH, ESI, m/z): calc. 238.26, found 238.31 [M]

1.6.3 *Synthesis of (6-((2,3-bis(((allyloxy)carbonyl)oxy)propyl)thio)hexyl) phosphonic acid (6C-diAC)*

1.6.3.1 Synthesis of (6-((2,3-bis(((allyloxy)carbonyl)oxy)propyl)thio)hexyl) phosphonate (Et-6C-diAC)

The synthesis of Et-6C-diAC was conducted according to General Procedure C from 6C-diOH (1 eq., 3.3 g, 10 mmol) with allyl chloroformate (4 eq., 4.3 mL, 40 mmol) and pyridine (4 eq., 4.3 mL, 40 mmol) in 120 mL THF. After silica flash column chromatography (EE), 3.38 g (68% of theory) of the desired compound were isolated as brown viscous liquid.

Yield: 3.38 g (68% theoretical yield)

RI $n_D^{20°C}$: 1.4774

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 6.00 – 5.85 (m, 2H, 2H, 2x $CH_2C\underline{H}=CH_2$), 5.41 – 5.22 (m, 4H, 2x $CH_2CH=C\underline{H_2}$), 5.01 – 4.92 (m, 1H, C<u>H</u>O), 4.67 – 4.58 (m, 4H, $C\underline{H_2}CH=CH_2$), 4.48 (dd, J = 11.9, 3.2 Hz, 1H, $C\underline{H_2}OC=O$), 4.30 (dd, J = 11.9, 5.9 Hz, 1H, $C\underline{H_2}OC=O$), 4.18 – 3.97 (m, 4H, $OC\underline{H_2}CH_3$), 2.83 – 2.69 (m, 2H, $SC\underline{H_2}CH$), 2.60 – 2.52 (m, 2H, $CH_2C\underline{H_2}S$ C_6), 1.79 – 1.51 (m, 6H, $PC\underline{H_2}$ C_1, $PCH_2C\underline{H_2}$ C_2, $C\underline{H_2}CH_2S$ C_5), 1.38 (m, 4H, $C\underline{H_2}$ C_3-C_4), 1.31 (t, J = 7.1 Hz, 6H, $OCH_2C\underline{H_3}$)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 154.77 (s, O<u>C</u>=OO), 154.42 (s, O<u>C</u>=OO), 131.44 (s, $OCH_2\underline{C}HCH_2$), 119.29 (s, $OCH_2CH\underline{C}H_2$), 119.21 (s, $OCH_2CH\underline{C}H_2$), 74.84 (s, <u>C</u>HO), 68.90 (d, J = 3.1 Hz, 2x $O\underline{C}H_2CHCH_2$), 66.97 (s, $\underline{C}H_2O$), 61.53 (d, $^2J_{CP}$ = 6.5 Hz, $O\underline{C}H_2CH_3$), 32.80 (s, $S\underline{C}H_2CH$), 31.95 (s, $CH_2\underline{C}H_2S$), 30.27 (d, $^3J_{CP}$ = 16.7 Hz, $\underline{C}H_2CH_2CH_2P$ C_3), 29.33 (s, $\underline{C}H_2CH_2S$), 28.34 (d, $^4J_{CP}$ = 1.3 Hz, $\underline{C}H_2$ C_4), 25.77 (d, $^1J_{CP}$ = 140.6 Hz, $P\underline{C}H_2$ C_1), 22.47 (d, $^2J_{CP}$ = 5.2 Hz, $PCH_2\underline{C}H_2$ C_2), 16.61 (d, $^3J_{CP}$ = 6.1 Hz, $OCH_2\underline{C}H_3$)

^{31}P-NMR (162 MHz, Chloroform-*d*) δ (ppm): 32.33

HR-MS (MeOH, ESI, m/z): calc. 496.55, found 496.49 [M]

1.6.3.2 Synthesis of (6-((2,3-bis(((allyloxy)carbonyl)oxy)propyl)thio)hexyl) phosphonic acid (6C-diAC)

6C-diAC was prepared from Et-6C-diAC (1 eq., 1.9 g, 3.8 mmol) with TMSBr (2.5 eq., 1.3 mL, 9.5 mmol) according to General Procedure D with 15 mL DCM and MeOH to afford the product in a yield of 1.61 g (87% of theory) as a brown viscous liquid without further purification.

