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Lactic acid oligomers (OLAs) as prodrug moieties

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In this paper we propose the use of lactic acid oligomers (OLAs) as prodrug moieties. Two synthetic approaches are presented, on the one hand a non selective oligomerisation of lactic acid and on the other hand a block synthesis to tetramers of lactic acid. Dimers of lactic acid were investigated with respect to their plasma stability and their adsorption to albumine. Ibuprofen was chosen as the first drug for OLAylation. The ester **19** of LA(1)-ibuprofen was evaluated with respect to the degradation to human plasma and the adsorption to albumine. All results indicate that lactic acid oligomers are promising prodrug moieties.

1. Introduction

A prodrug is by definition a derivative of a pharmacological agent that must undergo an enzymatic or chemical transformation *in vivo* to release the parent drug which can then elicit the desired pharmacological effect with a decelerated duration of action (Borchardt et al. 2007; Jarkko 2011; Rautio et al. 2008; Stella et al. 1985; Zhang et al. 2011, 2005). Prodrugs are a straightforward way to 'individualise' drug properties. Generally they are designed to change the HLB (hydrophilic-lipophilic balance) of a drug, to improve resorption and cellular uptake, to modulate organ specificity, to achieve retarded drug action, to increase plasma stability, to modify metabolism or to reduce toxicity. Typical prodrug moieties are e.g. long lipophilic chains that enhance lipid solubility and are frequently used to achieve slow release from injected drugs. PEGylation with polyethylglycol is a further frequently applied prodrug modification. Due to their amphiphilic character, PEGylated molecules show increased bioavailability in particular by enhancing plasma solubility. Although not broadly known, PEG has a polymeric structure, the conformation of which is largely defined by action of stereoelectronic effects of the type of the gauche effect. By this effect the chain adopts a stretched helical conformation also in aqueous solution, while lipophilic moieties tend to adopt a random compact conformation. The PEG units reach out into the surrounding space of the drug like an antenna, providing a perfect conformation for hydratisation. At the same time the interactions with the drug itself are comparatively low. This renders this modification particularly suited for bio-molecules, where their role is not only that of a prodrug, but as a rule rather that of a "next generation" compound. As a matter of fact PEGylation is more broadly used to modify the formulation than the drug itself.

Lactic acid is a central metabolite and is therefore physiologically well accepted. Due to the hydroxyl and acid functionalities it is able to form polyesters. In the contrast to PEG, these polylactic acids (PLA) are biodegradable and are broadly used as carrier for pharmaceutical active ingredients in drug delivery systems (Wischke and Schwendeman 2008). Oligomers of lactic acid (OLAs) have not yet been extensively studied (for a review see: Mehta et al. 2005). Several chain lengths have been described

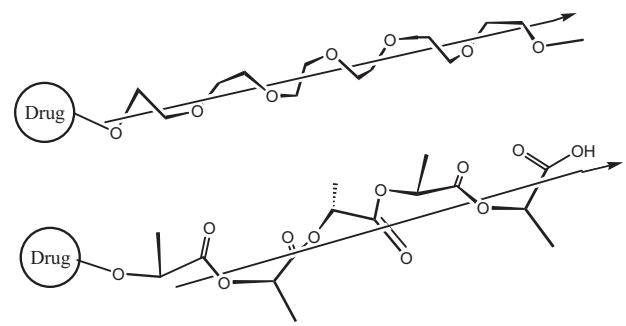
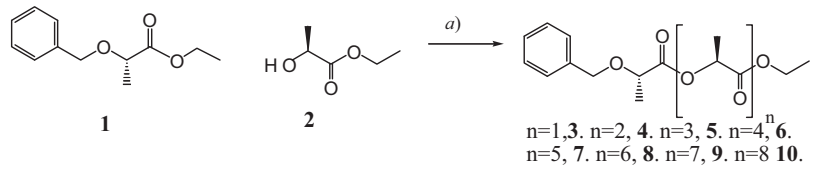


Fig. 1: Polyethylglycol (PEG) and polylacticacid (PLA) modified drugs

(Zhu et al. 2011). Surprisingly they have not yet been used in pharmaceutical research and practice in spite of their potential. Like PEGs, OLAs exhibit conformational properties defined by stereoelectronic effects, and might therefore be particularly promising candidates for the use as non toxic prodrug moieties. The preferred conformations of polylactic acid derived from L-lactic acid (PLLA) are two left handed helices that deviate only slightly from each other (α-helix –10/3 and β-helix –3/1) (Hoogsteen et al. 1990). In these systems the drug (often a hydrophobic compound) is non- covalently encapsulated in a PLA matrix, leading to slow release of the drug to be used as depot application. OLAs prefer also helical conformations (Fig. 1) and might therefore, due to their "antenna" conformation, be well suited as prodrug moieties.

In this paper we present the use of oligo-lactic moieties as prodrug modifications. Both alternative syntheses and stereochemical aspects are considered. Ibuprofen was selected as 'model drug' to investigate both methodology of prodrug synthesis and to assess first biological data. Covalent linkage was achieved by reaction of the lactic acid hydroxy group with the carboxyl functionality of ibuprofen. Due to the biological character of lactic acid oligomers it was of particular interest to investigate to which degree the enzymatic degradation is relevant. Therefore plasma stability of the prodrugs was the first parameter of interest. Since both enantiomers of lactic acid are bio-molecules, our work included stereochemical aspects.



Scheme 1: p-TosOH, toluene, RF, 35days, 4Å- mol sieves

Lactic acid oligomers may be synthesized via a non selective polymerisation of lactic acid derivatives to oligomers of mixed chain length or by convergent block synthesis to obtain lactic acid oligomers with a defined chain length.

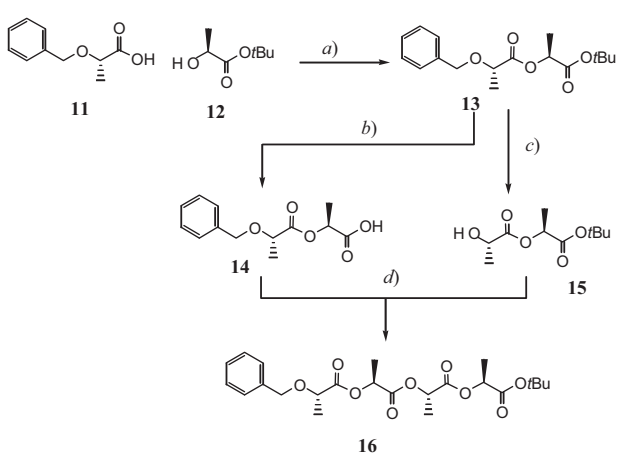
2. Investigations and results

2.1. Oligomer synthesis

Polylactic acid is usually obtained by ring opening of the cyclic lactic acid dimer (lactide) with Sn(II) (Penczek et al. 2000), Zn(II) (Williams et al. 2003) or Al(III) (Zhong et al. 2002) lewis acids. We chose an alternative approach (Scheme 1) by investigating the oligomerisation of (*S*)-lactic ethylester **2** with benzyl-*S*-lactic ethylester **1** as starting unit under acidic conditions (p-TosOH).

