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A cross metathesis-based synthesis of analogues of the 2-*O*-alkyl glycerate part of the moenomycins

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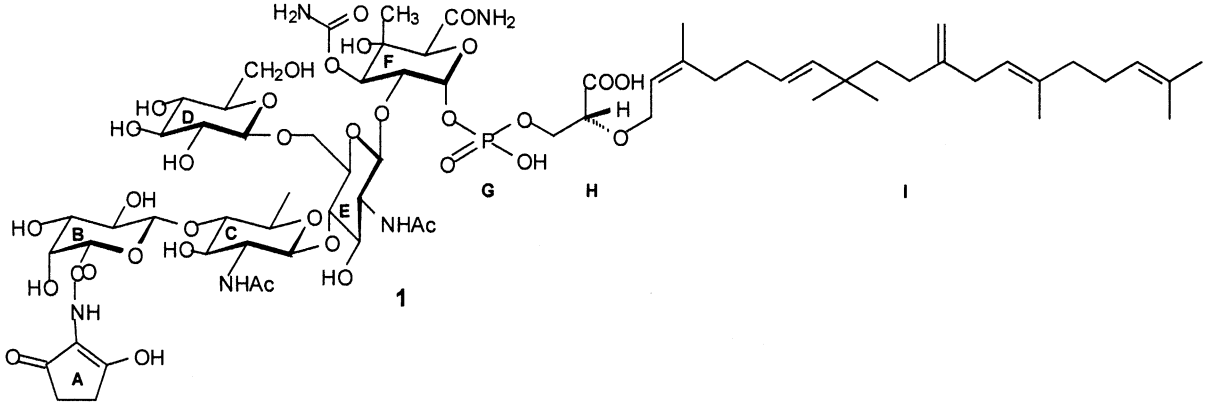
Abstract—Conditions are reported which allow to convert optically active methyl glycerate to the 2-*O*-allyl derivative without racemization. Cross metathesis reactions then lead to analogues of the 2-*O*-alkyl glycerate part of the moenomycin antibiotics.

1. Introduction

The peptidoglycan layer is an important component of bacterial cell walls. It consists of carbohydrate strands with peptide crosslinks. The final two steps in the assembly of peptidoglycan from a disaccharide–oligopeptide intermediate, a transglycosylation and a transpeptidation, occur at the extracellular face of the cytoplasmic membrane. The enzymes that catalyse these reactions are members of the penicillin binding protein (PBP) family.[1] The only compounds known with certainty[2] to inhibit the transglycosylase domain of bifunctional PBPs such as PBP **1a** and **1b** (at nanomolar concentrations) are the moenomycins (see moenomycin A, **1**[3]) (Scheme 1). Work on their mode of action has led to the conclusion that they are anchored to the cytoplasmic membrane via their lipid chain and are then highly selectively recognized at their sugar part by the binding site of the growing peptidoglycan strand which forms the glycosyl donor in the transglycosylation reaction[4].

Although membrane association is of prime importance for the antibiotic activity it also causes the poor pharmacokinetics of the moenomycins which has prevented their use in human medicine so far.[5]

These facts demand to define in detail the influence of different lipid chains on the antibiotic activity as well as on the pharmacokinetics.



Scheme 1.

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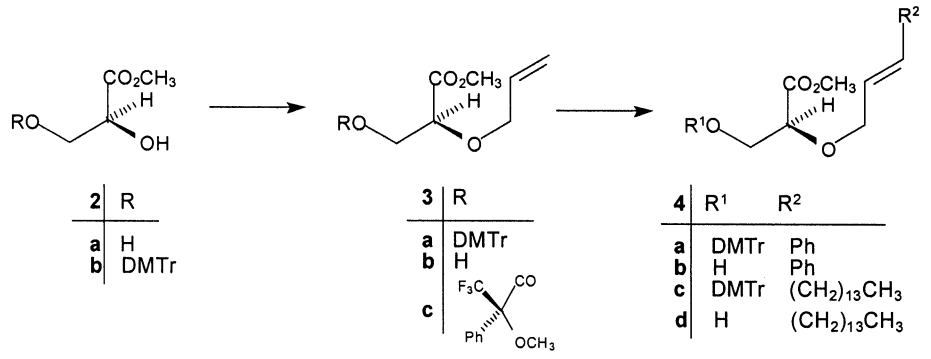


Scheme 2.

Two approaches have been taken on to gain access to moenomycin analogues with altered lipid chains, one modifying moenomycin itself,[6,7] the other one being based on synthesis commencing from 2-*O*-alkyl glycerates.[8] Neither of these methods has been particularly successful so far.

The synthesis of 2-*O*-alkyl glycerates is not straightforward since these β-hydroxy carboxylic acids are very prone to elimination. One route that avoids the elimination problem commences from D-mannitol and involves (i) protection of the 1-, 3-, 4-, 6-OH groups, (ii) alkylation of the OH-groups at C-2 and C-5, (iii) removal of the protecting groups, (iv) glycol cleavage, and (v) oxidation of the intermediate 2-*O*-alkylglyceraldehydes.[9] This sequence is lengthy, and it provides, when conducted as described, only one enantiomeric series.[10]