Yield: 1.61 g (99% theoretical yield)

RI $n_D^{20°C}$: 1.4877

^{1}H-NMR (400 MHz, Chloroform-d) δ (ppm): 7.90 (s, 2H, 2x $CH_2C\underline{H}=CH_2$), 6.01 – 5.84 (m, 2H), 5.43 – 5.23 (m, 4H, 2x $CH_2CH=C\underline{H_2}$), 5.04 – 4.92 (m, 1H, C<u>H</u>O), 4.68 – 4.58 (m, 4H, 2x $C\underline{H_2}CH=CH_2$), 4.48 (dd, J_{HH} = 11.9, 3.1 Hz, 1H, $C\underline{H_2}OC=O$), 4.31 (dd, J_{HH} = 11.9, 6.0 Hz, 1H, $C\underline{H_2}OC=O$), 2.80 – 2.72 (m, 2H, $SC\underline{H_2}CH$), 2.62 – 2.52 (m, 2H, $CH_2C\underline{H_2}S$ C_6), 1.90 – 1.73 (m, 2H, $PC\underline{H_2}$ C_1), 1.70 – 1.53 (m, 4H, $PCH_2C\underline{H_2}$ C_2, $C\underline{H_2}CH_2S$ C_5), 1.47 – 1.35 (m, 4H, $C\underline{H_2}$ C_3-C_4)

^{13}C-NMR (101 MHz, Chloroform-d) δ (ppm): 154.81 (s, O<u>C</u>=OO), 154.49 (s, O<u>C</u>=OO), 131.44 (s, $OCH_2\underline{C}HCH_2$), 119.29 (s, $OCH_2CH\underline{C}H_2$), 119.21 (s, $OCH_2CH\underline{C}H_2$), 74.84 (s, <u>C</u>HO), 68.97 (d, J = 3.1 Hz, 2x O<u>C</u>H_2CHCH_2), 67.03 (s, <u>C</u>H_2O), 32.72 (s, S<u>C</u>H_2CH), 31.94 (s, $CH_2\underline{C}H_2S$), 29.90 27 (d, $^3J_{CP}$ = 17.1 Hz, <u>C</u>$H_2CH_2CH_2P$ C_3), 29.21 (s, <u>C</u>H_2CH_2S), 28.15 (d, $^4J_{CP}$ = 1.3 Hz, <u>C</u>H_2 C_4), 25.32 (d, $^1J_{CP}$ = 140.4 Hz, P<u>C</u>H_2 C_1), 21.88 (d, $^2J_{CP}$ = 5.1 Hz, $PCH_2\underline{C}H_2$ C_2)

^{31}P-NMR (Chloroform-*d*) δ (ppm): 37.05

HR-MS (MeOH, ESI, m/z): calc. 440.44, found 440.41 [M]

2 pH-Measurements of Primer Solutions

According to Catel et al.[6] The pH of the primer molecules was determined in 20 wt% solutions in ethanol/water (1:1 w/w) with a calibrated pH electrode and measuring device.

Table S1. Measured pH values of synthesized primer molecules compared to the commercial dental primers 10-methacryloyloxydecyldihydrogenphosphate (MDP) and 2-(2-(ethoxycarbonyl)allyl)oxy)ethyl)phosphonic acid (MA 154) in ethanol/water at 20 °C.

primer	pH [-]
MA154	2.10
MDP	1.60
1C-NB	1.90
6C-NB	1.76
6C-diNB	1.78
1C-AE	1.86
6C-AE	1.72
6C-diAE	1.71
1C-AC	1.82
6C-AC	1.80
6C-diAC	1.75

3 Shear Bond Strength Measurements

3.1 Setup and Procedure

To determine the bond strength of adhesive formulations, each formulation was applied to the substrate using a cylindrical PP mold and clamping tool from Ultradent Products (**Figure S1**) to prevent the sample from exhibiting any stress prior to the tests, which could lead to

falsified results. The SBS measurements of the received samples were performed with a force gauge digital testing device with V-shaped test bar (**Figure S2**).

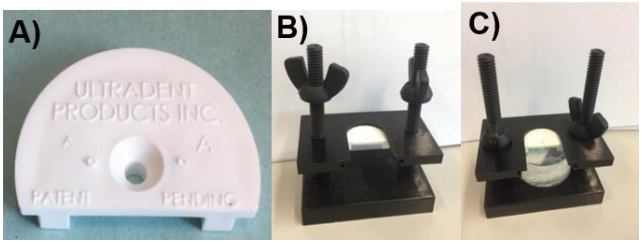


Figure S1. Shear bond strength setup. A) Cylindrical PP mold for adhesive application. B) Clamping tool with PP mold to prevent horizontal stress after removal. C) Clamping tool with PP mold and embedded HAP.