By the reaction of **1** with a tenfold excess of **2** we obtained oligomers with a chain length of n = 1–8 which could be separated by medium pressure liquid chromatography (MPLC). In a second experiment we performed this reaction with enantiomerically pure **1** and racemic lactic acid ethylester. By applying these conditions we obtained after MPLC two fractions for the diasteriomeric dimers and two fractions for the four diastereomeric trimers and no reasonable amounts of higher oligomers. The ratio of dimers was 1.2:1. The main product was identified as the *SS* product **3** by co-elution with the dimer **3** obtained by the oligomerisation described above. The ratio of trimers was investigated by HPLC yielding a ratio of 1,0 : 1,2 : 1,4 : 2,2. Again we identified the main product as the *SSS* product by co-elution to be compound **4**.

In our second synthetic approach to obtain oligomers, this time with a defined chain length, we applied a block synthesis (convergent way) (Scheme 2). We used benzyl lactic acid **11** (Kruse 2001) or *ent* **11** and lactic acid tertbutylester **12** or *ent* **12** (Kruse 2001) as monomeric units for the synthesis of the dimers. After trying DCC/2,4,5-trichlorophenol, DCC, and DCC/HOBt for the coupling, we finally found 2-chloro-1-methylpyridinium iodide (*Mukaiyama* reagent (Mukaiyama 1979, 1975)) to be most suitable for our purpose. In order to avoid significant racemisation we applied triethylamine in a sub-stochiometrical amount. The reaction of the monomers **11** and **12** in an equimolar ratio and 1.5 equivalents of *Mukaiyama* reagent and 1.5 equivalents of triethylamine yielded the dimer **13** in 60% yield after MPLC purification and ca. 5–10% racemisation at position 5.



Scheme 2: a) 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent), NEt3; 60%. b) TFA; 70%. c) H2 Pd/c; 70%. d) Mukaiyama reagent, NEt3; 10%

The dimer **13** was on the one hand debenzylated by hydrogenation with H_2 Pd/C in 65% yield (Kruse 2001), and on the other hand the *tert*-butyl ester was cleaved with TFA in 70% yield (Kruse 2001). These two building blocks **14** and **15** were again coupled under *Mukaiyama* conditions to give the tetramer **16** in a yield of 10%. By this protocol we prepared all four diastereomers of **13** (**13**, **13a-c**) (Fig. 2) and 13 of the 16 possible tetramers **16** (**16**, **16a-l**) (Fig. 3). In the ^{1}H NMR spectra of the dimers **13** we observed a 0.03 ppm highfield shift for the enantiomeric pair of *SR* and *RS* **13c** and **13b** corresponding to the benzylic H-atoms in comparison to the enantiomeric pair of *SS*/*RR* **13** and **13a**. By measurement of the optical rotation we found the same optical rotation values for **13** and **13a** but with opposite direction. The same was observed for the pair of enantiomers of **13b** and **13c** respectively. Therefore, we can conclude that **13/13a** and **13b/13c** are enantiomers.

The tetramers were analyzed by HPLC with a Nucleosil column (MN 250 x 4 Nucleosil 100_7) and a solvent mixture of *n*-hexane (99.2%), tertbutylmethylether (0.5%), isopropanol (0.2%) and methanol (0.1%).

In order to verify the position of racemisation we developed a capillary zone electrophoresis protocol. In a first experiment we tried to investigate the dimers **13**, **13a-c**. But due to their low solubility in the buffer these substrates were not suitable for this protocol. Therefore, we used all four diastereomers of **14**. In the electropherogram of the samples of **14**, **14a-c** we detected a main peak and a smaller peak with longer migration time which could be verified as the monomer **11** in the sample **14** and **14b** and *ent* **11** for **14a** and **14c** by co-elution (Fig. 4). This investigation prove that no racemisation had occured in position C(5) during deprotection. After optimisation of the capillary zone electrophoresis protocol we were able to detect all four dimers of **14** and the two enantiomeric monomers **11** with a good resolution.

In order to investigate the enantiomeric purity of the dimers **13**, **13a-c** we directly deprotected the dimers without purification and analysed the samples of **14** and **14a-c**. Therefore, we prepared a mixture of all six detectable products **14**, **14a-c**, **11** and *ent* **11** and mixed this to the deprotected sample **14** obtained from the dimerisation to **13**. In these co-elution experiments we observed an increase of the peak areas of **14**, **14b**, **11** and *ent* **11** but no increase of **14a** and **14c**. From this experiment we can conclude that racemisation had occured only at position 5 corresponding to the position of the activated acid.