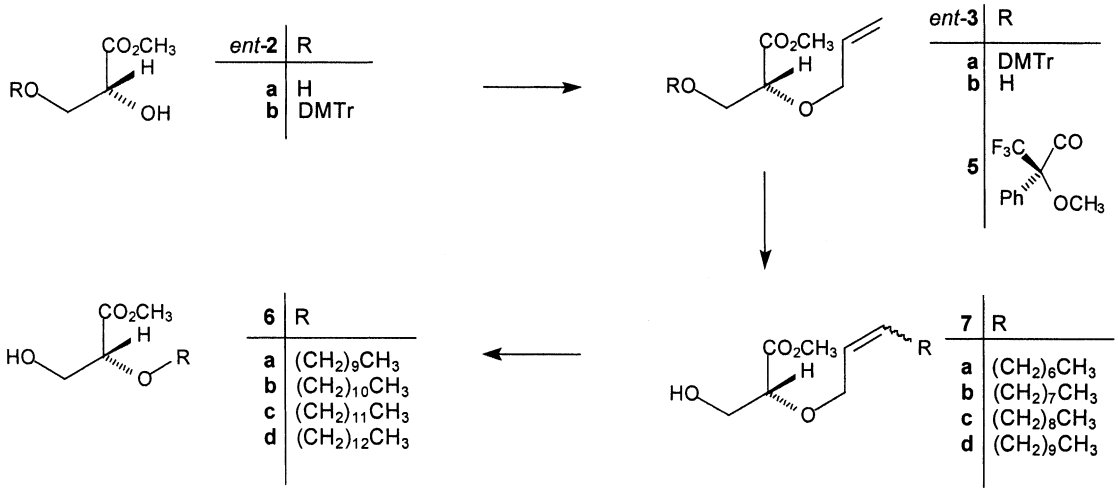
A second synthetic route is based on the hydroxymethylation of chiral enolates. The synthesis is flexible and permits the preparation of structurally diverse 2-*O*-substituted glycerates in both enantiomeric series. But the stereoselective hydroxymethylation is auxiliary-based and involves with the attachment and removal of the of the auxiliary two 'unproductive' steps.[11]

Thus, there is much room for finding more efficient procedures for the synthesis of 2-*O*-alkylated glycerates which, in addition, might be useful for the parallel synthesis of analogue libraries.

2. Results and discussion

As already mentioned alkylation of suitably protected glyceric acid esters suffers from poor yields caused by elimination. On the other hand direct alkylation seems to be the most direct way to 2-*O*-alkyl glycerates. If instead of an alkyl halide an allyl halide would be used two advantages are obvious, (i) the greater reactivity of allyl halides in comparison to alkyl halides, and (ii) the opportunity of using the allyl double bond to perform cross metathesis reactions (CMR)[12] and, thus, introduce really an element of library synthesis. These ideas could be reduced to practice.

Both methyl (*S*)- and (*R*)-glycerate (**2a** and *ent*-**2a**, obtained from the corresponding acetonides) have been selectively protected at the 3-position to give their 4,4′-dimethoxytrityl ethers **2b** and *ent*-**2b**. The silver oxide-mediated allylation reaction with allyl bromide proceeded completely eventually and provided the 2-*O*-allyl derivatives **3a** and *ent*-**3a** in more than 90% yield. The protecting group was removed with 80% acetic acid at 20°C to provide **3b** and *ent*-**3b** in about 90% yield. The two enantiomers were converted into their respective Mosher esters on reaction with (*S*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionyl chloride. NMR revealed that no racemization had occurred in the course of the allylation reaction (in the limits of the NMR analysis). In a model experiment **3a** and 1-hexadecene were submitted to CMR[13] under the influence of



Scheme 3.

the Grubbs catalyst (bis(tricyclohexylphosphine)benzilidine ruthenium(IV) dichloride)[12] (Scheme 2). The reaction product **4c** was obtained in 58% yield as a single (*E*)-stereoisomer. Removal of the dimethoxytrityl group was achieved under the conditions described above and furnished **4d** in 93% yield. When the CMR was performed with **3a** and styrene, **4a** was obtained in 54% yield again as a single (*E*)-isomer. The sample contained an impurity that could not be removed. We were unable to determine the structure of this impurity. Acetic acid removed the dimethyoxytrityl protecting group to provide pure **4b** after chromatographic separation in 88% yield.

It turned out that removal of the 3-*O*-protecting group prior to the CMR did not impair the yields very much. Thus, cross-coupling products **7a**–**d** have been obtained from *ent*-**3b** in respectable yields. In all these cases mixtures of (*E*)- and (*Z*)-disubstituted olefins have been isolated. From these results we are led to the conclusion that the dimethoxytrityloxy substituent in the 3-position influences the steric outcome of the CMR appreciably in this series (Scheme 3).

Finally, catalytic hydrogenation of **7a**–**d** provided the desired 2-*O*-alkyl glycerates **6a**–**d** in practically quantitative yields.

In conclusion, we have developed a very efficient route to the 2-*O*-alkyl glycerate motif of transglycosylase inhibitors of the moenomycin type that involves an element of library synthesis. Attaching these compounds to suitable sugar components is actively pursued.

3. Experimental

3.1. General

For general methods and instrumentation, see Ref. 14.

3.1.1. Methyl (*S*)-glycerate (2a). A solution of methyl (*S*)-2,3-*O*-isopropylideneglycerate (2.20 g, 13.70 mmol) in 70% acetic acid (13 mL) was stirred at 20°C for 48 h. The solution was evaporated to dryness under reduced pressure. Toluene (5 mL) was added and the solvent was evaporated. This procedure was repeated several times until acetic acid was removed completely. FC (CH_2Cl_2/acetone 9:1) furnished **2a** as a colourless oil (1.30 g, 79%). $[\alpha]_D^{25}=-10.71$ (c=1.12, $CHCl_3$). IR (KBr): 3385, 2959, 1740, 1258, 1106, 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=2.83 (bs, 1H, CH_2–O*H*), 3.61 (bs, 1H, CH–O*H*), 3.81 (s, 3H, OCH_3), 3.83–3.99 (m, 2H, CH_2-3), 4.28 (t, 1H, 2-H, $J_{2,3}$=3.3 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=53.25 (OCH_3), 64.47 (C-3), 72.14 (C-2), 174.05 (C-1). $C_4H_8O_4$ (120.10, 120.04), EI MS: m/z (%)=120 $[M]^+$ (<1), 90 (100). HRMS: calc. 120.0423, found 120.0423. *ent*-**2a** was prepared in the same way.