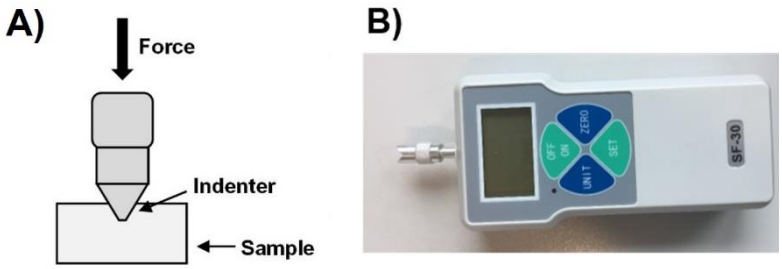


Figure S2. A) Shear bond strength measurement setup.[120] B) Digital force measuring device (Force Gauge SF-30).

3.2 Substrate Preparation:

HAP-Substrates. The HAP pellets for the HAP-substrates were prepared by cold-isostatic pressing of HAP powder kindly provided by Lithoz GmBH at 400 kN for 1 min and a subsequent sintering step in a Carbolite oven with a defined temperature program (2 K/min at 500 °C, 2 K/min at 1250 °C, 2 h waiting time, cooling down 3 K/min). The obtained pallets were afterwards embedded in an epoxy resin and ground with a 400-grit SiC paper.

Ti-Substrates. To obtain Ti-substrates, titanium dioxide (TiO_2) was laser sintered into pallets, embedded in a epoxy resin and grinded with SiC paper.

Bone-Substrates. Parts of bovine hooves 2nd Phallanx were cut via a bandsaw into 1 cm thick slices and afterwards in smaller pieces and were frozen in PBS buffer at -80°C. The bone pieces were unfrozen prior to SBS-measurements, embedded in epoxy resin and grinded with SiC paper.

After preparation, all substrates were stored in a desiccator prior to usage.

3.3 Shear bond strength measurements

3.3.1 *Optimization of the thiol:ene ratio for the two-step procedure*

To find the most appropriate thiol:ene ratio for the two-step procedure, three primer formulations were prepared with varying thiol:ene ratios. An equimolar ratio of TAI and TMPMP was used as matrix formulation with the photoinitiator Ivocerin®. The flexible thiol TMPMP was used in these preliminary studies. The best results were obtained with formulation A2, which contained 11 mol% of the primer 6C-diNB (equal to 15 wt% primer) and resulted in a thiol:ene ratio of 2.2:1.

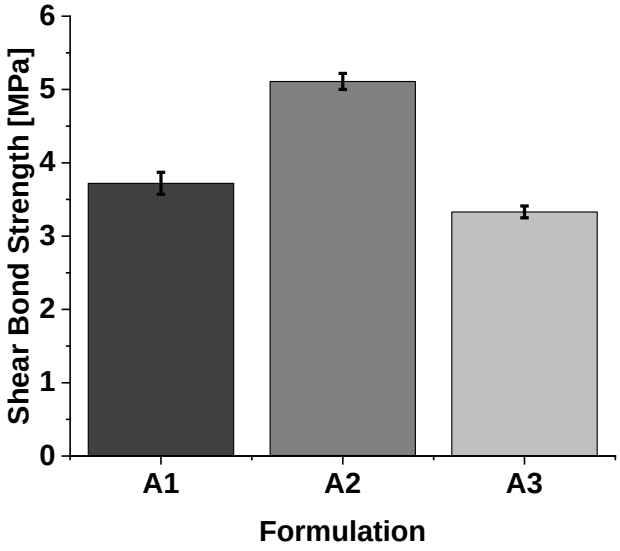


Figure S3. SBS measurements of primer formulations with varying thiol:ene ratios and the primer 6C-diNB.

Table S2. Components of the formulations A1-A3 with the primer 6C-diNB and the obtained SBS thereof. All formulations contained 1 wt% of Ivocerin® as photoinitiator and 0.02 wt% of pyrogallol as stabilizer.

Form.	**Primer [mol%]**	**TAI [mol%]**	**TMPMP [mol%]**	**Ratio thiol:ene**	**SBS [MPa]**	**SD [MPa]**
A1	11	29	59	**1.6:1**	3.72	0.15
A2	11	22	66	**2.2:1**	5.11	0.11
A3	11	16.5	71.5	**3:1**	3.33	0.08

3.3.2 *Variation of thiols*

The obtained shear bond strengths of the tested formulations depend on the rigidity of the used thiol compound. Thus, a study was performed with three different thiols to reveal the best-performing formulation. As in the study mentioned above 15 wt% of the primer were used in

this study. As the thiol di-PETMP bears six thiol groups, the weight proportions were adjusted. The best results were obtained with the rigid thiol TEMPIC.