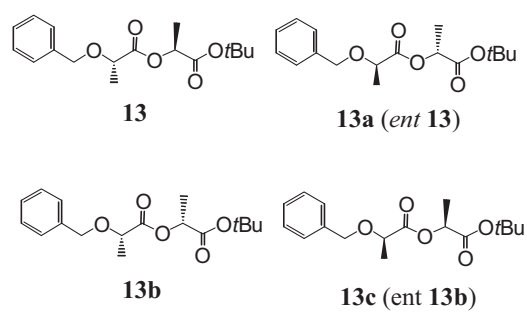


Fig. 2: All four possible diastereoisomers of lactic acid dimers

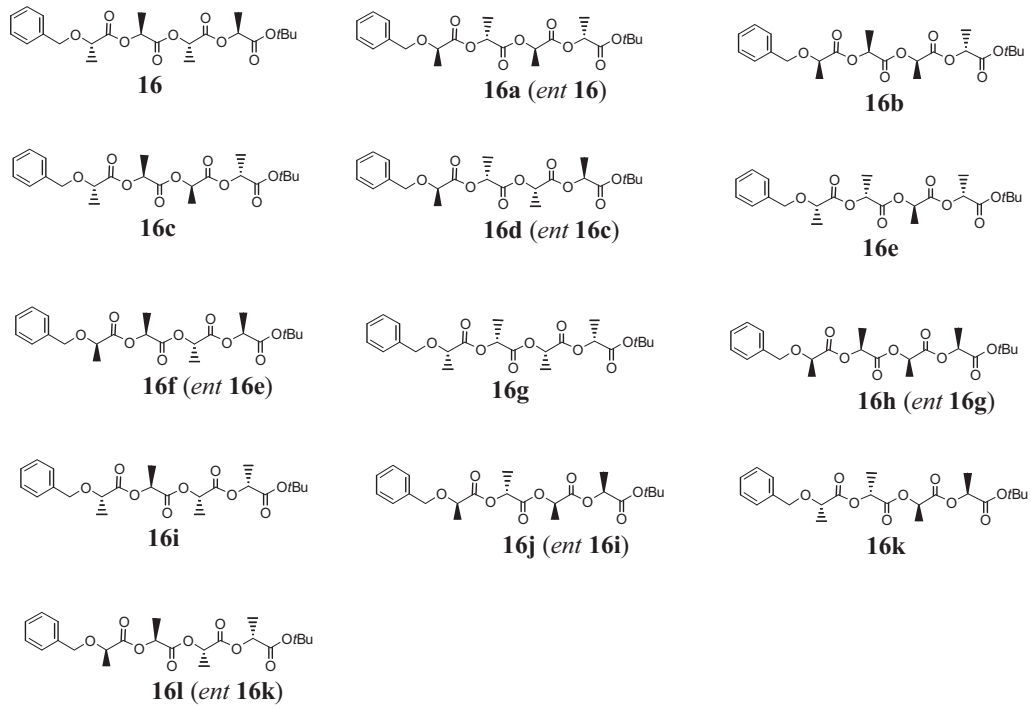


Fig. 3: 13 out of 16 possible diastereoisomers of lactic acid tetramers

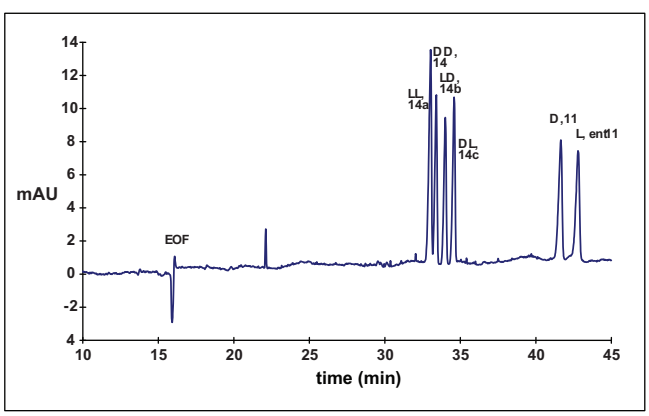


Fig. 4: Electropherogram of the four dimers 14 and the monomers 11 and ent 11. capillary: 77 cm overall length, 70 cm to the detector; buffer: 100 mM tetraborate, pH 10.3, 10 mM beta-cyclodextrine; separation conditions: 28 kV, 20°C

2.2. Plasma binding of lactic acid dimers

To investigate whether our oligomers were suitable as carriers in prodrugs we tested the plasma albumine binding and the plasma stability. As analytical method we applied the above mentioned capillary zone electrophoresis protocol.

To analyse albumine binding we used the dimeric acid **14b** with a albumine solution. After incubation of 0.5 h or 6 h at 25 or 37 °C we separated the absorbed **14b** by ultra filtration. Prior to the measurement *p*-methoxyphenylacidic acid was added as internal standard. The separation of the plasma bound lactic acid was performed by centrifugation (centrisat-C4 20.000 MWCO-filter with 9500 g in 20 h at 6 °C). By this protocol we could assure that no bound lactic acid was liberated again. In order to determine the amount of the dimer **14b** bound on the surface of the filter tubes during filtration we performed this protocol without albumine. This experiment resulted in recovery values/rates of over 90%.

As can be seen from the Table, the binding of **14b** on albumine found after centrifugation was approximately 30% of the original amount. The corresponding experiment with plasma yielded a binding of 70%. Neither the incubation times nor the stereochemistry at constant temperature had an influence on the binding. By increasing the temperature to 37 °C the amount bounded on plasma proteins also increased to approximately 77%. To investigate the influence of the stereochemistry we also tested the dimer **14** and found a similar binding with respect to **14b**.

2.3. Plasma stability of lactic acid dimers

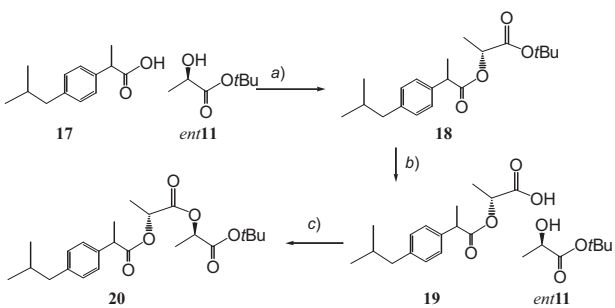
In order to test the lactic acids oligomers for their suitability for the use as prodrugs we examined also their stability against ubiquitous esterases. All experiments were performed in pooled blood plasma. After addition of **14b** to the plasma the samples were adjusted to 37 °C. The enzymatic reaction was stopped by addition of methanol after 18, 22 and 40 h. The lactic acid derivatives were liberated from the proteins by addition of a PIC-A/methanol mixture. The samples were treated with *p*-methoxyphenylacetic acid as internal standard and stored over night in a refrigerator. The final removal of the plasma residue was performed by centrifugation at 9500 × g. The supernatant was directly used for capillary electrophoretic analysis. To investigate the enzymatic degradation we also executed samples without plasma as blank to have a comparison in the series of measurements. In these experiments, we observed almost no degradation within the first hours and about 5% degradation after 40 h. The analogous result was obtained with dimer **14**. We analysed the degradation of phenylalanine ethylester under the conditions mentioned above to have a comparison to our results. In these experiments, we observed a 50% degradation and release of phenylalanine after 15 min.

2.4. Synthesis of lactic acid substituted ibuprofen

In order to work out a method for the attachment of the lactic acid moiety we synthesised the first OLA prodrug of ibuprofen with a dimeric lactic acid moiety (OLA(2)). Ibuprofen (**17**) was coupled to lactic acid *tert*-butylester *ent* **11** in 77% yield applying *Mukaijama* conditions (Scheme 3). This coupling product **18** was deprotected to the free acid **19** by treatment with TFA (35% yield) and again coupled to lactic acid *tert*-butylester as mentioned above to give the diester **20** in 11% yield.

Table: Albumin binding of compounds 14

Lactic acid	Medium	Reaction time	Temperature	Filtration	Albumine binding (%)
14b	Water	0.5h	25 °C	no	0
14b	Water	0.5h	25 °C	yes	8
14b	Albumine	0.5h	25 °C	yes	29
14b	Plasma	0.5h	25 °C	yes	68
14b	Plasma	0.5h	37 °C	yes	76
14b	Plasma	6.0h	37 °C	yes	77
14	Water	0.5h	25 °C	no	0
14	Plasma	6.0h	25 °C	yes	69



Scheme 3: a) Mukaiyama reagent, NEt3, 77%, b) TFA, 35%, c) 2-chloro-1-methyl-pyridinium iodide, NEt3, 11%

2.5. Plasma stability of LA(1)-ibuprofen

In order to test the use of ibuprofen lactic ester **19** as prodrug we investigated its stability in plasma. Therefore, we treated ibuprofen lactic ester **19** with plasma and adjusted the temperature to 37 °C. The reaction was stopped by addition of acetonitrile after 1, 2, 4, and 8 h and the corresponding reaction mixture was stored in the refrigerator. The final separation of the plasma protein was achieved by centrifugation with 10000 × g. The supernatant was treated with benzoic acid as internal standard and analysed by capillary electrophoresis. To confirm that the degradation was due to the enzymatic activity, we also made a blank with water instead of plasma. To test the esterase activity we also investigated the degradation of phenylalanine ethylester to phenylalanine. By these experiments we could demonstrate that the degradation of the *ibuprofen* lactic ester **19** due to non selective esterases was about 30% after 8 h, while the degradation of phenylalanine ethylester was complete after 2 h. The control value of the degradation of *ibuprofen* lactic ester in water was about 10% after 8 h. According to this experiment we could show that the liberation of ibuprofen lactic acid ester to ibuprofen is suited with respect to the use as prodrug with retarded duration of action.

2.6. Plasma binding of (LA(1)) ibuprofen

In the next step we examined the plasma albumine binding. Therefore we added human plasma to ibuprofen lactic ester **19** for 0.5 and 3 h at 37 °C. After filtration of the plasma bound part the solution was treated with benzoic acid as internal standard and analysed by capillary electrophoresis. The albumine bound ester was identified as 75% at 0.5 and 2 h respectively.

2.7. Conclusion

In this paper we presented a new type of oligomerisation to oligolactic acid and a convergent synthesis up to tetramers of lactic acid. Dimers of lactic acid were investigated with respect to their binding to plasma albumine and their stability in human plasma. We could show that the dimer **14b** was bound to plasma by around 70% and had a high stability towards non selective esterases. These properties should be favorable with regard to their use as carrier molecules. An LA(1)-modification **19** of ibuprofen was synthesised and tested with respect to plasma stability and plasma binding. The results demonstrate that OLA-moieties are promising candidates to be used as prodrugs.

