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Asymmetric synthesis of (3*S*,4*R*,7*S*)-(−)-3-hydroxy-7-methoxy-2,2,4-trimethyl-decanoic acid, a plausible polyketide fragment of halipeptin A

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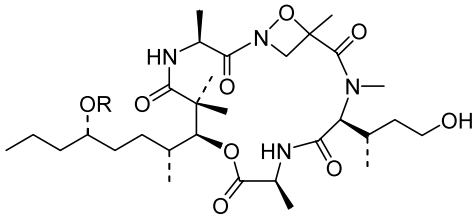
Abstract—The first enantioselective synthesis of (3*S*,4*R*,7*S*)-(−)-3-hydroxy-7-methoxy-2,2,4-trimethyl-decanoic acid **4** in 11 steps and 6% overall yield, starting from commercially available methyl 2,2-dimethyl-3-hydroxy propionate **5** is described. The stereochemical flexible synthetic pathway involves a Brown's crotylboration reaction and a Corey–Bakshi–Shibata (CBS) oxazaborolidine-mediated reduction.

1. Introduction

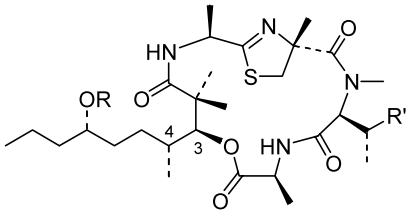
In 2001 Gomez-Paloma et al. reported the isolation and structure determination of two potent anti-inflammatory cyclic depsipeptides from a marine sponge belonging to the genus *Haliclona* which were named halipeptin A and B **1** and **2**, respectively (Fig. 1).[1]



1a, presumed halipeptin A, R = Me
2a, presumed halipeptin B, R = H

Figure 1.

After 1 year a structural revision, prompted by the isolation of a third member of the halipeptins (halipeptin C, **3**), was reported. In particular, the heterocyclic portion of the molecule, incorrectly assigned as an oxazetidine ring, was more convincingly characterized as Δ^2-thiazoline by comparison of the natural products' spectral data with those recorded from a synthetic model (Fig. 2).[2]



1b, revised halipeptin A, R = Me, R' = CH_2CH_2OH
2b, revised halipeptin B, R = H, R' = CH_2CH_2OH
3, halipeptin C, R = H, R' = CH_3

Figure 2.

Accurate NMR studies allowed the partial stereochemical assignment of **1**–**3**.[1,2] The relative stereochemistry at C-3 and C-4 of the 3-hydroxy-7-methoxy-2,2,4-trimethyl-(or 3,7-dihydroxy-2,2,4-trimethyl) decanoic acid residues, found in the halipetins, was established to be *threo* [(3*S*,4*R*) or (3*R*,4*S*)].

In order to settle the basis for future investigations toward halipeptin A total synthesis and with the idea to develop a stereochemically flexible synthetic strategy for the elaboration of its polyketide fragment, here we report the first asymmetric synthesis of the 3-hydroxy-7-methoxy-2,2,4-trimethyl-decanoic acid, applied for the preparation of the (3*S*,4*R*,7*S*) isomer **4**.

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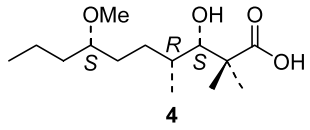

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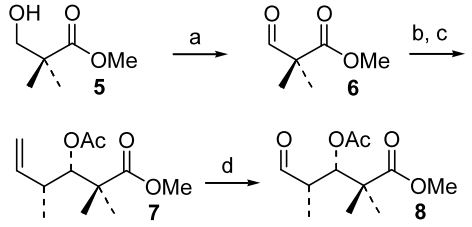
2. Results and discussion

Our approach to the stereodefined key intermediate, methyl (3*S*,4*R*)-3-acetoxy-2,2,4-trimethyl-hex-5-enoate **7**, was realised using the Brown's crotylboration reaction[3] on the easily synthesized, methyl 2,2-dimethyl-3-oxo propionate **6** (Scheme 1). This was obtained through PDC oxidation[4] of the commercially available methyl 2,2-dimethyl-3-hydroxy propionate **5**. Highly diastereoselective alkylation with the chiral (–)-(*Z*)-crotyl-Ipc$_2$-borane and subsequent acetylation of the crude reaction mixture, gave the expected *syn* adduct **7** in 85% e.e.[5] and *d.r.* >99%. Acetylation was necessary for purification purposes. The observed low yield (39%) was attributed to the steric congestion arising from the bulky bis-methylated C-2, adversely affecting the conformation of the stereodirecting Zimmerman–Traxler transition state.[6] Ozonolysis[7] of the terminal double bond of compound **7**, gave the required, but quite labile, methyl (3*S*,4*S*)-3-acetoxy-2,2,4-trimethyl-5-oxo-pentanoate **8**.

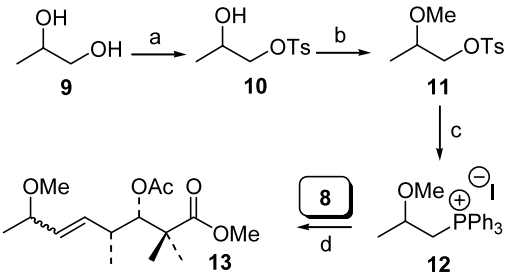


Scheme 1. *Reagents and conditions*: (a) PDC, CH_2Cl_2, *m.s.*, rt, 3 h, 85%; (b) *t*-BuOK, *n*-BuLi, (*Z*)-2-butene, (–)-Ipc$_2$-B(OMe), $BF_3{\cdot}Et_2O$, THF, –78°C, 7 h then NaOH, H_2O_2, rt, 12 h; (c) Ac_2O, DMAP, Py, CH_2Cl_2, rt, 2 h, 39% (two steps); (d) O_3, CH_2Cl_2, –78°C then PPh_3, –20°C, 12 h, 47%.

The first coupling attempt between aldehyde **8** and racemic C_3 β-methoxy ylid phosphonium reagent (2-methoxy-propyl)-triphenylphosphonium iodide, **12**, surrogate of the requested C_5 fragment), made use of the Wittig reaction.[8] **12** was chosen as the model being easily synthesized from 1,2-propandiol **9**, as shown in Scheme 2.