3.1.2. Methyl (*S*)-3-*O*-dimethoxytrityl-glycerate (2b). A solution of 4,4′-dimethoxytrityl chloride (4.66 g, 12.00 mmol) in dry THF (20 mL) was added dropwise to a solution of **2a** (1.30 g, 11.00 mmol) in dry pyridine (20 mL) at −5°C. The mixture was stirred at −5°C for 16 h. Then CH_2Cl_2 was added and the organic phase was sequentially washed with water, saturated aq. $NaHCO_3$ and saturated aq. NaCl. After drying, solvent evaporation and FC (toluene/acetone 9:1) **2b** was obtained as a colourless oil (3.20 g, 70%). $[\alpha]_D^{25}=+3.97$ (c=8.20, $CHCl_3$). IR (KBr): 3469, 2951, 1742, 1606, 1507, 1248, 1178, 1033, 829, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=3.21 (d, 1H, OH, $J_{OH,2}$=7.7 Hz), 3.37 (dd, 1H, 3-H, $J_{3,3'}$=9.4 Hz, $J_{3,2}$=3.4 Hz), 3.48 (dd, 1H, 3-H′, $J_{3',2}$=2.9 Hz), 3.78 (s, 3H, $COOCH_3$), 3.79 (s, 6H, 2×Ar–O–CH_3), 4.24–4.33 (m, 1H, 2-H), 6.79–7.45 (m, 13H, Ar–Hs). ^{13}C NMR (APT, 50.3 MHz, $CDCl_3$): δ=(−)52.88 ($COOCH_3$), (−)55.64 (2×Ar–O–CH_3), (+)65.59 (C-3), (−)71.26 (C-2), (+)86.34 (CH_2–O–C_{quart}), (−)113.65 (4, C-3^{Ar-OMe}, C-5^{Ar-OMe}), (−)127.36 (C-4^{Ph}), (−)128.37 (2, C-3^{Ph}, C-5^{Ph}), (−)128.59 (2, C-2^{Ph}, C-6^{Ph}), (−)130.53 (4, C-2^{Ar-OMe}, C-6^{Ar-OMe}), (+)136.24 (C-1^{Ar-OMe}), (+)136.30 (C-$1'^{Ar-OMe}$), (+)145.14 (C-1^{Ph}), (+)159.09 (2, C-4^{Ar-OMe}), (+)174.14 (C-1). $C_{25}H_{26}O_6$ (422.47, 422.17), EI MS: m/z (%)=422 $[M]^{+\cdot}$ (15), 303 (100). HRMS: calc. 422.1729, found 422.1734. *ent*-**2b** was prepared accordingly.

3.1.3. Methyl (*S*)-2-*O*-allyl-3-*O*-dimethoxytrityl)-glycerate (3a). To a solution of methyl **2b** (0.20 g, 0.47 mmol) in dry diethyl ether (20 mL) allyl bromide (0.11 g, 0.95 mmol) was added dropwise. The mixture was stirred under reflux for 10 min and over a period of 15 min silver oxide (0.28 g, 1.23 mmol) was added in three portions. Stirring was continued at reflux for 2 h and at 20°C for 48 h (exclusion of light). Solid material was removed by filtration and washed several times with diethyl ether. The combined organic solutions were worked up as usual. FC (toluene/acetone 50:1→2:1) furnished **3a** (0.20 g, 91%) as a colourless oil. $[\alpha]_D^{24}=-5.68$ (c=1.14, $CHCl_3$). IR (KBr): 3478, 2950, 1747, 1607, 1507, 1249, 1177, 1033, 830, 756 cm^{-1}. ^1H NMR (HH COSY, HOMO DECOUPLING, 200 MHz, $CDCl_3$): δ=3.41 (d, 2H, CH_2-3, $J_{3,2}$=4.9 Hz), 3.76 (s, 3H, $COOCH_3$), 3.79 (s, 3H, Ar–O–CH_3), 3.80 (s, 3H, Ar–O–CH_3), 4.05 (ddt, 1H, 1^{all}-H, $J_{1,1'}$=12.8 Hz, $J_{1,2}$=5.4 Hz, $J_{1,3}$=1.4 Hz), 4.13 (t, 1H, 2-H), 4.22 (ddt, 1H, 1^{all}-H′), 5.23 (ddt, 1H, 3^{all}-H_{cis}, $J_{3all\ cis,3all\ trans}$=1.8 Hz, $J_{3all\ cis,2all}$=10.3 Hz, $J_{3all\ cis,1all}$=1.3 Hz), 5.33 (ddt, 1H, 3^{all}-H_{trans}, $J_{3all\ trans,2all}$=17.2 Hz, $J_{3all\ trans,1all}$=1.6 Hz), 5.82–6.07 (m, 1H, 2^{all}-H), 6.78–7.53 (m, 13H, Ar–Hs). ^{13}C NMR (HETCOR, APT, 50.3 MHz, $CDCl_3$): δ=(+)52.38 ($COOCH_3$), (+)55.64 (2×Ar–O–CH_3), (+)64.71 (C-3), (+)72.14 (C-1^{all}), (−)78.35 (C-2), (+)86.57 (CH_2–O–C_{quart}), (−)113.62, (−)113.68 (4, Ar–Cs), (+)118.30 (C-3^{all}), (−)127.28 (Ar–C), (−)128.32 (2, Ar–Cs), (−)128.69 (2, Ar–Cs), (−)130.61 (4, Ar–Cs), (−)134.61 (C-2^{all}), (+)136.44 (2, Ar–Cs), (+)145.29 (Ar–C), (+)159.05 (2, Ar–Cs), (+)172.04 (C-1). $C_{28}H_{30}O_6$ (462.54, 462.20), EI MS: m/z (%)=462 $[M]^{+\cdot}$ (11), 303 (100). HRMS: calc. 462.2042, found 462.2034. *ent*-**3a** was prepared accordingly.