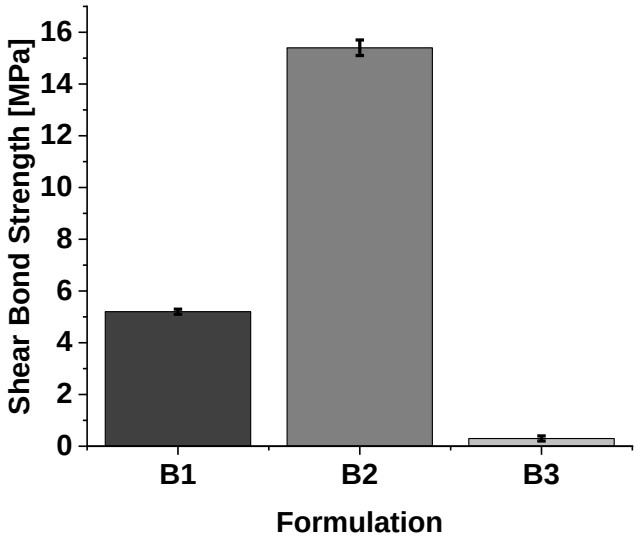


Figure S4. SBS measurements of one-step formulations with different thiols and the primer 6C-diNB (15 wt%).

Table S3: Components of the formulations B1-B3 with different thiols, 15 wt% of the primer 6C- diNB, and the obtained SBS thereof. All formulations contained 1 wt% of Ivocerin® as photoinitiator and 0.02 wt% of pyrogallol as stabilizer.

Form.	**TAI [wt%]**	**Thiol**	**Thiol [wt%]**	**Ratio thiol:ene**	**SBS [MPa]**	**SD [MPa]**
B1	27	**TMPMP**	57	**1:0.8**	5.2	0.1
B2	27	**TEMPIC**	57	**1:1**	15.4	0.3
B3	56	**di-PETMP**	28	**1:6.3**	0.3	0.1

3.3.3 *Variations of the primer content*

As TEMPIC was shown to be the most rigid thiol in the previous study, investigations toward the optimal primer content followed. The formulations C1-C3 contained different amounts of the primer, which was added to the equimolar formulation of TAI and TEMPIC. The best results were obtained with 15 wt% primer, which results in a one-step formulation with a final thiol:ene ratio of 1:1.2 (including the primer).

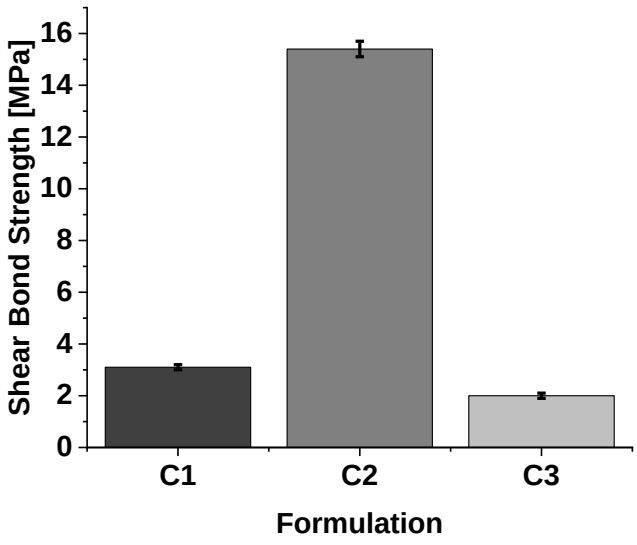


Figure S5. SBS measurements of one-step formulations with varying amounts of the primer 6C-diNB.

Table S4: Components of the formulations C1-C3 with varying amounts of the primer 6C-diNB and the obtained SBS thereof. All formulations contained 1 wt% of Ivocerin® as photoinitiator and 0.02 wt% of pyrogallol as stabilizer.

Form.	Primer [wt%]	TAI [wt%]	TEMPIC [wt%]	Ivocerin® [wt%]	SBS [MPa]	SD [MPa]
C1	**10**	28.5	60.5	1	3.1	0.1
C2	**15**	27	57	1	15.4	0.3
C3	**20**	25.5	53.5	1	2.0	0.1

3.3.4 *Detailed results of the SBS measurements of systems containing different primer molecules on HAP and TiO_2*

Table S5. SBS measurements of adhesive systems containing the different primer molecules in a 2-step system containing TAI as monomer and TEMPIC as thiol on HAP and TiO_2.