3. Experimental

3.1. Reagents and equipment

THF was distilled from Na/benzophenone, toluene from Na, petrol ether b.p. 50–75 °C. TLC: precoated silicagel plates (*Merck* silica gel 60 F_{254}): detection by spraying with Mostain solution (400 ml of 10% aq. H_2SO_4, 20 g of $(NH_4)_6Mo_7O_2.H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel Merck 60 (0.04–0.063 mm). ^{1}H- and ^{13}C-NMR: at 200 MHz and 50 MHz.

Capillary electrophoresis separation: Beckmann P/ACE 5500 with a diode array detector.

Capillaries: Uncoated fused silica, outside polyamide coated Beckmann eCAP, 50 µm I.D. 375 µm O.D. Detection: UV 214 nm, detector on the cationic side

Separation buffer was prepared by diluting a 0.1 M stock solution of sodium tetraborate and adjusted with 0.1 M NaOH to the respective pH.

Separation conditions at the measurements of the albumine binding and the plasma stability:

Capillary: 37 cm, 30 cm to the detector, buffer: 50 mmol sodium tetraborate + 10 mmol SDS, pH 10.3, temp.: 20 °C, voltage 10 kV.

Separation conditions at the measurements of the phenylalanine ethylester degradation: Capillary: 37 cm, 30 cm to the detector, buffer: 50 mmol sodium tetraborate + 10 mmol SDS, pH 9.8, temp.: 20 °C, voltage 10 kV.

3.2. Synthesis of the compounds

3.2.1.
*(2S)-2{(2(S)-2(Benzyloxy)-propanoyloxy)propanoicacidethylester (**3**), (2S)-2{(2(S)-2-(2S)-2-(Benzyloxy)-propanoyloxy}propanoyloxy} propanoicacidethylester (**4**), (2S)-2{(2(S)-2-{(2S)-2-{(2S)-2-(Benzyloxy)-propanoyloxy}propanoyloxy}-propanoyloxy}-propanoicacidethylester (**5**), (2S)-2{(2(S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(Benzyloxy)-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoicacidethylester (**6**), (2S)-2{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-{(2S)-{(Benzyloxy)-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoicacidethylester (**7**), (2S)-2{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-{(2S)-{(Benzyloxy)-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoicacidethylester (**8**), (2S)-2{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-{(2S)-{(Benzyloxy)-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoicacidethylester (**9**), (2S)-2{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-2-{(2S)-{(2S)-{(Benzyloxy)-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoyloxy}-propanoicacidethylester (**10**)*

A solution of *O*-benzyl-*S*-(-)-lactic acid ethylester (**1,** 8.33 g, 40 mmol) and *S*-lactic acid ethylester (2, 47.3 g, 400 mmol) in 200 ml toluene was treated with *p*-TosOH (0.5 g) and heated for 7 days to reflux. The apparatus was equipped with an *Soxhlet* extractor filled with 4 Å mol sieve. After 3 days additionally *p*-TosOH (0.5 g) was added and after 6 days the mol sieve was reconditioned. After 7 days the reaction mixture was cooled to RT, treated

with $NaHCO_3$ (5 g), stirred for 30 min, extracted for three times with water and the water phase reextracted with Et_2O. The combined organic phases were dried with Na_2SO_4 and evaporated. The crude mixture was purified by MPLC (petrol ether/Et_2O 10:1).

Data of **3**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.43. ^{1}H NMR (200 MHz, $CDCl_3$): 7.39–7.27 (*m*, 5 arom. H); 5.15 (*q*, J = 7.1, C*H); 4.75–4.46 (*d*, J = 11.6, OCH_2-Ar); 4.20 (*q*, *J* = 7.1, CH_2-CH_3); 4.13 (*q*, *J* = 6.9, C-H*); 1.52 (*d*, *J* = 7.1, H_3C-C*); 1.49 (*d*, *J* = 7.0, H_3C-C*); 1.29 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.4 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 71.9 (t, O-CH_2Ph); 68.8 (d, Me-C*H); 61.4 (*t*, *C*H_2-CH_3); 18.7 (*q*, H_3*C*-C*), 14.0 (*q*, H_3*C*-CH_2). MS ($C_{15}H_{20}O_5$, 280.32): 280.94.

Data of **4**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.34. ^{1}H NMR (200 MHz, $CDCl_3$): 7.39–7.28 (*m*, 5 arom. H); 5.20 (*q*, J = 7.0, C*H); 5.15 (*q*, J = 7.2, C*H); 4.74–4.45 (*d*, J = 11.6, OCH_2-Ar); 4.22–4.12 (*m*, CH_2-CH_3, C*H); 1.60 (*d*, *J* = 7.1, *H*$_3$C-C*); 1.53–1.50 (*m*, 2 H_3C-C*); 1.26 (*t*, *J* = 7.2, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.1 (*s*, *C*O); 169.9 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.2 (*d*, MeC*H); 68.6 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 18.7 (*q*, H_3*C*-C*); 16.9 (*q*, H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2). MS ($C_{18}H_{24}O_7$, 352.39): 351.

Data of **5**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.28. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.27 (*m*, 5 arom. H); 5.20 (*q*, J = 7.0, C*H); 5.23–5.11 (*m*, 3 C*H); 4.72–4.43 (*d*, J = 11.6, OCH_2-Ar); 4.21–4.111 (*m*, CH_2-CH_3, C*H); 1.61–1.44 (*m*, 4 H_3C-C*); 1.26 (*t*, *J* = 7.2, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.1 (*s*, *C*O); 169.9 (*s*, *C*O); 169.6 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.3 (*d*, MeC*H); 68.9 (*d*, MeC*H); 68.5 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 18.7 (*q*, H_3*C*-C*); 16.7 (*q*, 3 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2). MS ($C_{21}H_{28}O_9$, 424.45): 423.

Data of **6**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.21. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.27 (*m*, 5 arom. H); 5.20–5.11 (*m*, 4 C*H); 4.72–4.43 (*d*, J = 11.6, OCH_2-Ar); 4.19–4.11 (*m*, CH_2-CH_3, C*H); 1.61–1.44 (*m*, 5 H_3C-C*); 1.25 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.0 (*s*, *C*O); 169.9 (*s*, *C*O); 169.6 (*s*, 2 *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.3 (*d*, MeC*H); 68.9 (*d*, MeC*H); 68.6 (*d*, MeC*H); 68.5 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 18.7 (*q*, 2 H_3*C*-C*); 16.7 (*q*, 3 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2). MS ($C_{24}H_{32}O_{11}$, 496.51): 495.

Data of **7**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.16. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.27 (*m*, 5 arom. H); 5.20–5.13 (*m*, 4 C*H); 4.72–4.43 (*d*, J = 11.6, OCH_2-Ar); 4.19–4.11 (*m*, CH_2-CH_3, C*H); 1.60–1.47 (*m*, 6 H_3C-C*); 1.26 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.1 (*s*, *C*O); 169.9 (*s*, *C*O); 196.7 (*s*, *C*O); 169.6 (*s*, 2 *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.3 (*d*, MeC*H); 68.9 (*d*, MeC*H); 68.6 (*d*, MeC*H); 68.5 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 18.7 (*q*, 2 H_3*C*-C*); 16.7 (*q*, 4 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2). MS ($C_{27}H_{36}O_{13}$, 568.58): 523 (M-C_2H_5O).