3.1.4. Methyl (*S*)-2-*O*-allyl-glycerate (3b). A solution of **3a** (80 mg, 0.17 mmol) in 80% acetic acid (10 mL) was stirred at 20°C for 3 h. The reaction mixture was then diluted with a pyridine/water mixture and evaporated. Dry pyridine (5 mL) was added and the solvent was removed under reduced pressure. FC (CH_2Cl_2/acetone 50:1→1:1)

provided **3b** (24.3 mg, 89%) as a colourless oil. $[\alpha]_D^{25}=-6.59$ (c=0.97, $CHCl_3$). IR (KBr): 3458, 2959, 1743, 1259, 1114, 797 cm^{-1}. ^1H NMR (HOMO DECOUPLING, 200 MHz, $CDCl_3$): δ=2.23 (t, 1H, OH), 3.78 (s, 3H, OCH_3), 3.79–3.92 (m, 2H, CH_2-3), 4.02 (ddt, 1H, 1^{all}-H, $J_{1,1'}$=12.5 Hz, $J_{1,2}$=6.0 Hz, $J_{1,3}$=1.5 Hz), 4.06 (t, 1H, 2-H, $J_{2,3}$=4.8 Hz), 4.28 (ddt, 1H, 1^{all}-H′), 5.24 (ddt, 1H, 3^{all}-H_{cis}, $J_{3all\ cis,3all\text{-}trans}$=1.3 Hz, $J_{3all\ cis,2all}$=10.6 Hz, $J_{3all\ cis,1all}$=1.3 Hz), 5.31 (ddt, 1H, 3^{all}-H_{trans}, $J_{3all\ trans,2all}$=17.2 Hz), 5.83–6.05 (m, 1H, 2^{all}-H). ^{13}C NMR (APT, 50.3 MHz, $CDCl_3$): δ=(−)54.14 (OCH_3), (+)65.42 (C-3), (+)73.90 (C-1^{all}), (−)80.46 (C-2), (+)120.39 (C-3^{all}), (−)135.67 (C-2), (+)173.09 (C-1). $C_7H_{12}O_4$ (160.16, 160.07), EI MS: m/z (%)=160 $[M]^{+\cdot}$ (<1), 130 (5), 41 (100). HRMS: calc. 160.0736, found 160.0744. *ent*-**3b** was prepared accordingly.

3.1.5. Methyl (*R*)-2-*O*-allyl-1-*O*-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionyl)-glycerate (5). The mixture of *ent*-**3b** (25 mg, 0.16 mmol), (*S*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionyl chloride (50 μL, 0.4 mmol, 2.5 equiv.), triethylamine (100 μL) and a catalytic amount of *N*,*N*-dimethylaminopyridine in CH_2Cl_2 (0.5 mL) was stirred under argon for 14 h. TLC indicated the formation of only one compound. The solvents were evaporated. Removal of excess reagent by FC (petroleum ether/ethyl acetate, 3:1) furnished **5** (30 mg, 56%). ^1H NMR (200 MHz, $CDCl_3$): δ=7.56–7.38 (m, 5H, Ar–Hs), 5.81–5.77 (m, 1H, C*H*=CH_2), 5.32–5.17 (m, 2H, CH=CH_2), 4.71–4.49 (m, 2H, CH_2O), 4.25–4.16 (m, 2H, C*H*–$COOCH_3$, CH–OC*H*H′–CH=CH_2), 4.04–3.94 (m, 1H, OCH*H*′–CH=CH_2), 3.74 (s, 3H, $COOCH_3$), 3.56 (s, 3H, CF_3–C–OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=169.88 (*C*$OOCH_3$), 166.34 (O*C*OC_{qu}), 133.63, 132.24 (*C*H=CH_2), 129.75, 128.52, 127.64 (Ar–Cs), 118.34 (CH=*C*H_2), 75.66 (*C*H–$COOCH_3$), 71.97 (O–*C*H_2–CH=CH_2), 65.70 (CH_2–O), 55.67 (CF_3–CO–*C*H_3), 52.14 ($COOCH_3$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ=4.49. ^{19}F NMR (282.3 MHz, C_6D_6): δ=5.86. **3c** was prepared accordingly. **5** and **3c** were indistinguishable by TLC, but in benzene solution the ^{19}F signals of the two diasteroisomers were well separated.