	Primer	HAP		TiO_2	
		SBS [MPa]	SD [MPa]	SBS [MPa]	SD [MPa]
2-step-procedure	**REF**	1.8	0.0	3.4	0.2
	1C-NB	3.0	0.1	2.8	0.1
	1C-AE	3.1	0.1	1.7	0.2
	1C-AC	2.7	0.2	1.8	0.0
	6C-NB	3.8	0.1	2.7	0.1
	6C-AE	3.5	0.1	2.3	0.1
	6C-AC	3.1	0.1	2.2	0.1
	6C-diNB	11.0	0.6	7.9	0.1
	6C-diAE	5.2	0.1	2.3	0.1
	6C-diAC	4.1	0.1	2.4	0.1

Table S6. SBS measurements of adhesive systems containing the different primer molecules in a 1-step system containing TAI as monomer and TEMPIC as thiol on HAP, TiO_2 and bovine bone. *was not determined.

	Primer	HAP		TiO_2		bovine bone	
		SBS [MPa]	SD [MPa]	SBS [MPa]	SD [MPa]	SBS [MPa]	SD [MPa]
1-step-procedure	**REF**	8.1	0.1	4.1	0.2	2.4	0.5
	1C-NB	0.0	0.0	0.0	0.0	*	*
	1C-AE	1.6	0.2	1.8	0.2	*	*
	1C-AC	1.8	0.2	1.8	0.1	*	*
	6C-NB	8.0	0.2	3.6	0.1	*	*
	6C-AE	3.6	0.2	2.8	0.2	*	*
	6C-AC	3.6	0.2	2.7	0.2	*	*
	6C-diNB	15.4	0.3	8.0	0.4	9.6	0.4
	6C-diAE	3.5	0.2	2.2	0.2		
	6C-diAC	3.5	0.1	2.1	0.2	*	*

3.3.5 *Influence of surface conditions on shear bond strength*

In order to more accurately mimic the conditions during surgical procedures, SBS measurements were also performed on wetted bone substrates. For this, the substrates were sprayed three times with distilled water and then the photopolymerization step was performed, which is referred to as “wet” samples. Additionally, other samples were tested, which were wetted as described above but were additionally treated with an air-drying step for 5 s prior to application of the photopolymerizable formulation, which is surgically-realizable. These samples are referred to as “moist” samples. The results showed that upon air-drying no

significant differences in SBS were observed. Although wet samples exhibited a slight decrease in SBS, these values on bone are still sufficiently high for the application as bone adhesives.

Table S7. Components of the formulations for the measurements conducted on dry, moist and wet bone substrates and the SBS thereof. All formulations contained 0.02 wt% of pyrogallol as a stabilizer.

Form.	Primer [wt%]	TAI [wt%]	TEMPIC [wt%]	Ivocerin® [wt%]	SBS [MPa]	SD [MPa]
Dry	**15**	27	57	1	9.6	0.4
Moist s	**15**	27	57	1	9.6	0.4
Wet	**15**	27	57	1	4.6	1.6

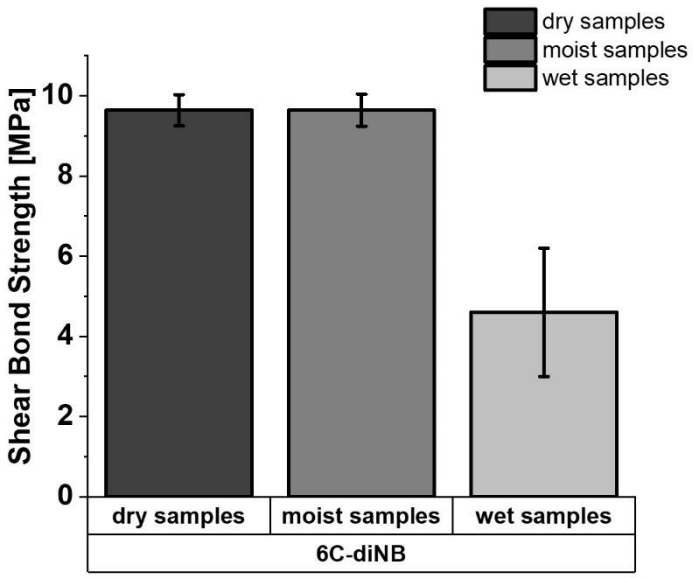


Figure S6. SBS measurements of one-step formulations on bone substrates with different surface conditions.