Data of **8**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.12. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.27 (*m*, 5 arom. H); 5.20–5.13 (*m*, 5 C*H); 4.72–4.43 (*d*, J = 11.6, OCH_2-Ar); 4.19–4.11 (*m*, CH_2-CH_3, C*H); 1.61–1.47 (*m*, 7 H_3C-C*); 1.26 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 170.1 (*s*, *C*O); 170.0 (*s*, *C*O); 196.7 (*s*, *C*O); 169.6 (*s*, 3 *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.3 (*d*, MeC*H); 69.0 (*d*, MeC*H); 68.9 (*d*, MeC*H); 68.6 (*d*, MeC*H); 68.5 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 18.7 (*q*, 2 H_3*C*-C*); 16.8 (*q*, 5 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2). MS ($C_{27}H_{36}O_{13}$, 640.64.58): 595 (M-C_2H_5O).

Data of **9**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.12. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.30 (*m*, 5 arom. H); 5.20–5.13 (*m*, 7 C*H); 4.72–4.43 (*d*, J = 11.6, OCH_2-Ar); 4.21–4.14 (*m*, CH_2-CH_3, C*H); 1.60–1.49 (*m*, 8 H_3C-C*); 1.25 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.9 (*s*, *C*O); 172.8 (*s*, *C*O); 170.1 (*s*, *C*O); 170.0 (*s*, *C*O); 169.9 (*s*, *C*O); 169.7 (*s*, *C*O); 169.6 (*s*, 2*C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.5 (*d*, MeC*H); 69.3 (*d*, MeC*H); 69.0 (*d*, MeC*H); 68.9 (*d*, MeC*H); 68.6 (*d*, 2 MeC*H); 66.7 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 20.5 (*q*, H_3*C*-C*); 18.7 (*q*, (H_3C-C*); 16.8 (*q*, 6 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2).

Data of **10**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.10. ^{1}H NMR (200 MHz, $CDCl_3$): 7.35–7.29 (*m*, 5 arom. H); 5.23–5.13 (*m*, 8 C*H); 4.73–4.44 (*d*, J = 11.6, OCH_2-Ar); 4.21–4.14 (*m*, CH_2-CH_3, C*H); 1.61–1.51 (*m*, 9 H_3C-C*); 1.25 (*t*, *J* = 7.1, CH_2-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 172.9 (*s*, *C*O); 172.8 (*s*, *C*O); 172.7 (*s*, *C*O); 170.0 (*s*, *C*O); 169.9 (*s*, *C*O); 169.7 (*s*, *C*O); 169.6 (*s*, 2*C*O); 169.5 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.3 (*d*, MeC*H); 69.1 (*d*, MeC*H); 69.0 (*d*, MeC*H); 68.9 (*d*, 2 MeC*H); 68.8 (*d*, MeC*H); 68.6 (*d*, MeC*H); 66.7 (*d*, MeC*H); 61.5 (*t*, *C*H_2-CH_3); 20.5 (*q*, H_3*C*-C*); 18.7 (*q*, (H_3C-C*); 16.8 (*q*, 6 H_3*C*-C*); 14.0 (*q*, H_3*C*-CH_2)

3.2.2. 2-{2-(Benzyloxy)-propanoyloxy}propanoicacid-tert.-butylester (general procedure)

A solution of *O*-benzyllactic acid (2.7 g, 15 mmol), lactic acid-*tert*.butylester (2.19 g, 15 mmol) and 2-chlor-1-methylpyridinium iodide (4.6 g 18 mmol) in 40 ml abs. CH_2Cl_2 was treated with NEt_3 (1.82 g, 18 mmol) and heated to reflux for 48 h. After cooling to RT the solution was diluted with 100 ml Et_2O, washed for 3 times with 2 N NaOH (50 ml), 3 times with 2 N HCl (50 ml), and one time with water (30 ml), dried with Na_2SO_4 and evaporated. FC (petrol ether/ether 3:1) gave 60% of dimer.

Data of **13**: Colorless oil. R_f (petrol ether/Et_2O 2:1) 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): 7.38–7.30 (*m*, 5 arom. H); 5.00 (*q*, J = 7.1, C*H); 4.77, 4.46 (*d*, J = 11.6, OCH_2-Ar); 4.12 (*q*, *J* = 6.9, C-H*); 1.49 (*d*, *J* = 6.9, H_3C-C*); 1.48 (*d*, *J* = 7.1, H_3C-C*); 1.45 (*s*, C(CH_3)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.5 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.1 (*s*, *C*$(CH_3)_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.4 (d, Me-C*H); 27.9 (*q*, C(CH_3)$_3$); 18.8 (*q*, H_3*C*-C*); 16.9 (*q*, H_3*C*-C*). Anal. calc. for $C_{17}H_{24}O_3$ (308.38): C 66.21, H 7.84; found: C 66.41, H 7.87. $[\alpha]_D^{25} = -88.9$ ($CHCl_3$).

Data of **13a**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): 7.38–7.30 (*m*, 5 arom. H); 5.00 (*q*, J = 7.1, C*H); 4.77, 4.46 (*d*, J = 11.6, OCH_2-Ar); 4.12 (*q*, *J* = 6.9, C-H*); 1.49 (*d*, *J* = 6.9, H_3C-C*); 1.48 (*d*, *J* = 7.1, H_3C-C*); 1.45 (*s*, C(CH_3)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.5 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.1 (*s*, *C*$(CH_3)_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH_2Ph); 69.4 (d, Me-C*H); 27.9 (*q*, C(CH_3)$_3$); 18.8 (*q*, H_3*C*-C*); 16.9 (*q*, H_3*C*-C*). Anal. calc. for $C_{17}H_{24}O_3$ (308.38): C 66.21, H 7.84; found: C 66.09, H 7.86. $[\alpha]_D^{25} = 89.5$ ($CHCl_3$).

Data of **13b**: Colorless oil. R_f (petrol ether/Et_2O 2:1) 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): 7.39–7.28 (*m*, 5 arom. H); 5.00 (*q*, J = 7.1, C*H); 4.70, 4.46 (*d*, J = 11.6, OCH_2-Ar); 4.13 (*q*, *J* = 6.8, C-H*); 1.48–1.45 (*m*, *2* H_3C-C*); 1.46 (*s*, C(CH_3)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.5 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.3 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.0 (*s*, *C*$(CH_3)_3$); 73.8 (*d*, MeC*H); 71.9 (t, O-CH_2Ph); 69.4 (d, Me-C*H); 27.9 (*q*, C(CH_3)$_3$); 18.6 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{17}H_{24}O_3$ (308.38): C 66.21, H 7.84; found: C 66.00, H 7.85. $[\alpha]_D^{25} = -31.4^\circ$ ($CHCl_3$).

Data of **13c**: Yellow oil. R_f (petrol ether/Et_2O 2:1) 0.40. ^{1}H NMR (200 MHz, $CDCl_3$): 7.39–7.28 (*m*, 5 arom. H); 5.00 (*q*, J = 7.1, C*H); 4.70, 4.46 (*d*, J = 11.6, OCH_2-Ar); 4.13 (*q*, *J* = 6.8, C-H*); 1.48–1.45 (*m*, *2* H_3C-C*); 1.46 (*s*, C(CH_3)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.5 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.3 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.0 (*s*, *C*$(CH_3)_3$); 73.8 (*d*, MeC*H); 71.9 (t, O-CH_2Ph); 69.4 (d, Me-C*H); 27.9 (*q*, C(CH_3)$_3$); 18.6 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{17}H_{24}O_3$ (308.38): C 66.21, H 7.84; found: C 66.25, H 7.76. $[\alpha]_D^{25} = -32.4^\circ$ ($CHCl_3$).