3.1.6. Methyl (*S*)-3-*O*-dimethoxytrityl-2-*O*-((*E*)-2-heptadecen-1-yl)-glycerate (4c). Through a solution of methyl **3a** (75 mg, 0.17 mmol) in dry 1,2-dichloroethane (5 mL) nitrogen was bubbled to remove oxygen. Bis(tricyclohexylphosphine)benzilidine ruthenium(IV) dichloride (STREM, 7.24 mg, 8×10^{-4} mmol) was added. Under a stream of nitrogen 1-hexadecene (79.70 mg, 0.34 mmol) was added and the mixture was stirred under nitrogen for 72 h at 20°C. After solvent evaporation and FC (toluene/acetone 50:1) **4c** (36.73 mg, 58%) was obtained as a colourless oil. $[\alpha]_D^{25}=-6.08$ (c=1.26, $CHCl_3$). IR (KBr): 2924, 2850, 1751, 1606, 1506, 1458, 1298, 1250, 1207, 1178, 829 cm^{-1}. ^1H NMR (HOMO DECOUPLING, 200 MHz, $CDCl_3$): δ=0.83 (t, 3H, CH_3-17^{hd}, $J_{17,16}$=6.4 Hz), 1.15–1.40 (m, 24H, CH_2-5^{hd}–CH_2-16^{hd}), 1.95–2.12 (m, 2H, CH_2-4^{hd}), 3.38 (d, 2H, CH_2-3, $J_{3,2}$=5.1 Hz), 3.75 (s, 3H, $COOCH_3$), 3.79 (s, 6H, 2×Ar–O–CH_3), 3.93 (dd, 1H, 1^{hd}-H, $J_{1,1'}$=12.1 Hz, $J_{1,2}$=6.2 Hz), 4.06 (t, 1H, 2-H), 4.06 (dd, 1H, 1^{hd}-H), 5.49, 5.67 (2×dt, 2H, 2^{hd}-H, 3^{hd}-H, $J_{2,3}$=15.3 Hz), 6.78–7.50 (m, 13H, Ar–Hs). ^{13}C NMR (HETCOR, APT, 50.3 MHz, $CDCl_3$): δ=(−)14.27 (CH_3-17′), (+)22.84, (+)29.18, (+)29.36, (+)29.40, (+)29.51, (+)29.66, (+)29.76, (+)29.83, (+)32.07 (C-5^{hd}–C16^{hd}), (+)32.46 (C-4^{hd}), (−)52.06 ($COOCH_3$), (−)55.32 (2, Ar–Cs), (+)64.34 (C-3), (+)71.67 (C-1^{hd}), (−)77.50 (C-2), (+)86.17 (CH_2–O–C_{qu}), (−)113.19, (−)113.28 (4, Ar–Cs), (−)125.55 (C-2^{hd}), (−)126.83, (−)127.88, (−)128.27, (−)129.25 (5, Ar–Cs), (−)130.19 (4, Ar–Cs), (+)136.02 (2, Ar–Cs), (−)136.06 (C-3^{hd}), (+)144.86 (Ar–C), (+)158.56, (+)158.74 (2, Ar–Cs), (+)171.81 (C-1). $C_{21}H_{40}O_4$ (658.92, 658.42), ESI MS: $C_{42}H_{58}NaO_6$ $[M+Na]^+$: calc. 681.4133, found 681.4125.

3.1.7. Methyl (*S*)-2-*O*-((*E*)-2-heptadecen-1-yl)-glycerate (4d). 4c (180 mg, 0.27 mmol) was deprotected as described for **3a**. FC (petroleum ether/ethyl acetate 5:1) provided **4d** (89.7 mg, 0.25 mmol, 93%) as a colourless oil. $[\alpha]_D^{25}=-5.88$ (c=2.54, $CHCl_3$). IR (KBr): 3471, 2924, 1747, 1466, 1436, 1207, 1124, 1066, 974 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=0.88 (t, 3H, CH_3-17^{hd}, ^3J=6.4 Hz), 1.20–1.48 (m, 24H, CH_2-5^{hd}–CH_2-16^{hd}), 1.95–2.12 (m, 2H, CH_2-4^{hd}), 3.77 (s, 3H, OCH_3), 3.75–3.90 (m, 1H, 3-H), 3.84 (t, 1H, 3-H, $J_{2,3}$=5.9 Hz), 3.97 (dd, 1H, 1^{hd}-H, ^2J=11.7 Hz, ^3J=6.6 Hz), 4.06 (dd, 1H, 3-H′, $J_{3',2}$=3.7 Hz), 4.21 (dd, 1H, 1^{hd}-H, ^3J=5.9 Hz), 5.56, 5.74 (2×dt, 2H, 2^{hd}-H, 3^{hd}-H, ^3J=15.4 Hz). ^{13}C NMR (APT, 50.3 MHz, $CDCl_3$): δ=(−)14.24 (CH_3-17′), (+)22.82, (+)29.10, (+)29.34, (+)29.48, (+)29.61, (+)29.73, (+)29.81, (+)32.05 (C-5^{hd}–C-16^{hd}), (+)32.39 (C-4^{hd}), (−)52.21 (O*C*H_3), (+)63.53 (C-3), (+)71.88 (C-1^{hd}), (−)78.12 (C-2), (−)125.17 (C-2^{hd}), (−)136.77 (C-3^{hd}), (+)171.38 (C-1). $C_{21}H_{40}O_4$ (356.54, 356.29). ESI MS: $C_{42}H_{80}NaO_8$ $[2M+Na]^+$: calc. 735.57454, found 735.57406.

3.1.8. Methyl (*S*)-3-*O*-dimethoxytrityl-2-*O*-((*E*)-3-phenyl-2-propen-1-yl)-glycerate (4a). 3a (75 mg, 0.16 mmol) and styrene (33 mg, 0.32 mmol), bis(tricyclohexylphosphine)-benzilidine ruthenium(IV) dichloride (7.24 mg, 8×10^{-4} mmol) was performed as described for **4c**. FC (toluene/acetone 50:1) furnished **4a** (46.80 mg, 54%) as a colourless oil. $[\alpha]_D^{25}=-7.56$ (c=3.82, $CHCl_3$). IR (KBr): 3465, 2927, 1745, 1606, 1506, 1446, 1296, 1248, 1176, 1124, 1032, 829 cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): δ=3.42 (d, 2H, CH_2-3, $J_{3,2}$=4.9 Hz), 3.73 (s, 3H, $COOCH_3$), 3.78 (s, 6H, 2×Ar–O–CH_3), 4.16 (t, 1H, 2-H, $J_{2,3}$=5.1 Hz), 4.21 (dd, 1H, 1^{prop}-H, ^2J=11.9 Hz, ^3J=6.5 Hz), 4.36 (dd, 1H, 1^{prop}-H′, ^3J=5.9 Hz), 6.30 (dt, 1H, 2^{prop}-H, $J_{2,3}$=15.9 Hz, $J_{2,1}$=6.0 Hz), 6.63 (d, 1H, 3^{prop}-H), 6.78–7.50 (m, 18H, Ar–Hs). ^{13}C NMR (APT, 75.5 MHz, $CDCl_3$): δ=(−)52.11 ($COOCH_3$), (−)55.33 (2×Ar–O–*C*H_3), (+)64.44 (C-3), (+)71.49 (C-1^{prop}), (−)77.97 (C-2), (+)86.28 (CH_2–O–*C*), (−)113.25, (−)113.32 (4, Ar–Cs), (−)125.48 (C-2^{prop}), (−)126.72, (−)127.21, (−)127.93, (−)128.32, (−)128.70, (−)129.28 (10×C^{Ph}), (−)130.22 (4, Ar–Cs), (−)133.33 (C-3^{prop}), (+)136.03 (2, Ar–Cs), (+)139.63, (+)144.86 (2, Ar–Cs), (+)158.63, (2, Ar–Cs), (+)171.64 (C-1). The second product gave ^1H signals at δ=3.80 (s), 4.13 (dd), 4.44 (dd), and additional signals in the aromatic region and ^{13}C signals at δ=(−)52.29, (−)55.38, (+)64.44, (+)71.76, (−)78.59, (−)125.48, (−)126.74, (−)126.89, (−)127.98, (−)128.13, (−)128.74, (−)133.99, (+)136.70, (+)145.23, (+)158.79, (+)171.53. $C_{34}H_{34}O_6$ (538.64, 538.23), ESI MS: $C_{34}H_{34}NaO_6$ $[M+Na]^+$: calc. 561.22553, found 561.22330.