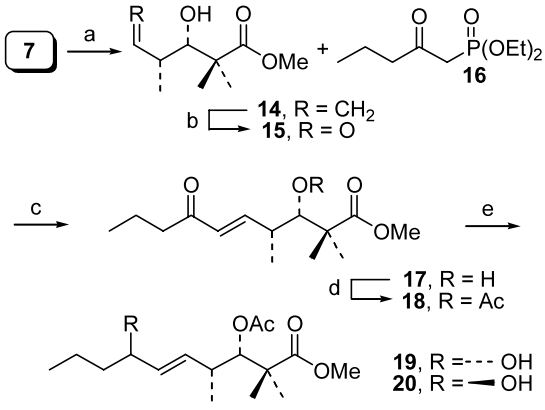
Thus, commercially available **9** was regioselectively tosylated,[9] methylated and converted in the phosphonium salt[10] **12** in 23% overall yield. Unfortunately, repeated efforts to obtain adduct **13** failed, resulting in an extensive decomposition of the starting materials.

To reduce the basic strength of the phosphorus stabilized carbanion and with the aim to decrease the base-sensitivity of the labile β-acetoxy aldehyde **8**, a Horner–Wadsworth–Emmons coupling reaction, between the β-ketophosphonate **16** and the less prone



Scheme 2. *Reagents and conditions*: (a) Ts-Cl, Py, CH_2Cl_2, rt, 12 h, 70%; (b) Ag_2O, CH_3I, CH_3CN, 80°C, 48 h, 91%; (c) NaI, CH_3CN, 80°C then PPh_3, CH_3CN, 80°C, 48 h, 33%; (d) *n*-BuLi, THF, –78°C, **8**, then –20°C, 18 h.

to elimination[11] free alcohol **15**, was planned (Scheme 3). With this alternative plan, the introduction of the C-7 stereogenic centre had to be postponed to a later synthetic stage.

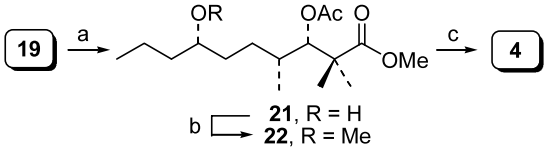


Scheme 3. *Reagents and conditions*: (a) K_2CO_3 in MeOH, 50°C, 5 h, 89%; (b) O_3, CH_2Cl_2, –78°C then PPh_3, rt, 12 h, 80%; (c) **16**, DIPEA, LiCl, CH_3CN, rt, 28 h, 66% (d) Ac_2O, DMAP, CH_2Cl_2, rt, 1 h, 96% (e) (*R*)-MeCBS reagent, $BH_3{\cdot}THF$, THF, –20°C, 1 h, **19** (66%), **20** (13%).

Thus, deacetylation and subsequent ozonolysis[7] of the methyl hexenoate derivative **7**, gave the methyl (3*S*,4*S*)-3-hydroxy-2,2,4-trimethyl-5-oxo-pentanoate **15** in 71% overall yield. The latter was coupled with the (2-oxo-pentyl)-phosphonic acid diethyl ester **16**, under Masamune–Roush conditions[12] to produce, in decent yield, a geometrically pure (*E*)-α,β-unsaturated ketone **17**, without detectable epimerization at the C-4 stereogenic centre. Acetylation and stereoselective reduction with the chiral non-racemic (*R*)-Me-Corey–Bakshi–Shibata [(*R*)-MeCBS] oxazaborolidine–borane reagent,[13] used in stoichiometric quantities, delivered to a 5:1 mixture of the diastereomeric alcohols **19**–**20**. The C-7 configuration of the major diastereoisomer **20** was confirmed to be (*S*), applying the advanced Mosher method[14] to the minor isomer **20**, whose configuration proved to be (*R*).

Finally, non-deoxygenative Δ^5-hydrogenation,[15] O-methylation with Ag_2O in refluxing acetonitrile[16] and

KOH-mediated hydrolysis of the methyl (3*S*,4*R*,7*S*)-3-acetoxy-7-methoxy-2,2,4-trimethyl-decanoate **22** furnished the requested **4** in 65% overall yield from **19** (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) H_2, Pt/C, NEt_3, MeOH, 3 h, 87%; (b) Ag_2O, CH_3I, CH_3CN, 80°C, 48 h, 80%; (c) 10% aq. KOH, MeOH, 60°C, 8 h, 94%.

3. Conclusion

In summary, we have demonstrated a viable route for the asymmetric synthesis of the (3*S*,4*R*,7*S*)-(−)-3-hydroxy-7-methoxy-2,2,4-trimethyl-decanoic acid **4**, based on the Brown's crotylboration and the CBS oxazaborolidine-mediated reduction, as key steps. The flexibility of the asymmetric approach and the choice of the synthetic sequence allow easy elaboration of alternative stereochemical arrangements, necessary for the C-3 and C-4 configuration assignment. Further studies are underway toward the total synthesis of **1b**.

4. Experimental

All reactions were carried out under a dry argon atmosphere using freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene and methylene chloride were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over P_2O_5 or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light, I_2, or spraying with $KMnO_4$, *p*-anysaldehyde or phosphomolybdic acid solutions and drying.

Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure materials. The NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer (400 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta=7.26$, $^{13}CDCl_3$: $\delta=77.0$; CD_2HOD: $\delta=3.34$, $^{13}CD_3OD$: $\delta=49.0$). Electron impact (EIMS) spectra (EI, 70 eV) were performed on a VG TRIO 2000 mass spectrometer. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.1. 2,2-Dimethyl-3-oxo-propionic acid methyl ester 6

To a solution of 3-hydroxy-2,2-dimethyl-propionic acid methyl ester (2.1 g, 15.0 mmol) in dry CH_2Cl_2 (12.0 ml), 4 Å molecular sieves (4.2 g) and PDC (11.6 g, 30.0 mmol) were added. The mixture was stirred at room temperature for 3 h, then diluted with diethyl ether (25.0 ml) and allowed to stir for additional 45 min. Filtration through a short pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash-chromatographed under N_2 (30% diethyl ether in petroleum ether) to afford **6** (1.7 g, 85%) as a pale yellow oil. $R_f=0.45$ (30% diethyl ether in petroleum ether). ^1H NMR ($CDCl_3$): δ 1.35 (6H, s, -C(CH_3)$_2$), 3.75 (3H, s, -COOCH_3), 9.66 (1H, s, -C*H*O). ^{13}C NMR ($CDCl_3$): δ 19.7 (×2), 52.5, 70.7, 173.2, 199.0. HR-EIMS m/z 130.0634 (M^+) (calcd 130.0630 for $C_6H_{10}O_3$).