3.2.3. 2-{2-(Benzyloxy)-propanoyloxy}propanoic acid (general procedure)

A solution of 2-[2-(benzyloxy)-propanoyloxy]propanoic acid-*tert*.butylester (0.86 g, 2.8 mmol) in CH_2Cl_2 (15 ml) was treated dropwise with a solution of TFA (3.18 ml, 28 mmol) in CH_2Cl_2 (10 ml), heated to reflux and stirred for 4 h. The solution was cooled to RT, diluted with 50 ml Et_2O and extracted 3 times with 30 ml of a 5% $NaHCO_3$ solution. The combined aqu. phases were acidified with conc. HCl to pH 1 and extracted three times with Et_2O. The combined organic phases were dried with Na_2SO_4 and evaporated giving 70% yield.

Data of **14**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.35–7.26 (*m*, 5 arom. H); 5.20 (*q*, J = 7.1, C*H); 4.75, 4.47 (*d*, J = 11.5, OCH_2-Ar); 4.14 (*q*, *J* = 6.9, C-H*); 1.58 (*d*, J = 7.0, H_3C-C*); 1.48 (*d*, J = 6.9, H_3C-C*).

Data of **14a**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.20 (*q*, J = 7.1, C*H); 4.74, 4.47 (*d*, J = 11.5, OCH_2-Ar); 4.13 (*q*, *J* = 6.9, C-H*); 1.57 (*d*, J = 7.1, H_3C-C*); 1.48 (*d*, J = 6.9, H_3C-C*).

Data of **14b**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.38–7.26 (*m*, 5 arom. H); 5.18 (*q*, J = 7.1, C*H); 4.70, 4.46 (*d*, J = 11.7, OCH_2-Ar); 4.15 (*q*, *J* = 6.9, C-H*); 1.57 (*d*, J = 7.1, H_3C-C*); 1.46 (*d*, J = 6.9, H_3C-C*).

Data of **14c**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.28 (*m*, 5 arom. H); 5.18 (*q*, J = 7.1, C*H); 4.70, 4.46 (*d*, J = 11.7, OCH_2-Ar); 4.15 (*q*, *J* = 6.9, C-H*); 1.57 (*d*, J = 7.1, H_3C-C*); 1.46 (*d*, J = 6.9, H_3C-C*).

3.2.4. 2-{2-(Hydroxy)-propanoyloxy}propanoicacid-tert.butylester (general procedure)

A solution of 2-[2-(benzyloxy)-propanoyloxy]propanoic acid-*tert*.butylester (0.86 g, 2.8 mmol) in Et_2O (20 ml) was treated with 0.2 g Pd/C (10%), saturated with hydrogen and stirred over night. The excess of hydrogen was

removed with N_2 and the solution was filtered over celite, washed with Et_2O, dried with Na_2SO_4, evaporated and separated by FC yielding 65% product. Data of 1**5**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 5.02 (*q*, J = 7.1, C*H); 4.32 (*dq*, *J* = 6.9, C-H*); 2.77 (*bs*, C-OH); 1.48 (*d*, *J* = 7.0, H_3C-C*); 1.48 (*d*, *J* = 7.1, H_3C-C*); 1.45 (*s*, C(C*H*$_3$)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.2 (*s*, *C*O); 82.4 (*s*, *C*(CH$_3$)$_3$); 69.9 (*d*, MeC*H); 66.7 (d, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 20.5 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{10}H_{18}O_5$ (218.25): C 55.03, H 8.31; found: C 54.78, H 8.13. $[\alpha]_D^{25} = -40.7$ ($CHCl_3$).

Data of 1**5a**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 5.02 (*q*, J = 7.1, C*H); 4.33 (*q*, *J* = 6.9, C-H*); 2.73 (*bs*, C-OH); 1.49 (*d*, *J* = 7.0, H_3C-C*); 1.48 (*d*, *J* = 7.2, H_3C-C*); 1.45 (*s*, C(C*H*$_3$)). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.2 (*s*, *C*O); 82.3 (*s*, *C*(CH$_3$)$_3$); 69.9 (*d*, MeC*H); 66.7 (d, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 20.5 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{10}H_{18}O_5$ (218.25): C 55.03, H 8.31; found: C 54.81, H 8.36. $[\alpha]_D^{25} = 39.6$ ($CHCl_3$).

Data of 1**5b**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 5.02 (*q*, J = 7.1, C*H); 4.37 (*dq*, *J* = 6.9, C-H*); 2.75 (*bs*, C-OH); 1.48 (*d*, *J* = 7.0, H_3C-C*); 1.45 (*s*, C(C*H*$_3$)); 1.44 (*d*, *J* = 6.7, H_3C-C*);. ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.3 (*s*, *C*O); 82.4 (*s*, *C*(CH$_3$)$_3$); 70.0 (*d*, MeC*H); 66.7 (d, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 20.1 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{10}H_{18}O_5$ (218.25): C 55.03, H 8.31; found: C 54.86, H 8.37. $[\alpha]_D^{25} = 30.0$ ($CHCl_3$).

Data of 1**5c**: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): 5.02 (*q*, J = 7.1, C*H); 4.35 (*dq*, *J* = 6.9, C-H*); 2.80 (*bs*, C-OH); 1.48 (*d*, *J* = 7.1, H_3C-C*); 1.45 (*s*, C(C*H*$_3$)); 1.44 (*d*, *J* = 6.7, H_3C-C*);. ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.3 (*s*, *C*O); 82.4 (*s*, *C*(CH$_3$)$_3$); 70.0 (*d*, MeC*H); 66.7 (d, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 20.1 (*q*, H_3*C*-C*); 16.8 (*q*, H_3*C*-C*). Anal. calc. for $C_{10}H_{18}O_5$ (218.25): C 55.03, H 8.31; found: C 54.80, H 8.29. $[\alpha]_D^{25} = -36.7^\circ$ ($CHCl_3$).

3.2.5. 2-{2-{-2{-2(Benzyloxy)propanoyloxy}propanoyloxy}propanoyloxy}propanoicacid-tert.butylester (general procedure)

A solution of 2-{2-(benzyloxy)-propanoyloxy}propanoic acid (1 equ.), NEt_3 (1.5 equ.) and 2-chlor-1-methylpyridinium iodide (1.5 equ.) in CH_2Cl_2 (20 ml) under N_2 atmosphere was heated for 1 h to reflux and treated dropwise with a solution of 2-[2-(hydroxy)-propanoyloxy]-propanoicacid-*tert*.-butylester (1 equ.) in CH_2Cl_2 (5 ml) and stirred for 20 h under reflux. The reaction mixture was cooled to r.t., diluted with Et_2O (50 ml), extracted for 3 times with NaOH (2 N, 25 ml), 3 times with HCl (2 N, 25 ml), one time with water and dried with Na_2SO_4 and evaporated. The crude product was purified by HPLC. Yield *ca*. 10%.