3.1.9. Methyl (*S*)-2-*O*-((*E*)-3-phenyl-2-propen-1-yl)-glycerate (4b). Deprotection of **4a** (120 mg, 0.22 mmol) was performed as described for **3a**. FC (petroleum ether/ethyl acetate 5:1) gave **4b** (46.2 mg, 88%) as a colourless oil. $[\alpha]_D^{25}=-10.42$ ($c=1.16$, $CHCl_3$). IR (KBr): 3442, 2949, 1743, 1446, 1272, 1207, 1128, 1065, 972, 744 cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): $\delta=2.16$ (bs, 1H, OH), 3.78 (s, 3H, OCH_3), 3.84 (dd, 1H, 3-H, $J_{3,3'}=11.7$ Hz, $J_{3,2}=5.9$ Hz), 3.93 (dd, 1H, 3-H′, $J_{3',2}=3.7$ Hz), 4.12 (dd, 1H, 2-H), 4.21 (ddd, 1H, 1^{prop}-H, $J_{1,1'}=12.3$ Hz, $J_{1,2}=6.8$ Hz, $J_{1,3}=1.2$ Hz), 4.43 (ddd, 1H, 1^{prop}-H′), 6.30 (dt, 1H, 2^{prop}-H, $J_{2,3}=15.9$ Hz), 6.63 (d, 1H, 3^{prop}-H), 7.70–7.42 (m, 5H, Ph–Hs). ^{13}C NMR (APT, 75.5 MHz, $CDCl_3$): $\delta=$ (−)52.44 (OCH_3), (+)63.69 (C-3), (+)71.89 (C-1^{prop}), (−)78.69 (C-2), 125.00 (C-2^{prop}), (−)126.86, (−)128.26, (−)128.86, (+)136.56 (6, Ph–Cs), 134.15 (C-3^{prop}), (+)171.64 (C-1).

3.1.10. Methyl (*R*)-2-*O*-(2-decen-1-yl)-glycerate (7a). The mixture of *ent*-**3b** (92 mg, 0.57 mmol) and bis(tricyclohexylphosphine)benzilidine ruthenium(IV) dichloride (catalytic amount) in dichloroethane (2 mL) were stirred at 20°C for 1 h under nitrogen, bubbled directly into the reaction mixture. Then 1-nonene (0.19 mL, 1.14 mmol) was added and the reaction mixture was stirred under the same conditions for 62 h. Solid material was removed by filtration. The filtrate was evaporated. FC (CH_2Cl_2/acetone 20:1) furnished **7a** as a mixture of (*E*)-/(*Z*)-isomers. (0.105 g, 70%). R_f: 0.65 (toluene/acetone 9:1). IR (film): 3347 (OH), 1706 (C=O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=5.80–5.40$ (m, 2H, $OCH_2–CH=CH$), 4.16–3.73 (m, 5H, $CH–COOCH_3$, $OCH_2–CH=CH$, CH_2OH), 3.75 (s, 3H, OCH_3), 2.30 (broad s, 1H, $CH_2–OH$), 2.02 (m, 2H, $OCH_2–CH=CH–CH_2$), 1.25 (m, 10H, $(CH_2)_5–CH_3$), 0.86 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.41$ ($COOCH_3$), 136.75/135.39, 125.17/124.78 ($O–CH_2–CH=CH$), 78.15 ($CH–COOCH_3$), 71.84 ($O–CH_2–CH=CH_2$), 64.02/63.49 ($CH_2–OH$), 52.20 ($COOCH_3$), 32.38 ($CH=CH–CH_2–(CH_2)_5–$), 31.92, 29.27, 29.07, 27.70 ($–CH=CH–CH_2–(CH_2)_4–$), 22.76 ($CH_2–CH_3$), 14.21 (ω-CH_3). $C_{14}H_{26}O_4$ (258.35, 258.18), FAB MS: $m/z=281.2$ $[M+Na]^+$.