4.2. (3*S*,4*R*)-3-Acetoxy-2,2,4-trimethyl-hex-5-enoic acid methyl ester 7

A mixture of (*Z*)-2-butene (1.2 ml, 13.0 mmol) and *t*-BuOK (1 M in THF, 7.8 ml, 7.8 mmol) was cooled to −78°C, and *n*-BuLi (1.6 M in hexane, 4.9 ml, 7.8 mmol) was added dropwise. The resultant bright yellow solution was stirred at −45°C for 15 min and recooled to −78°C. A solution of (−)-Ipc$_2$BOMe (2.9 g, 9.1 mmol) in dry THF (15.0 ml) was then introduced dropwise and the mixture was further stirred for 30 min. After dropwise treatment with $BF_3{\cdot}Et_2O$ (1.2 ml, 9.8 mmol), aldehyde **6** (0.850 g, 6.50 mmol) in dry THF (15.0 ml) was immediately added dropwise and the mixture was allowed to stir at −78°C for 7 h. The reaction mixture was treated with 3N NaOH (15.0 ml) and 30% H_2O_2 (7.0 ml) and then it was allowed to slowly warm to room temperature and to stir overnight. The mixture was concentrated in vacuo to remove the excess THF and the aqueous layer was diluted with brine followed by extraction with diethyl ether (3×50.0 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was dissolved in dry CH_2Cl_2 (20.0 ml) under N_2 at room temperature. To this solution was added dry pyridine (9.12 ml, 118.0 mmol) followed by Ac_2O (8.8 ml, 93.0 mmol) and DMAP (0.230 g, 1.9 mmol). The resulting mixture was stirred for 2 h at room temperature and then quenched with 2N HCl until pH 4–5. The mixture was extracted with CH_2Cl_2 (3×40.0 ml) and the combined organic layers were washed successively with saturated $NaHCO_3$ and brine, dried, filtered and concentrated in vacuo. The residue was flash-chromatographed (5–30% diethyl ether in petroleum ether) to give pure **7** (0.568 g, 39% for two steps) as a pale yellow oil. $R_f=0.5$ (20% diethyl ether in petroleum ether). ^1H NMR ($CDCl_3$): δ 0.94 (3H, d, $J=6.8$ Hz, -CHCH_3), 1.12 (3H, s, -C(CH_3)CH$_3$), 1.19 (3H, s, -C(CH$_3$)CH_3), 2.09 (3H, s, O_2CCH_3), 2.45 (1H, m, CH_2=CH-C*H*-), 3.61 (3H, s, -COOCH_3), 4.92 (1H, d, $J=10.3$ Hz, HC*H*=CH-), 5.02 (1H, d, $J=17.1$ Hz, *H*CH=CH-), 5.23 (1H, d, $J=8.9$ Hz, -C*H*-OOCCH$_3$), 5.56 (1H, m, CH_2=C*H*-). ^{13}C

NMR ($CDCl_3$): δ 17.9, 18.6, 20.7, 24.4, 40.6, 46.0, 51.5, 78.6, 115.2, 139.7, 170.5, 176.1. HR-EIMS m/z 228.1368 (M^+) (calcd 228,1362 for $C_{12}H_{20}O_4$). $[\alpha]_D^{25} = +8.5$ (c 1.0, $CHCl_3$).

4.3. (3*S*,4*S*)-3-Acetoxy-2,2,4-trimethyl-5-oxo-pentanoic acid methyl ester 8 and 2,2,4-trimethyl-5-oxo-pent-3-enoic acid methyl ester 8a

A stream of O_2/O_3 was bubbled through a solution of **7** (0.099 g, 0.43 mmol) in dry CH_2Cl_2 (20.0 ml) at −78°C until a faint blue color persisted. A stream of argon was then bubbled through the solution until it became colorless. Triphenylphosphine (0.137 g, 0.52 mmol) was added and the mixture was allowed to warm to −20°C and to stir overnight. The solution was then concentrated and the residue was flash-chromatographed (20–30% diethyl ether in petroleum ether) to give **8** (0.046 g, 47%) and **8a** (0.013 g, 17%). **8**: $R_f = 0.25$ (40% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.02 (3H, d, $J = 7.2$ Hz, -CH-CH_3), 1.22 (6H, s, -C(CH_3)$_2$), 2.05 (3H, s, -O_2CCH_3), 2.52 (1H, m, CHO-CH-), 3.66 (3H, s, -COOCH_3), 5.45 (1H, d, $J = 4.4$ Hz, -CH-OOCCH$_3$), 9.60 (1H, s, OHC-). ^{13}C NMR ($CDCl_3$): δ 9.6, 20.4, 20.5, 22.6, 46.7, 47.1, 52.2, 74.7, 170.4, 175.6, 201.7. HR-EIMS m/z 230.1150 (M^+) (calcd 230,1154 for $C_{11}H_{18}O_5$). $[\alpha]_D^{25} = +13.1$ (c 1.0, $CHCl_3$). **8a**: ^{1}H NMR ($CDCl_3$): δ 1.45 (6H, s, -C(CH_3)$_2$), 1.68 (3H, s, =C(CHO)CH_3), 3.72 (3H, s, COOCH_3), 6.45 (1H, s, CH=CCH$_3$), 9.36 (1H, s, OHC-). HR-EIMS m/z 170.0947 (M^+) (calcd 170,0943 for $C_9H_{14}O_3$).

4.4. Toluene-4-sulfonic acid 2-hydroxy-propyl ester 10

To solution of 1,2-propandiol (1.49 g, 19.0 mmol) in dry CH_2Cl_2 (25.0 ml), dry pyridine (2.4 ml, 30.0 mmol) was added at 0°C followed by addition of tosyl chloride (4.2 g, 22.0 mmol) over 3 h. The reaction mixture was allowed to warm to room temperature and to stir overnight. The reaction was treated with aq. 2N HCl and extracted with CH_2Cl_2 (3×30.0 ml). The organic layer was washed with saturated aq. $NaHCO_3$ and water. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was flash-chromatographed (30–70% diethyl ether in petroleum ether) to give **10** (3.06 g, 70%). $R_f = 0.5$ (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.13 (3H, d, $J = 6.4$ Hz, CH_3-CHOH-), 2.43 (3H, s, Ph-CH_3), 3.83 (1H, dd, $J = 9.9$, 7.1 Hz, TsOCHH-), 3.96 (1H, dd, $J = 9.9$, 3.2 Hz, TsOCHH-), 4.01 (1H, m, -CHOH-), 7.34 and 7.78 (2×2H, 2×d, $J = 8.1$ Hz, -C$_6H_4$-). HR-EIMS m/z 230.0617 (M^+) (calcd 230,0617 for $C_{10}H_{14}O_4S$).