Data of **16**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (*m*, 5 arom. H); 5.18 (*q*, 2H, *J* = 7.1, C*H); 4.97 (*q*, *J* = 7.0, C*H); 4.74, 4.45 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.11 (*q*, *J* = 6.9, C-H); 1.60–1.42 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.9 (*s*, *C*O); 169.5 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.7 (*d*, Me-C*H); 68.9 (*d*, Me-C*H); 68.5 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.7 (*q*, H_3*C*-C*), 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = -95.6$ ($CHCl_3$).

Data of **16a**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (*m*, 5 arom. H); 5.18 (*q*, 2H, *J* = 7.0, C*H); 4.97 (*q*, *J* = 7.1, C*H); 4.74, 4.45 (AB, *J* = 11.5, OC*H*$_2$-Ar); 4.11 (*q*, *J* = 6.9, C-H); 1.60–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.9 (*s*, *C*O); 169.5 (*s*, *C*O); 169.2 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.8 (*d*, Me-C*H); 68.9 (*d*, Me-C*H); 68.6 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.7 (*q*, H_3*C*-C*), 16.8 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = 96.9$ ($CHCl_3$).

Data of **16b**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.21 (*q*, *J* = 7.4, C*H); 5.18 (*q*, *J* = 7.4, C*H); 4.98 (*q*, *J* = 7.1, C*H); 4.69, 4.44 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.9, C-H); 1.56–1.42 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.6 (*s*, *C*O); 169.2 (*s*, *C*O); 169.1 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.8 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.7 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.8 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.5 (*q*, H_3*C*-C*), 16.8 (*q*, H_3*C*-C*); 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = 63.9$ ($CHCl_3$).

Data of **16c**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.376–7.26 (*m*, 5 arom. H); 5.22 (*q*, *J* = 7.0, C*H); 5.15 (*q*, *J* = 7.0, C*H); 4.98 (*q*, *J* = 7.1, C*H); 4.74, 4.44 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.12 (*q*, *J* = 6.9, C-H); 1.56–1.42 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.7 (*s*, *C*O); 169.3 (*s*, *C*O); 169.2 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.9 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.8 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.8 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.7 (*q*, H_3*C*-C*), 16.8 (*q*, 2 H_3*C*-C*). $[\alpha]_D^{25} = 18.4^\circ$ ($CHCl_3$).

Data of **16d**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.23 (*q*, *J* = 7.0, C*H); 5.16 (*q*, *J* = 7.4, C*H); 4.98 (*q*, *J* = 7.0, C*H); 4.74, 4.44 (AB, *J* = 11.5, OC*H*$_2$-Ar); 4.12 (*q*, *J* = 6.8, C-H); 1.57–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.67 (*s*, *C*O); 169.3 (*s*, *C*O); 169.2 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.9 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (*t*, O-CH$_2$Ph); 69.8 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.8 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.5 (*q*, H_3*C*-C*), 16.9 (*q*, H_3*C*-C*); 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = 18.8$ ($CHCl_3$).

Data of **16e**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.19 (*q*, *J* = 7.1, C*H); 5.16 (*q*, *J* = 7.1, C*H); 4.97 (*q*, *J* = 7.0, C*H); 4.69, 4.43 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.8, C-H); 1.60–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.9 (*s*, *C*O); 169.5 (*s*, *C*O); 169.2 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.6 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.7 (*d*, Me-C*H); 68.9 (*d*, Me-C*H); 68.9 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.6 (*q*, H_3*C*-C*), 16.8 (*q*, H_3*C*-C*); 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = 15.4^\circ$ ($CHCl_3$).

Data of **16f**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.19 (*q*, *J* = 7.1, C*H); 5.16 (*q*, *J* = 7.4, C*H); 4.97 (*q*, *J* = 7.0, C*H); 4.69, 4.43 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.8, C-H); 1.60–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.9 (*s*, *C*O); 169.2 (*s*, *C*O); 169.1 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.1 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.6 (*d*, MeC*H); 71.9 (t, O-CH$_2$Ph); 69.7 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.6 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.6 (*q*, H_3*C*-C*), 16.7 (*q*, H_3*C*-C*); 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = -27.0^\circ$ ($CHCl_3$).

Data of **16g**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.34–7.26 (*m*, 5 arom. H); 5.20 (*q*, *J* = 7.2, C*H); 5.18 (*q*, *J* = 7.2, C*H); 4.95 (*q*, *J* = 7.1, C*H); 4.68, 4.44 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.9, C-H); 1.56–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.6 (*s*, *C*O); 169.2 (*s*, *C*O); 169.1 (*s*, *C*O); 137.4 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.9 (*d*, C(4) of Ph); 82.3 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 70.0 (*d*, Me-C*H); 69.4 (*d*, Me-C*H); 68.7 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.6 (*q*, H_3*C*-C*), 16.9 (*q*, H_3*C*-C*); 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = -18.5^\circ$ ($CHCl_3$).

Data of **16h**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (*m*, 5 arom. H); 5.21 (*q*, *J* = 7.4, C*H); 5.18 (*q*, *J* = 7.4, C*H); 4.95 (*q*, *J* = 7.0, C*H); 4.68, 4.43 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.8, C-H); 1.56–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.6 (*s*, *C*O); 169.2 (*s*, *C*O); 169.1 (*s*, *C*O); 137.4 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 69.9 (*d*, Me-C*H); 69.3 (*d*, Me-C*H); 68.7 (*d*, Me-C*H); 27.8 (*q*, C(*C*H$_3$)$_3$); 18.6 (*q*, H_3*C*-C*), 16.8 (*q*, 2 H_3*C*-C*). $[\alpha]_D^{25} = 22.2^\circ$ ($CHCl_3$).

Data of **16i**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 5.21 (*q*, *J* = 7.1, C*H); 5.19 (*q*, *J* = 7.4, C*H); 4.94 (*q*, *J* = 7.1, C*H); 4.75, 4.46 (AB, *J* = 11.5, OC*H*$_2$-Ar); 4.12 (*q*, *J* = 6.9, C-H); 1.59–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.7 (*s*, *C*O); 169.4 (*s*, *C*O); 169.1 (*s*, *C*O); 137.6 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.3 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (t, O-CH$_2$Ph); 70.0 (*d*, Me-C*H); 69.1 (*d*, Me-C*H); 68.5 (*d*, Me-C*H); 27.8 (*q*, C(*C*H$_3$)$_3$); 18.7 (*q*, H_3*C*-C*), 16.8 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = -60.7^\circ$ ($CHCl_3$).

Data of **16j**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (*m*, 5 arom. H); 5.21 (*q*, *J* = 7.1, C*H); 5.19 (*q*, *J* = 7.4, C*H); 4.94 (*q*, *J* = 7.1, C*H); 4.75, 4.46 (AB, *J* = 11.5, OC*H*$_2$-Ar); 4.132 (*q*, *J* = 6.9, C-H); 1.60–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.7 (*s*, *C*O); 169.4 (*s*, *C*O); 169.0 (*s*, *C*O); 137.5 (*s*, C(1) of Ph); 128.4 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.3 (*s*, *C*(CH$_3$)$_3$); 73.7 (*d*, MeC*H); 72.0 (*t*, O-CH$_2$Ph); 70.0 (*d*, Me-C*H); 69.1 (*d*, Me-C*H); 68.5 (*d*, Me-C*H); 27.9 (*q*, C(*C*H$_3$)$_3$); 18.7 (*q*, H_3*C*-C*), 16.8 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = 62.9$ ($CHCl_3$).