3.1.11. Methyl (*R*)-2-*O*-(2-undecen-1-yl)-glycerate (7b). *ent*-**3b** (109 mg, 0.68 mmol) and 1-decene (0.26 mL, 1.36 mmol) were submitted to the cross metathesis as described for **7a**. Reaction time: 40 h. FC (CH_2Cl_2/acetone 10:1) provided **7b** (87 mg, 50%, mixture of (*E*)-/(*Z*)-isomers, 92% based on consumed *ent*-**3b**), 0.05 g (45%) of *ent*-**3b** were recovered. R_f: 0.65 (toluene/acetone 9:1). IR (film): 3475 (OH), 1745, 1706 (C=O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=5.75–5.39$ (m, 2H, $OCH_2–CH=CH$), 4.10 (d, 1H, $CH–COOCH_3$), 4.10–3.99 (m, 2H, $OCH_2–CH=CH$), 3.96–3.80 (m, 2H, CH_2OH), 3.76 (s, 3H, OCH_3), 2.04 (broad s, 1H, $CH_2–OH$), 2.03 (m, 2H, $OCH_2–CH=CH–CH_2$), 1.24 (m, 12H, $(CH_2)_6–CH_3$), 0.87 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.40$ ($COOCH_3$), 136.73/135.35, 125.18/124.98 ($O–CH_2–CH=CH$), 78.15 ($CH–COOCH_3$), 71.85 ($O–CH_2–CH=CH_2$), 63.51 ($CH_2–OH$), 52.19 ($COOCH_3$), 32.38 ($CH=CH–CH_2–(CH_2)_5–$), 31.98, 29.54, 29.40, 29.36, 29.07 ($CH=CH–CH_2–(CH_2)_5–$), 22.78 ($CH_2–CH_3$), 14.21 (ω-CH_3). $C_{15}H_{28}O_4$ (272.38, 272.20), FAB MS: $m/z=295.2$ $[M+Na]^+$.

3.1.12. Methyl (*R*)-2-*O*-(2-dodecen-1-yl)-glycerate (7c). *ent*-**3b** (78 mg, 0.49 mmol) and 1-undecene (0.19 mL, 0.98 mmol) were submitted to the cross metathesis as described for **7a**. Reaction time: 62 h. FC (CH_2Cl_2/acetone 20:1) furnished **7c** (65 mg, 47%, (*E*)-/(*Z*)-isomers). R_f: 0.65 (toluene/acetone 9:1). IR (film): 3394 (OH), 1739 (C=O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=5.76–5.45$ (m, 2H, $OCH_2–CH=CH$), 4.30–3.76 (m, 5H, $CH–COOCH_3$, $OCH_2–CH=CH$, CH_2OH), 3.76 (s, 3H, OCH_3), 2.22 (broad s, 1H, $CH_2–OH$), 2.02 (m, 2H, $OCH_2–CH=CH–CH_2$), 1.25 (m, 14H, $(CH_2)_7–CH_3$), 0.87 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.40$ ($COOCH_3$), 136.75/135.40, 125.17/124.78 ($O–CH_2–CH=CH$), 78.43/78.15 ($CH–COOCH_3$), 71.85 ($O–CH_2–CH=CH_2$), 66.36/63.51 ($CH_2–OH$), 52.20 ($COOCH_3$), 32.39 ($CH=CH–CH_2–(CH_2)_6–$), 32.01, 29.67, 29.43, 29.32, 29.08, 27.70 ($CH=CH–CH_2–(CH_2)_6–$), 22.80 ($CH_2–CH_3$), 14.23 (ω-CH_3). $C_{16}H_{30}O_4$ (286.41, 286.21), FAB MS: $m/z=309.2$ $[M+Na]^+$.

3.1.13. Methyl (*R*)-2-*O*-(2-tridecen-1-yl)-glycerate (7d). *ent*-**3b** (100 mg, 0.62 mmol) and 1-dodecene (208 mg, 0.274 mL, 1.24 mmol) were submitted to the cross metathesis as described for **7a**. Reaction time: 62 h. FC (CH_2Cl_2/acetone 20:1) **7d** (76 mg, 41%, (*E*)-/(*Z*)-isomers), 51% based on consumed *ent*-**3b**), 20 mg (20%) of *ent*-**3b** were recovered. R_f: 0.65 (toluene/acetone 9:1). IR (film): 3444 (OH), 1747 (C=O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=5.80–5.45$ (m, 2H, $OCH_2–CH=CH$), 4.30–3.80 (m, 5H, $CH–COOCH_3$, $OCH_2–CH=CH$, CH_2OH), 3.77 (s, 3H, OCH_3), 2.04 (m, 2H, $OCH_2–CH=CH–CH_2$), 1.26 (m, 16H, $(CH_2)_7–CH_3$), 0.87 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.15$ ($COOCH_3$), 136.71/135.42, 125.28/124.88 ($O–CH_2–CH=CH$), 78.49/78.22 ($CH–COOCH_3$), 71.91 ($O–CH_2–CH=CH_2$), 66.46/63.571 ($CH_2–OH$), 52.19 ($COOCH_3$), 32.42 ($CH=CH–CH_2–(CH_2)_5–CH_2–CH_3$), 32.06, 29.76, 29.63, 29.48, 29.36, 29.14, 27.76 ($CH=CH–CH_2–(CH_2)_7–CH_2–CH_3$), 22.83 ($CH_2–CH_3$), 14.23 (ω-$CH_3$). $C_{17}H_{32}O_4$ (300.43, 300.23), FAB MS: $m/z=323.3$ $[M+Na]^+$.

3.1.14. Methyl (*R*)-2-*O*-decyl-glycerate (6a). A mixture of **7a** (70 mg, 0.26 mmol), methanol (4 mL), 5% Pd/C (catalytic amount) was stirred under hydrogen at 20°C and atmospheric pressure. After the reaction was complete (1 h, TLC: CH_2Cl_2/acetone 10:1), the mixture was filtered (Celite®) and the solvent was evaporated. FC (CH_2Cl_2/acetone 10:1) furnished **6a** (70 mg, 99%). R_f: 0.65 (C_2H_2/acetone 10:1). IR (film): 3392 (OH), 1739 (CO) cm^{-1}. ^1H NMR (HH COSY, $CDCl_3$): $\delta=3.99–3.64$ (m, 4H, $CH–COOCH_3$, CH_2OH, OCH_2), 3.76 (s, 3H, OCH_3), 3.46–3.38 (m, 1H, OCH_2), 2.22 (broad s, 1H, $CH_2–OH$), 1.60 (m, 2H, $OCH_2CH_2–C_8H_{17}$), 1.25 (m, 14H, $(CH_2)_7–CH_3$), 0.86 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.39$ ($COOCH_3$), 79.74 ($CH–COOCH_3$), 71.54 ($O–CH_2–C_9H_{19}$), 63.53 ($CH_2–OH$), 52.06 ($COOCH_3$), 31.99, 29.78, 29.67, 29.52, 29.40, 26.08, 22.78 ($OCH_2–(CH_2)_7–$), 22.77 ($CH_2–CH_3$), 14.16 (ω-CH_3). $C_{14}H_{28}O_4$ (260.37, 260.20), ESI MS: $[M+H]^+$ calc. 261.20658, found 261.20595, $[M+Na]^+$ calc. 283.18853, found 283.18791, $[2M+Na]^+$ calc. 543.38729, found 543.38672.