3.3.6 *Influence of degradable monomers on shear bond strength*

VDB was synthesized as described by Baudis *et al.*[10] To evaluate the influence of degradable monomers on the SBS, new measurements were performed with the novel hydrolytically degradable boronic ester VDB developed by our group. In order to still maintain a rigid material, TAI was only partially replaced by the new monomer VDB.

The new formulation contained 50 mol% TAI and 50 mol% VDB as the ene-monomers and TEMPIC as the thiol compound, resulting in a thiol:ene ratio of 1:1. The SBS measurements were performed immediately after photopolymerization on the dry surface, which is referred to as "dry" sample. Additionally, a new formulation with the same composition was prepared and SBS measurements were performed after storage in m-SBF for 24 h at 37 °C. This measurement is referred to as "stored in SBF".

Table S8. Components of the formulation containing 50 mol% TAI and 50 mol% VDB and the obtained SBS thereof. All formulations contained 1 wt% of Ivocerin® as photoinitiator and 0.02 wt% of pyrogallol as stabilizer. SBS of dry samples ([a]) and samples stored in SBF ([b]).

Form.	**Primer [wt%]**	**TAI [wt%]**	**VDB [wt%]**	**TEMPIC [wt%]**	**Ratio thiol:ene**	**SBS [MPa]**	**SD [MPa]**
50% VDB	15	15	16	52	**1:1**	12.1[a]	0.7
						3.4[b]	0.5

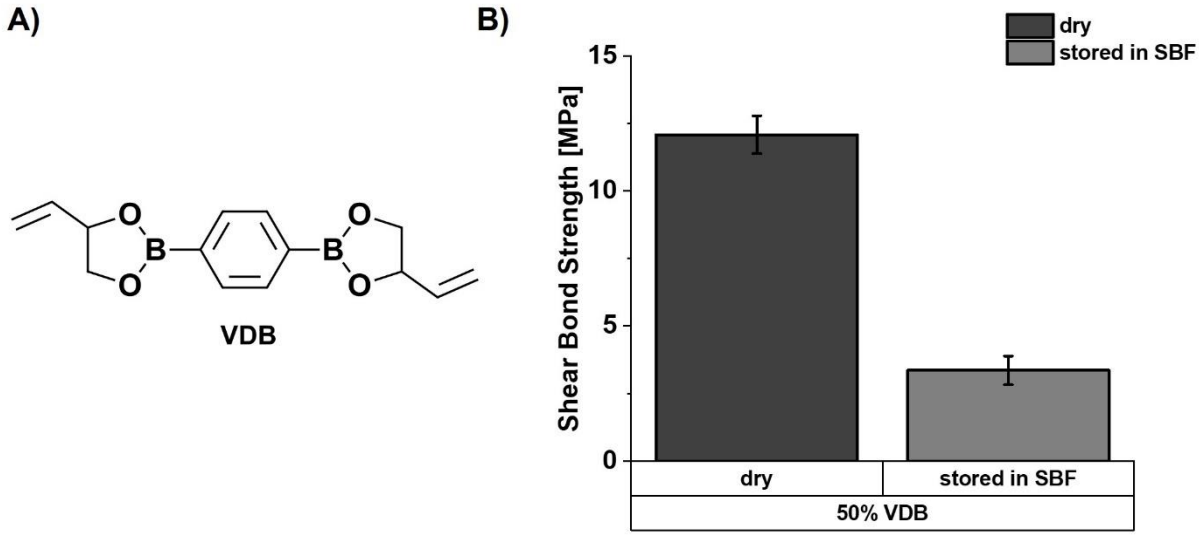


Figure S7. A) Chemical structure of the hydrolytically degradable boronic ester VDB and B) SBS measurements of the formulation containing 50 mol% VDB as ene monomer.

4 Indentation Tests

Table S9. Detailed results of indentation tests on rat calvariae.

Test	Indentation Force [N mm^{-2}]
Adhesive on cranium-calvaria gap	19.3
	18.9
Cranium covered with adhesive	8.3
	7.4

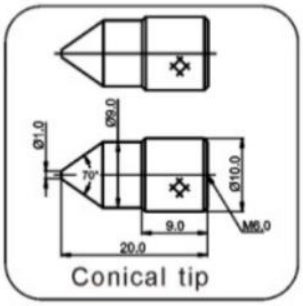


Figure S8. Dimensions of the conical tip of the digital force measuring device (Force Gauge SF-30) used for indentation tests.