4.5. Toluene-4-sulfonic acid 2-methoxy-propyl ester 11

Compound **10** (0.163 g, 0.71 mmol) was dissolved in dry acetonitrile (2.0 ml) and methyl iodide (0.624 g, 4.4 mmol) and kept in the dark. Ag_2O (0.376 g, 2.2 mmol) was added. The mixture was refluxed and stirred for 2 days then it was filtered and the filtrate was concentrated to afford pure **11** (0.159 g, 91%) as an oil. $R_f = 0.6$ (30% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, d, $J = 6.4$ Hz, CH_3-CHOCH$_3$), 2.45 (3H, s, Ph-CH_3), 3.29 (3H, s, -CH-OCH_3), 3.55 (1H, m, -CHOCH$_3$), 3.95 (2H, bd, TsOCH_2-CHOMe), 7.34 (2H, d, $J = 8.1$ Hz, -C$_6H_4$-), 7.78 (2H, d, $J = 8.1$ Hz, -C$_6H_4$-). HR-EIMS m/z 244.0765 (M^+) (calcd 244,0765 for $C_{11}H_{16}O_4S$).

4.6. (2-Methoxy-propyl)-triphenylphosphonium iodide 12

To a solution of **11** (1.05 g, 4.3 mmol) in dry acetonitrile (12.0 ml), under N_2 at room temperature NaI (0.873 g, 5.8 mmol) was added and the mixture was stirred and refluxed for 24 h. After cooling the suspension was filtered washing with acetonitrile. The yellow solution was then treated with triphenylphosphine (2.25 g, 8.6 mmol) and the mixture was allowed to warm until reflux temperature and stirred for 20 h. After cooling the solvent was removed under reduced pressure to give a crude residue. The solid was washed with petroleum ether and then purified by silica gel column chromatography (5% methanol in dichloromethane) to give **12** (0.640 g, 33% for two steps). $R_f = 0.4$ (5% methanol in dichloromethane). ^{1}H NMR (CD_3OD): δ 1.40 (3H, bdd, $J = 5.4$, 2.6 Hz, CH_3-CHOMe), 2.79 (3H, s, -CHOCH_3), 3.47 (1H, m, CH$_3$-CHOMe), 3.61 (1H, ddd, $J = 14.7$, 13.5, 3.4 Hz, -HCHPPh$_3^+$I$^-$), 3.84 (1H, ddd, 15.7, 13.5, 11.2 Hz, -HCHPPh$_3^+$I$^-$), 7.78 (15H, m, -P$^+$(C$_6H_5$)$_3$). ^{13}C NMR δ (CD_3OD): 19.4 ($J = 14.7$ Hz), 32.5 ($J = 53$ Hz), 56.0, 72.6 ($J = 5.7$ Hz), 131.1 ($J = 13.6$ Hz), 135.1 ($J = 9.9$ Hz), 135.8. HR-EIMS m/z 461.0536 (M^+) (calcd 461,0531 for $C_{22}H_{23}IOP$).

4.7. Attempt to synthesise (3*S*,4*R*)-3-Acetoxy-7-methoxy-2,2,4-trimethyl-oct-5-enoic acid methyl ester 13

A suspension of **12** (0.435 g, 0.920 mmol) in dry THF (15.0 ml) was cooled to −78°C, under N_2, and n-BuLi (1.6 M in hexane, 0.540 ml, 0.864 mmol) was added dropwise. The brown mixture was stirred for 1 h and then a solution of **8** (0.103 g, 0.460 mmol) in dry THF (5.0 ml) was slowly added via *cannula*. After 3 h at −78°C, the reaction mixture was allowed to warm to −20°C and to stir overnight. After quenching with water (3.0 ml), the mixture was allowed to warm to room temperature and then concentrated in vacuo to remove the excess THF. The aqueous residue was extracted with diethyl ether (3×5.0 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR ($CDCl_3$) of crude yellow solid residue did not reveal the presence of desired product **13**.

4.8. (3*S*,4*R*)-3-Hydroxy-2,2,4-trimethyl-hex-5-enoic acid methyl ester 14

Compound **7** (0.590 g, 2.60 mmol) was dissolved in methanol (10.0 ml) and K_2CO_3 (0.018 g, 0.13 mmol) was added. The reaction mixture was stirred for 5 h at 50°C and then quenched with $CHCl_3$ (7.0 ml). Solvents were concentrated in vacuo to the half of their volume. The procedure was repeated several times to precipitate the carbonate. The solution was concentrated in vacuo and the residue was flash-chromatographed (10–20%

diethyl ether in petroleum ether) to give **14** (0.432 g; 89%). R_f=0.3 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.99 (3H, d, J=6.7 Hz, -CHCH_3), 1.20 (3H, s, -C(CH_3)CH$_3$), 1.24 (3H, s, -C(CH$_3$)CH_3), 2.36 (1H, m, CH$_2$=CH-CH-), 3.58 (1H, d, J=5.7 Hz, -CH-OH), 3.66 (3H, s, -COOCH_3), 4.93 (1H, d, J=10.3 Hz, HCH=CH-), 4.99 (1H, d, J=17.2 Hz, HCH=CH-), 5.74 (1H, m, CH$_2$=CH-). ^{13}C NMR ($CDCl_3$): δ 15.7, 22.4, 22.7, 41.1, 46.3, 51.8, 79.5, 113.9, 142.1, 178.2. HR-EIMS m/z 186.1260 (M$^+$) (calcd 186,1256 for $C_{10}H_{18}O_3$). $[\alpha]_D^{25}$=+12.2 (c 1.0, $CHCl_3$).

4.9. (3*S*,4*R*)-3-Benzyloxy-2,2,4-trimethyl-hex-5-enoic acid methyl ester 14a

Compound **14** (0.100 g, 0.540 mmol) was dissolved in dry acetonitrile (2.0 ml) and benzyl bromide (0.260 g, 1.60 mmol) in a reacti-vial in the dark. Ag_2O (0.174 g, 0.80 mmol) was added. The mixture was refluxed and stirred overnight, then filtered and concentrated. Flash chromatography of the residue (1–30% diethyl ether in petroleum ether) gave **14a** (0.046 g, 31%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.13 (3H, d, J=6.7 Hz, -CHCH_3), 1.19 (3H, s, -C(CH_3)CH$_3$), 1.28 (3H, s, -C(CH$_3$)CH_3), 2.43 (1H, m, CH$_2$=CH-CH-), 3.60 (3H, s, -COOCH_3), 3.66 (1H, d, J=6.5 Hz, -CH-OBn), 4.54 (1H, d, J=12.9 Hz, -CH-O-CHH-Ph), 4.67 (1H, d, J=12.9 Hz, -CH-O-CHH-Ph), 4.91 (1H, d, J=10.2 Hz, HCH=CH-), 5.00 (1H, d, J=17.2 Hz, HCH=CH), 5.71 (1H, m, CH$_2$=CH-), 7.36 (5H, m, -OCH$_2$-C$_6H_5$). HR-EIMS m/z 276.1730 (M$^+$) (calcd 276,1725 for $C_{11}H_{18}O_5$).