3.1.15. Methyl (*R*)-2-*O*-undecyl-glycerate (6b). 7b

(80 mg, 0.29 mmol) was hydrogenated as described above. Reaction time: 40 min (TLC: CH_2Cl_2/acetone, 10:1). FC (CH_2Cl_2/acetone 10:1) provided **6b** (75 mg, 92%). $[\alpha]_D^{25}=+32$ (*c* 0.04, $CHCl_3$). R_f: 0.60 (C_2H_2/acetone 10:1). IR (film): 3450 (OH), 1660 (C=O) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.02–3.70$ (m, 3H, C*H*–$COOCH_3$, CH_2OH), 3.79 (s, 3H, OCH_3), 3.50–3.41 (m, 2H, OCH_2), 2.22 (broad s, 1H, CH_2–OH), 1.64 (m, 2H, OCH_2CH_2–C_9H_{19}), 1.29 (m, 16H, $(CH_2)_8$–CH_3), 0.90 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.43$ (*C*$OOCH_3$), 79.74 (*C*H–$COOCH_3$), 71.54 (O–*C*H_2–$C_{10}H_{21}$), 63.52 (CH_2–OH), 52.12 ($COOCH_3$), 32.01, 29.76, 29.71, 29.67, 29.52, 29.43, 26.07 (OCH_2–(*C*H_2)$_8$–CH_2–CH_3), 22.78 (*C*H_2–CH_3), 14.19 (ω-CH_3). $C_{15}H_{30}O_4$ (274.40, 274.21), ESI MS: $[M+Na]^+$ calc. 297.20418, found 297.20355, $[2M+Na]^+$ calc. 571.41859, found 571.41816.

3.1.16. Methyl (*R*)-2-*O*-dodecyl-glycerate (6c). 7c (50 mg, 0.17 mmol) was hydrogenated as described above. Reaction time: 30 min (TLC: CH_2Cl_2/acetone 10:1). FC (CH_2Cl_2/acetone 10:1) furnished **6c** (47 mg, 93%). R_f: 0.57 (C_2H_2/acetone 10:1). IR (film): 1652 (CO), 1589 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.00–3.68$ (m, 4H, C*H*–$COOCH_3$, CH_2OH, OCH_2), 3.76 (s, 3H, OCH_3), 3.40 (m, 1H, OCH_2), 2.19 (broad s, 1H, CH_2–OH), 1.61 (m, 2H, OCH_2CH_2–$(CH_2)_9$–), 1.25 (m, 18H, (–C*H*$_2$)$_9$–), 0.87 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.40$ (*C*$OOCH_3$), 79.76 (*C*H–$COOCH_3$), 71.56 (O–*C*H_2–$C_{11}H_{23}$), 63.55 (CH_2–OH), 52.08 ($COOCH_3$), 32.04, 29.77, 29.68, 29.54, 29.10, 26.11 (OCH_2–(*C*H_2)$_9$–), 22.80 (*C*H_2–CH_3), 14.18 (ω-CH_3). $C_{16}H_{32}O_4$ (288.42, 288.23), FAB MS: *m*/*z*=289.3 $[M+H]^+$, 311.2 $[M+Na]^+$.

3.1.17. Methyl (*R*)-2-*O*-tridecyl-glycerate (6d). Methyl (*R*)-2-*O*-(tridec-2-enyl)-glycerate **7d** (60 mg, 0.20 mmol) was hydrogenated as described above. Reaction time: 30 min (TLC: CH_2Cl_2/acetone 10:1). FC (CH_2Cl_2/acetone 10:1) furnished **6d** (59 mg, 98%). $[\alpha]_D^{25}=+72$ (*c* 0.03, $CHCl_3$). R_f: 0.55 (CH_2Cl_2/acetone 10:1). IR (film): 3388 (OH), 1743 (CO) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.00–3.68$ (m, 4H, C*H*–$COOCH_3$, CH_2OH, OCH_2), 3.76 (s, 3H, OCH_3), 3.40 (m, 1H, OCH_2), 2.13 (broad s, 1H, OH), 1.59 (m, 2H, OCH_2CH_2–$(CH_2)_{10}$–), 1.24 (m, 20H, (CH_2)$_{10}$), 0.86 (t, 3H, ω-CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=171.45$ (*C*$OOCH_3$), 79.74 (*C*H–$COOCH_3$), 71.57 (O–*C*H_2–$C_{12}H_{25}$), 63.55 (CH_2–OH), 52.14 ($COOCH_3$), 32.05, 29.91, 29.81, 29.78, 29.74, 29.70, 29.54, 29.47, 26.09 (O–CH_2–(*C*H_2)$_{10}$–CH_2–CH_3), 22.81 (*C*H_2–CH_3), 14.22 ((ω-CH_3). $C_{17}H_{34}O_4$ (302.45, 302.25), FAB MS: *m*/*z*=303.2 $[M+H]^+$, 325.2 $[M+Na]^+$.

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