5 Cytotoxicity Tests

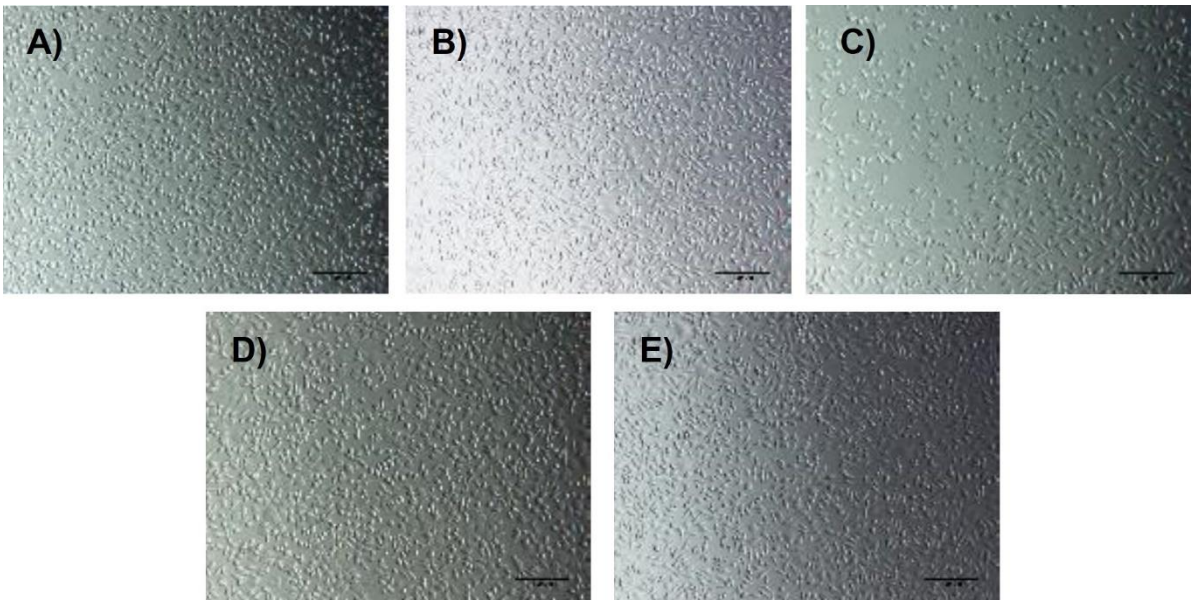


Figure S9. Qualitative assessment of cell morphology according to ISO 10993-5 under the microscope after 24 h of incubation with the respective substances A) 5.0 mM TAI, B) 2.5 mM TEMPIC, and C) 5.0 mM 6C-diNB compared to the control cells treated with D) PBS buffer or E) 1% DMSO.

Table S10. Cell viability at the different concentrations of the test substances measured by fluorescence. Values represent the mean of three measurements.

Substance	**Cell viability 10 mM [%]**	**Cell viability 7.5 mM [%]**	**Cell viability 5 mM [%]**	**Cell viability 2.5 mM [%]**
TAI	1.0	44.0	**88.7**	**108.9**
TEMPIC	21.4	23.9	32.3	46.2
6C-diNB	8.1	67.3	**85.7**	**112.1**

6 Real-Time Near-Infrared (RT-NIR) Photorheology[11]

RT-NIR-photorheology experiments were performed on an Anton Paar MCR 302 WESP rheometer with a P-PTD 200 heating chamber, a peltier glass plate, and a PP25 measuring system. To determine the conversion over time, a Bruker Vertex 80 FTIR spectrometer was coupled with the rheometer. 170 µL of monomer formulation were placed at the center of the glass plate which was covered with polyethylene tape (TESA 4668 MDPE) and the measurements were performed at 25 °C and a constant gap of 200 µm. The samples were sheared with a strain of 1% and a frequency of 1 Hz. UV light was used to cure the formulation, which was emitted via an Exfo OmniCureTM 200 device with a broadband Hg lamp (300 s irradiation, 400-500 nm, light intensity 10 mW cm^{-2} on the surface of the glass plate, measured with an Ocean Optics USB 2000+ spectrometer). Irradiation was induced 65 s after the start of each measurement and the measurements were performed in triplicates. The double bond conversion (DBC) was determined by recording a set of single spectra (time interval ~0.26 s) with an OPUS 7.0 software and by integrating the respective double bond band (6080-6240 cm^{-1}). Further important parameters like t_{gel}, t_{95} and $G'_{final,}$ were obtained by evaluation of the rheological properties with the Software Anton Paar Rheo Compass 1.24.