4.10. (3*S*,4*R*)-3-Benzyloxy-2,2,4-trimethyl-hex-5-en-1-ol 14b

To a solution of **14a** (0.046 g, 0.17 mmol) in dry THF (1.0 ml), at 0°C, $LiAlH_4$ (1 M in THF, 0.510 ml, 0.510 mmol) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h and the quenched with ethyl acetate. The solution was then treated with 30% aq. NH_4OH (2.0 ml). The suspension was filtered on a pad of Celite® washing with ethyl acetate. Solvents were removed in vacuo and the residue was flash-chromatographed (10–30% diethyl ether in petroleum ether) to give **14b** (0.017 g, 41%). R_f=0.4 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.92 (3H, s, -C(CH_3)CH$_3$), 0.99 (3H, s, -C(CH$_3$)CH_3), 1.17 (3H, d, J=6.9 Hz, -CHCH_3), 2.58 (1H, m, CH$_2$=CH-CH-), 3.33 (1H, d, J=10.9 Hz, -CHHOH), 3.35 (1H, d, J=6.5 Hz, -CH-OBn), 3.55 (1H, d, J=10.9 Hz, -CHHOH), 4.45 (1H, d, J=11.1 Hz, -CH-O-CHH-Ph), 4.65 (1H, d, J=11.1 Hz, -CH-O-CHH-Ph), 4.98 (1H, d, J=10.5 Hz, HCH=CH-), 5.04 (1H, d, J=17.2 Hz, HCH=CH), 5.96 (1H, m, CH$_2$=CH-), 7.30 (5H, m, -OCH$_2$-C$_6H_5$). ^{13}C NMR ($CDCl_3$): δ 15.0, 20.9, 23.7, 38.5, 40.5, 71.3, 74.7, 89.6, 112.8, 127.7 (×3), 128.4 (×2), 138.1, 145.2. HR-EIMS m/z 248.1780 (M$^+$) (calcd 248,1776 for $C_{16}H_{24}O_2$). $[\alpha]_D^{25}$=+29.8 (c 1.0, $CHCl_3$).

4.11. Mosher ester 14c

To a solution of **14b** (0.006 g, 0.023 mmol) in dry pyridine (0.046 ml, 0.57 mmol) a catalytic amount of DMAP and (*S*)-MTPA-Cl (0.021 ml, 0.11 mmol) were added. The reaction was stirred for 1 h at room temperature. The solvents were then removed under N_2 stream and the crude residue was flash-chromatographed (5–10% diethyl ether in petroleum ether) to give **14c** (0.013 g). ^{1}H NMR ($CDCl_3$): δ 0.98 (6H, s, -C(CH_3)$_2$), 1.10 (3H, d, J=6.9 Hz -CHCH_3), 2.52 (1H, m, CH$_2$=CH-CH-), 3.24 (1H, d, J=6.5 Hz, -CH-OBn), 3.54 (3H, s, -OCH$_3$), 4.07 (1H, d, J=10.6 Hz, -CHHOOC), 4.25 (1H, d, J=11.3 Hz, -CH-O-CHH-Ph), 4.29 (1H, d, J=10.6 Hz, -CHHOOC-), 4.52 (1H, d, J=11.3 Hz, -CH-O-CHH-Ph), 4.93 (1H, d, J=10.5 Hz, HCH=CH), 4.98 (1H, d, J=17.2 Hz, HCH=CH), 5.85 (1H, m, CH$_2$=CH-), 7.40 (10H, m, -OCH$_2$-C$_6H_5$+-OOC-C-C$_6H_5$).

4.12. Mosher ester 14d

To a solution of **14b** (0.006 g, 0.023 mmol) in dry pyridine (0.046 ml, 0.57 mmol) a catalytic amount of DMAP and (*R*)-MTPA-Cl (0.021 ml, 0.11 mmol) were added. The reaction was stirred for 1 h at room temperature. The solvents were then removed under N_2 stream and the crude residue was flash-chromatographed (5–10% diethyl ether in petroleum ether) to give **14d** (0.013 g). ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, s, -C(CH_3)CH$_3$), 0.98 (3H, s, -C(CH$_3$)CH_3), 1.09 (3H, d, J=6.9 Hz, -CHCH_3), 2.51 (1H, m, CH$_2$=CH-CH-), 3.23 (1H, d, J=6.5 Hz, -CH-OBn), 3.53 (3H, s, -OCH$_3$), 4.16 (1H, d, J=10.6 Hz, -CHHOCO), 4.25 (1H, d, J=11.3 Hz, -CH-O-CHH-Ph), 4.32 (1H, d, J=10.6 Hz, -CHHOCO-), 4.57 (1H, d, J=11.3 Hz, -CH-O-CHH-Ph), 4.93 (1H, d, J=10.5 Hz, HCH=CH), 4.98 (1H, d, J=17.2 Hz, HCH=CH), 5.85 (1H, m, CH$_2$=CH-), 7.40 (10H, m, -OCH$_2$-C$_6H_5$+-OOC-C-C$_6H_5$).

4.13. (3*S*,4*S*)-3-Hydroxy-2,2,4-trimethyl-5-oxo-pentanoic acid methyl ester 15

A stream of O_2/O_3 was bubbled through a solution of **14** (0.290 g, 1.50 mmol) in dry CH_2Cl_2 (40.0 ml) at −78°C until a faint blue color persisted. A stream of argon was then bubbled through the solution until it became colorless. Triphenylphosphine (0.490 g, 1.90 mmol) was added and the mixture was allowed to warm to room temperature and stir overnight. The solution was then concentrated and the residue was flash-chromatographed (30–70% diethyl ether in petroleum ether) to give **15** (0.226 g, 80%). R_f=0.20 (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.04 (3H, d, J=7.1 Hz, -CHCH_3), 1.18 (3H, s, -C(CH_3)CH$_3$), 1.28 (3H, s, -C(CH$_3$)CH_3), 2.51 (1H, m, CHO-CH-), 3.45 (1H, d, J=7.9 Hz, -OH), 3.68 (3H, s, COOCH_3), 4.13 (1H, dd, J=7.9, 3.5 Hz, -CH-OH), 9.61 (1H, s, OHC-). ^{13}C NMR ($CDCl_3$): δ 7.9, 21.7, 24.0, 45.8, 48.6, 52.2, 74.9, 178.0, 203.6. HR-EIMS m/z 188.1045 (M$^+$) (calcd 188,1049 for $C_9H_{16}O_4$). $[\alpha]_D^{25}$=13.8 (c 1.0, $CHCl_3$).