Data of **16k**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.35–7.26 (*m*, 5 arom. H); 5.23 (*q*, *J* = 7.0, C*H); 5.16 (*q*, *J* = 7.4, C*H); 4.95 (*q*, *J* = 6.9, C*H); 4.69, 4.43 (AB, *J* = 11.6, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.8, C-H); 1.58–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.6 (*s*, *C*O); 169.3 (*s*, *C*O); 169.0 (*s*, *C*O); 137.4 (*s*, C(1) of Ph); 128.3 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$); 73.6 (*d*, MeC*H); 71.9 (t, O-CH$_2$Ph); 69.9 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.5 (*d*, Me-C*H); 27.8 (*q*, C(*C*H$_3$)$_3$); 18.6 (*q*, H_3*C*-C*), 16.7 (*q*, H_3*C*-C*). $[\alpha]_D^{25} = -22.2$ ($CHCl_3$).

Data of **16l**: Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (*m*, 5 arom. H); 5.23 (*q*, *J* = 7.4, C*H); 5.16 (*q*, *J* = 7.4, C*H); 4.95 (*q*, *J* = 7.1, C*H); 4.69, 4.43 (AB, *J* = 11.7, OC*H*$_2$-Ar); 4.13 (*q*, *J* = 6.8, C-H); 1.58–1.43 (*m*, H_3C-C*, C(CH$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): 172.8 (*s*, *C*O); 169.6 (*s*, *C*O); 169.3 (*s*, *C*O); 169.0 (*s*, *C*O); 137.4 (*s*, C(1) of Ph); 128.3 (*d*, C(2,6) of Ph); 128.0 (*d*, C(3,5) of Ph); 127.8 (*d*, C(4) of Ph); 82.2 (*s*, *C*(CH$_3$)$_3$);

73.5 (*d*, MeC*H); 71.9 (t, O-CH_2Ph); 69.9 (*d*, Me-C*H); 69.0 (*d*, Me-C*H); 68.5 (*d*, Me-C*H); 27.9 (*q*, C(CH_3)$_3$); 18.7 (*q*, H_3C-C*), 16.7 (*q*, H_3C-C*). $[\alpha]_D^{25} = 22.5^\circ$ ($CHCl_3$).

*3.2.6. (±)-Ibuprofen-*D*-lactic acid-tert-butylester (***18***)*

A solution of ibuprofen (3 g, 15 mmol), D-lactic acid-*tert*.-butylester (2.2 g, 15 mmol) and 2-chlor-1-methylpyridinium iodide (4.6 g, 18 mmol) in CH_2Cl_2 (40 ml) was treated dropwise with a solution of NEt_3 (1.8 g) in CH_2Cl_2 (10 ml) and heated to reflux for 24 h. The solution was cooled to r.t., diluted with ether (50 ml) and extracted for 3 times with 2 N NaOH (30 ml), 3 times with 2 N HCl (30 ml) and one time with water (30 ml). The organic phase was dried with Na_2SO_4 and evaporated. The crude product was purified by FC (petrolether/ethyl acetate = 19:1) to give **18** (76.8%).
^{1}H NMR (200 MHz, $CDCl_3$): 7.26–7.07 (m, 4 arom. H); 4.91 (1 H); 3.76 (1 H); 2.43 (2 H); 1.84 (1 H); 1.53 (3 H); 1.44 (6 H); 1.37 (5 H); 1.34 (3H), 0.90 (6 H). ^{13}C NMR (50 MHz, $CDCl_3$): 129.3 (*d*, C(3″,5″) of Aryl); 127.3 (*d*, C(2″,6″ of Aryl); 81.8 (*s*, *C*(CH_3)$_3$); 69.3 (d, C(2)); 45.0 (*t*, *C*H_2CH(CH_3)$_2$); 44,7 (*d*, C(2′); 29,7 (*d*, CH_2*C*H(CH_3)$_2$); 27.9 (*q*, C(*C*H_3)$_3$); 22.4 (*q*, CH_2(CH(*C*H_3)$_2$)); 18.7 (*q*, C(3′)), 16.8 (*q*, C(3)).

*3.2.7. (±)-Ibuprofen-*D*-lactic acid (***19***)*

A solution of **18** (1.67 g, 5 mmol) in CH_2Cl_2 (30 mL) was treated dropwise with TFA (5,7 g, 50 mmol) in CH_2Cl_2 (20 ml) and heated to reflux for 4 h. The solution was cooled to r.t. and diluted with 50 ml ether and extracted for 3 times with $NaHCO_3$ (5% aqu. 20 ml). The combined aqu. phases were adjusted with conc. HCl to pH 1 and extracted for 3 times with ether (50 ml). The combined org. phases were dried with Na_2SO_4 and evaporated to give **19** (35.2% yield).
^{1}H NMR (200 MHz, $CDCl_3$): 7.26–7.07 (m, 4 arom. H); 5.08 (1 H); 3.79 (1 H); 2.44 (2 H); 1.85 (1 H); 1.53 (6 H); 1.34 (3H), 0.90 (6 H). ^{13}C NMR (50 MHz, $CDCl_3$): 174.8 (*s*, CO); 129.3 (*d*, C(3″,5″) of Aryl); 127.3 (*d*, C(2″,6″ of Aryl); 68.5 (*d*, C(2)); 45.1 (*t*, *C*H_2(CH(CH_3)$_2$)); 44,7 (*d*, C(2′); 30.1 (*d*, CH_2*C*H(CH_3)$_2$); 22.3 (*q*, CH_2CH(*C*H_3)$_2$); 18.3 (*q*, C(3′)), 16.6 (*q*, C(3)).

*3.2.8. (2R)-2-{(2R)-2-((±)-Ibuprofen)-propanoyloxy}propanoic acid-tert.butylester (***20***)*

A solution of **19** (460 mg, 1.65 mmol), D-lactic acid-*tert*.-butylester (245 mg, 1.65 mmol) and 2-chlor-1-methylpyridinium iodide (510 mg, 1.89 mmol) in CH_2Cl_2 (20 ml) was treated dropwise with a solution of NEt_3 (280 mg) in CH_2Cl_2 (5 ml) and heated to reflux for 24 h. The solution was cooled to r.t., diluted with ether (20 ml) and extracted for 3 times with 2N NaOH (10 ml), 3 times with 2N HCl (10 ml) and one time with water (30 ml). The organic phase was dried with Na_2SO_4 and evaporated. The crude product was purified by FC (petrolether/ethyl acetate = 20:1) to give **20** (11%).
^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.07 (m, 4 arom. H); 4.93 (2 H); 3.72 (1 H); 2.35 (2 H); 1.77 (1 H); 1.38 (18 H); 0.83 (6 H). ^{13}C NMR (50 MHz, $CDCl_3$): 129.3 (*d*, C(3‴,5‴) of Aryl); 127.3 (*d*, C(2‴,6‴ of Aryl); 82.0 (*s*, *C*(CH_3)$_3$); 69.6 (*d*, C(2)); 68.5 (*d*, C(2′); 45.0 (*t*, *C*H_2CH(CH_3)$_2$); 44,6 (*d*, C(2″); 30.1 (*d*, CH_2*C*H(CH_3)$_2$); 27.9 (*q*, C(*C*H_3)$_3$); 22.4 (*q*, CH_2(CH(*C*H_3)$_2$)); 18.6 (*d*, C(3″)); 16.8 (*q*, C(3′)), 16.7 (*q*, C(3)).

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