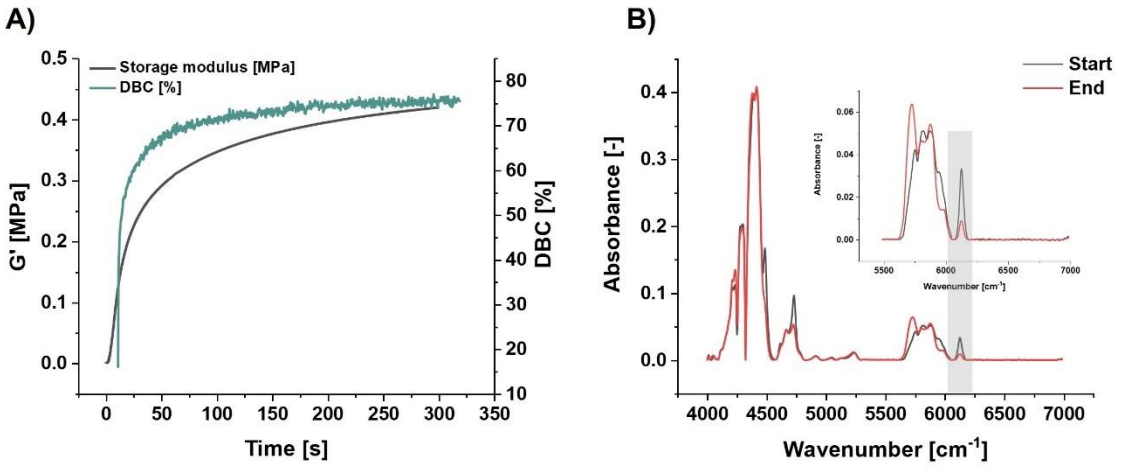


Figure S10: Results obtained from the photorheogical analysis of the primer formulation: A) Storage modulus [G'] and double bond conversion [DBC] over time; B) NIR-spectra before (start) and after (end) the photorheology measurement, marked region used for the calculation of DBC.

Table S11: Results obtained from the photorheogical analysis of the primer formulation. t_{gel}: time until gel-point is reached; DBC_{gel}: double bond conversion at gel point; t_{95}: time when 95% of the final storage modulus is reached; DBC_{final}: final double bond conversion and G'_{final}: final storage modulus

t_{gel} [s]	DBC_{gel} [%]	t_{95} [%]	DBC_{final} [%]	G'_{final} [MPa]
7 ± 1	54± 2	209 ± 2	74 ± 1	0.414 ± 0.004

7 References

1. P. Antoni, M. J. Robb, L. Campos, M. Montanez, A. Hult, E. Malmström, M. Malkoch and C. J. Hawker, *Macromolecules*, 2010, **43**, 6625-6631.
2. V. Granskog, S. García-Gallego, J. von Kieseritzky, J. Rosendahl, P. Stenlund, Y. Zhang, S. Petronis, B. Lyvén, M. Arner, J. Håkansson and M. Malkoch, *Advanced Functional Materials*, 2018, **28**, 1800372.
3. V. Besse, L. L. Pluart, W. D. Cook, T.-N. Pham and P. J. J. J. o. P. S. P. A. Madec, 2013, **51**, 149-157.
4. M. A. Derbanne, V. Besse, S. L. Goff, M. J. Sadoun, T.-N. J. P. D. Pham and Stability, 2013, **98**, 1688-1698.
5. N. Pelaprat, G. Rigal, B. Boutevin, A. Manseri and M. Belbachir, *European Polymer Journal*, 1996, **32**, 1189-1197.
6. Y. Catel, S. Schörpf and N. Moszner, 2015, **300**, 1010-1022.
7. B. Boutevin, Y. Hervaud, A. J. P. Boulahna, Sulfur,, Silicon and t. R. Elements, 2004, **179**, 1423 - 1433.
8. T. M. Putvinski, M. L. Schilling, H. E. Katz, C. E. D. Chidsey, A. M. Mujsce and A. B. J. L. Emerson, 1990, **6**, 1567-1571.
9. C.-G. Chae, Y.-G. Yu, H.-B. Seo, M.-J. Kim, R. H. Grubbs and J.-S. Lee, *Macromolecules*, 2018, **51**, 3458-3466.
10. L. Sinawehl, R. Wolff, T. Koch, J. Stampfl, R. Liska and S. Baudis, *ACS Applied Polymer Materials*, 2023, **5**, 5758-5771.
11. C. Gorsche, R. Harikrishna, S. Baudis, P. Knaack, B. Husar, J. Laeuger, H. Hoffmann and R. Liska, *Analytical Chemistry*, 2017, **89**, 4958-4968.