4.14. (2-Oxo-pentyl)-phosphonic acid diethyl ester 16

To a stirred solution of diethylmethylphosphonate (1.30 g, 8.30 mmol) in dry THF (2.0 ml) at −78°C, under N_2,

was added *n*-BuLi (1.6 M in hexane, 6.10 ml, 9.70 mmol) dropwise. The resultant yellow solution was stirred for 45 min before a solution of butyric aldehyde (0.500 g, 6.90 mmol) in dry THF (3.0 ml) was added slowly via *cannula*. The solution was stirred for an additional 2 h. Brine (10.0 ml) was added, and the mixture was allowed to warm to room temperature. THF was removed in vacuo and the aqueous residue was extracted with ethyl acetate (3×10.0 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in dry CH_2Cl_2 (8.0 ml) and 4 Å molecular sieves (3.1 g) and PDC (5.2 g, 13.8 mmol) were added. The mixture was stirred at room temperature for 2 h, then diluted with diethyl ether (8.0 ml) and allowed to stir for additional 45 min. Filtration with ethyl acetate through a short pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution which was concentrated in vacuo. The crude oil was flash-chromatographed (80–100% ethyl acetate in petroleum ether and then 10% methanol in ethyl acetate) to give **16** as a yellow oil (0.921 g, 50% for two steps). $R_f=0.45$ (ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 0.85 (3H, t, $J=7.3$ Hz, $CH_3CH_2CH_2C=O$), 1.27 (6H, t, $J=7.1$ Hz, CH_3CH_2O-), 1.55 (2H, m, $CH_3CH_2CH_2C=O$), 2.54 (2H, t, $J=7.2$ Hz, $CH_3CH_2CH_2C=O$), 3.00 (2H, d, $J=22.8$ Hz, $O=C$-CH_2-$P=O$), 4.08 (4H, m, CH_3CH_2O-). ^{13}C NMR ($CDCl_3$): δ 13.4, 16.2 (×2), 16.8, 42.3 ($J=126$ Hz), 45.8, 62.4, 62.5, 202.0. HR-EIMS m/z 222.1025 (M^+) (calcd 222,1021 for $C_9H_{19}O_4P$).

4.15. (3*S*,4*R*)-3-Hydroxy-2,2,4-trimethyl-7-oxo-dec-5-enoic acid methyl ester 17

To a mixture of LiCl (dried overnight at 140°C at 0.5 Torr, 0.022 g, 0.48 mmol) and **16** (0.100 g, 0.45 mmol) in dry acetonitrile (3.0 ml) at room temperature under N_2 dry diisopropylethylamine (0.072 ml, 0.415 mmol) was added. The resultant yellow solution was stirred for 15 min before a solution of **15** (0.065 g, 0.346 mmol) in dry acetonitrile (3.0 ml) was added via *cannula*. After the reaction mixture was stirred for 28 h, it was diluted with ethyl acetate, washed with 1N aq. HCl, H_2O and brine. The organic phase was dried on Na_2SO_4, filtered and concentrated in vacuo. The residue was flash-chromatographed (30–50% diethyl ether in petroleum ether) to give **17** (0.058 g, 66%). $R_f=0.40$ (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.92 (3H, t, $J=7.3$ Hz, CH_3CH_2-), 1.04 (3H, d, $J=6.8$ Hz, -CHCH_3), 1.19 (3H, s, -C(CH_3)CH_3), 1.24 (3H, s, -C(CH_3)CH_3), 1.61 (2H, m, CH_3CH_2-), 2.50 (3H, m, $CH_3CH_2CH_2CO$+=CH-CH-, overlapped), 2.99 (1H, d, $J=7.9$ Hz, -OH), 3.64 (1H, d, $J=7.9$, 5.9 Hz, -CHOH), 3.65 (3H, s, $COOCH_3$), 6.05 (1H, d, $J=15.8$ Hz, OC-CH=), 6.76 (1H, dd, $J=15.8$, 8.7 Hz, OC-CH=CH). ^{13}C NMR ($CDCl_3$): δ 13.8, 15.2, 17.5, 22.6, 22.7, 39.9, 42.0, 46.3, 52.1, 79.1, 129.3, 149.6, 178.0, 200.8. HR-EIMS m/z 256.1680 (M^+) (calcd 256,1675 for $C_{14}H_{24}O_4$). $[\alpha]_D^{25}=+12.1$ (c 1.0, $CHCl_3$).

4.16. (3*S*,4*R*)-3-Acetoxy-2,2,4-trimethyl-7-oxo-dec-5-enoic acid methyl ester 18

To a solution of **17** (0.126 g, 0.492 mmol) in dry CH_2Cl_2 (5.0 ml) under N_2 at room temperature was added DMAP (0.240 g, 1.97 mmol) followed by Ac_2O (0.200 ml, 1.72 mmol). The resulting mixture was stirred for 1 h at room temperature and then quenched with 0.1 N aq. HCl. The mixture was extracted with CH_2Cl_2 (3×10.0 ml) and the combined organic layers were washed successively with saturated $NaHCO_3$ and brine, dried, filtered and concentrated in vacuo. The residue was flash-chromatographed (30–40% diethyl ether in petroleum ether) to give pure **18** (0.141 g, 96%) as an oil. $R_f=0.5$ (40% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, t, $J=7.4$ Hz, CH_3-CH_2-), 0.98 (3H, d, $J=6.8$ Hz, CH_3-CH-), 1.09 (3H, s, -C(CH_3)CH_3), 1.15 (3H, s, -C(CH_3)CH_3), 1.62 (2H, m, CH_3-CH_2-CH_2-), 2.07 (3H, s, O_2CCH_3), 2.45 (2H, m, -CH_2CO), 2.57 (1H, m, CH_3CH-), 3.56 (3H, s, -$COOCH_3$), 5.26 (1H, d, $J=8.6$ Hz, -CH-OAc), 6.02 (1H, d, $J=15.9$ Hz, OC-CH=CH-), 6.56 (1H, dd, $J=15.9$ Hz and $J=9.7$ Hz, OC-CH=CH-). ^{13}C NMR ($CDCl_3$): δ 13.7, 17.2, 17.3, 18.6, 20.6, 24.3, 39.3, 42.2, 46.1, 51.9, 77.8, 130.0, 146.6, 170.3, 175.7, 200.3. HR-EIMS m/z 298.1775 (M^+) (calcd 298,1780 for $C_{16}H_{26}O_5$). $[\alpha]_D^{25}=+30.6$ (c 1.0, $CHCl_3$).

4.17. (3*S*,4*R*,7*S*)-3-Acetoxy-7-hydroxy-2,2,4-trimethyl-dec-5-enoic acid methyl ester 19 and (3*S*,4*R*,7*R*)-3-acetoxy-7-hydroxy-2,2,4-trimethyl-dec-5-enoic acid methyl ester 20

(*R*)-Me-CBS reagent (1 M in toluene, 0.470 ml, 0.470 mmol) and BH_3·THF (1 M in THF, 0.700 ml, 0.700 mmol) were mixed, under N_2 and at room temperature, and allowed to stir for 15 min. The mixture was cooled at −20°C and a solution of **18** (0.141 g, 0.470 mmol) dissolved in dry THF (5.0 ml) was then added via *cannula*. The reaction mixture was stirred for 1 h. Methanol (10.0 ml) was then added and the solution was stirred for an additional hour and allowed to warm to room temperature. The solvents were then removed in vacuo and the crude was flash-chromatographed (40–100% diethyl ether in petroleum ether) to give **19** (0.093 g; 66%) and **20** (0.018 g, 13%). **19**: $R_f=0.55$ (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, $J=6.7$ Hz, -CH_2CH_3), 0.90 (3H, d, $J=6.6$ Hz, -CHCH_3), 1.07 (3H, s, -C(CH_3)CH_3), 1.13 (3H, s, -C(CH_3)CH_3), 1.25–1.44 (4H, m, -CH_2 overlapped), 1.83 (1H, bs, -OH), 2.05 (3H, s, -Ac), 2.39 (1H, m, -CHCH_3), 3.63 (3H, s, -OCH_3) 3.96 (1H, m, -CHOH), 5.19 (1H, d, $J=8.8$ Hz, -CHOAc), 5.36 (1H, dd, $J=15.5$, 9.2 Hz, HOCHCH=CH), 5.50 (1H, dd, $J=15.5$, 5.9 Hz, HOCHCH=CH). ^{13}C NMR ($CDCl_3$): δ 14.0, 18.2, 18.5 (×2), 20.7, 24.5, 39.0, 39.4, 46.1, 51.7, 71.5, 78.8, 131.2, 134.3, 170.6, 176.3. HR-EIMS m/z 300.1941 (M^+) (calcd 300,1937 for $C_{16}H_{28}O_5$). $[\alpha]_D^{25}=+24.2$ (c 1.0, $CHCl_3$). **20**: $R_f=0.45$ (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, $J=6.7$ Hz, -CH_2CH_3), 0.92 (3H, d, $J=6.6$ Hz, -CHCH_3), 1.09 (3H, s, -C(CH_3)CH_3), 1.18 (3H, s, -C(CH_3)CH_3), 1.24–1.42 (3H, m, -CH_2CHHCHOH

overlapped), 1.54 (1H, m, -$CH_2CHHCHOH$ overlapped), 2.10 (3H, s, -Ac), 2.24 (1H, bs, -O*H*), 2.42 (1H, m, -C*H*CH_3), 3.68 (3H, s, -OCH_3) 3.88 (1H, m, -C*H*OH), 5.20 (1H, dd, $J=15.3$, 10.0 Hz, HOCHCH= *CH*), 5.23 (1H, d, $J=9.7$ Hz, -C*H*OAc), 5.20 (1H, dd, $J=15.3$, 8.0 Hz, HOCHC*H*= *C*H). ^{13}C NMR ($CDCl_3$) δ 14.0, 17.5, 18.3, 18.5, 20.8, 25.1, 38.6, 40.1, 46.0, 51.8, 73.2, 78.4, 131.9, 134,9, 170.7, 177.5. HR-EIMS m/z 300.1941 (M^+) (calcd 300,1937 for $C_{16}H_{28}O_5$). $[\alpha]_D^{25}=-1.8$ (*c* 0.6, $CHCl_3$).

4.18. (3*S*,4*R*,7*S*)-3-Acetoxy-7-hydroxy-2,2,4-trimethyldecanoic acid methyl ester 21

To a solution of **19** (0.430 mmol, 0.129 g) in methanol (6.0 ml) triethylamine (0.006 ml, 0.04 mmol) and a catalytic amount of 5% platinum on carbon were added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then stirred vigorously under hydrogen for 3 h. It was filtered through a pad of Celite® and concentrated. Flash chromatography of the residue (50–90% diethyl ether in petroleum ether) gave **21** (0.113 mg, 87%) as a colorless oil. (Found: C, 63.1; H, 10.1. $C_{16}H_{30}O_5$ requires: C, 63.5; H, 10.0). $R_f=0.45$ (60% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.80 (3H, d, $J=6.7$ Hz, CH_3CH-), 0.87 (3H, t, $J=6.8$ Hz, CH_3CH_2-), 1.11 (3H, s, -C(CH_3)CH_3), 1.13 (3H, s, -C(CH_3)CH_3), 1.21–1.42 (8H, m, $CH_3CH_2CH_2CH(OH)CH_2CH_2$-, overlapped), 1.65 (1H, m, CH_3CH-), 1.82 (1H, bs, -CHO*H*), 2.02 (3H, s, OCCH_3), 3.48 (1H, m, -C*H*OH), 3.61 (3H, s, COOCH_3), 5.08 (1H, d, $J=3.5$ Hz, -C*H*OAc). ^{13}C NMR ($CDCl_3$): δ 14.1, 15.3, 18.8, 20.3, 20.7, 23.1, 31.4, 34.2, 34.8, 39.6, 46.7, 51.9, 71.3, 79.0, 170.7, 176.5. HR-EIMS m/z 302.2098 (M^+) (calcd 302,2093 for $C_{16}H_{30}O_5$). $[\alpha]_D^{25}=+17.2$ (*c* 1.0, $CHCl_3$).

4.19. (3*S*,4*R*,7*S*)-3-Acetoxy-7-methoxy-2,2,4-trimethyldecanoic acid methyl ester 22

Compound **21** (0.079 g, 0.260 mmol) was dissolved in dry acetonitrile (1.0 ml) and methyl iodide (0.405 ml, 6.50 mmol) was added, in a reacti-vial in the dark. Ag_2O (0.180 g, 0.780 mmol) was added. The mixture was refluxed and stirred for 2 days then it was filtered and concentrated. The residue was flash-chromatographed (20–40% diethyl ether in petroleum ether) to afford **22** (0.066 g, 80%) as an oil. (Found: C, 64.8; H, 10.5. $C_{17}H_{32}O_5$ requires: C, 64.5; H, 10.2). Rf = 0.7 (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.82 (3H, d, $J=6.9$ Hz, CH_3CH-), 0.87 (3H, t, $J=6.8$ Hz, CH_3CH_2-), 1.13 (3H, s, -C(CH_3)CH_3), 1.15 (3H, s, -C(CH_3)CH_3), 1.18–1.47 (8H, m, $CH_3CH_2CH_2CH(OH)CH_2CH_2$-, overlapped), 1.64 (1H, m, CH_3CH-), 2.04 (3H, s, OCCH_3), 3.05 (1H, bs, -C*H*OCH_3), 3.26 (3H, s, -CHOCH_3), 3.63 (3H, s, -COOCH_3), 5.10 (1H, d, J = 3.8 Hz, -C*H*OAc). ^{13}C NMR ($CDCl_3$): δ 14.3, 15.4, 18.4, 20.3, 20.7, 23.1, 31.0, 31.1, 34.5, 35.6, 46.7, 51.8, 56.4, 79.1, 80.6, 170.6, 176.4. HR-EIMS m/z 316.2245 (M^+) (calcd 316,2250 for $C_{17}H_{32}O_5$). $[\alpha]_D^{25}=+12.9$ (*c* 1.0, $CHCl_3$).

4.20. (3*S*,4*R*,7*S*)-3-Hydroxy-7-methoxy-2,2,4-trimethyldecanoic acid 4

To a solution of **22** (0.050 g, 0.160 mmol) in methanol (3.0 ml), 10% aqueous KOH was added (0.360 ml, 0.640 mmol) and the mixture was stirred at 60°C for 8 h. The reaction was then treated with aqueous 1 M HCl until pH 4 and then extracted with ethyl acetate (3×5.0 ml). The organic phase was dried on Na_2SO_4, filtered and concentrated in vacuo. The residue was flash-chromatographed (50–70% ethyl acetate in petroleum ether) to give **4** (0.039 g, 94%). $R_f=0.4$ (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$): δ 0.82 (3H, d, $J=6.8$ Hz, -CHCH_3), 0.90 (3H, t, $J=7.3$ Hz, -CH_2CH_3), 1.15 (3H, s, -C(CH_3)CH_3), 1.34 (3H, s, -C(CH_3)CH_3), 1.35–1.49 (8 H, m, CH_2 overlapped), 1.69 (1H, m, -C*H*CH_3), 3.16 (1H, m, -C*H*OCH_3), 3.31 (3H, s, -CHOCH_3), 3.53 (1H, bs, -C*H*OH). ^{13}C NMR ($CDCl_3$): δ 12.9, 14.3, 18.5, 21.6, 25.6, 30.8 (×2), 34.6, 35.4, 45.1, 56.3, 79.9, 81.1, 181.9. HR-EIMS m/z 260.1984 (calcd 260,1988 for $C_{14}H_{28}O_4$). $[\alpha]_D^{25}=-31.8$ (*c* 1.0, $CHCl_3$).

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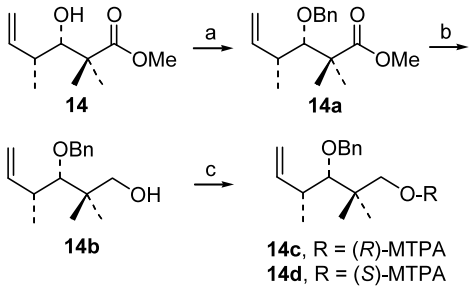
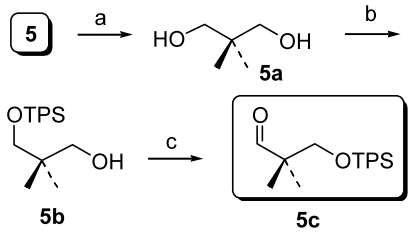
5. The e.e. of compound **7** was evaluated through deacetylation to give **14** (reported later) and transformation of the ester according the reported synthetic sequence (see Section 4), because of the very low reactivity of the C-3 secondary alcohol of **14** toward the MTPA chlorides (Scheme 5).
6. In an attempt to increase the crotylboration's yields we chose the supposed sterically less demanding 3-[(*tert*-butyl-diphenylsilyl)-oxy]-2,2-dimethyl-propanal **5c** (synthesized through the reported reaction sequence). However, also in this case, the yields of the crotylboration step were low (25–35%) (Scheme 6).
7. Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523–2533 (ozonolysis of **7** gave

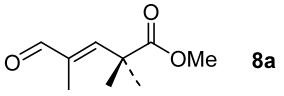


Scheme 5. *Reagents and conditions*: (a) Ag_2O, BnBr, CH_3CN, 80°C, 12 h, 31%; (c) $LiAlH_4$, THF, 0°C, 1 h, 41%; (d) (*R*)-MTPA-Cl or (*S*)-MTPA-Cl, Py, DMAP, rt, 1 h, quant.



Scheme 6. *Reagents and conditions*: (a) 2.0 equiv. of $LiAlH_4$, THF, 0°C, 1 h; (b) 0.9 equiv. of TBDPS-Cl, 1.4 equiv. of DBU, CH_2Cl_2, 0°C, 1 h; (c) 2.0 equiv. of PDC, *m.s.*, CH_2Cl_2, 60% (three steps).

also some α,β-unsaturated aldehyde **8a**, see experimental part)



8a

8. (a) Amemiya, S.; Kojima, K.; Sakai, K. *Chem. Pharm. Bull.* **1984**, *32*, 4746–4751; (b) Corey, E. J.; Marfat, A.; Hoover, D. J. *Tetrahedron Lett.* **1981**, *22*, 1587–1590.
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11. β-Hydroxy aldehydes appear to be less base-labile than β-acetoxy aldehydes. This seemed evident, for example, considering that the ozonolysis of the omoallyl alcohol **14** gave no elimination byproducts.
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13. (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504; (b) Motoyoshi, H.; Ishigami, K.; Kitahara, T. *Tetrahedron* **2001**, *57*, 3899–3908. Substoichiometric amounts of (*R*)-MeCBS reagent gave lower yields of diastereomeric alcohols; lower temperatures (–40°C) did not increase the *d.r.*
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