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Tandem cross-metathesis/hydrogenation: application to an enantioselective synthesis of pentadecyl 6-hydroxydodecanoate

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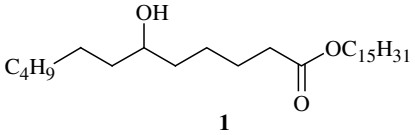
ABSTRACT

The synthesis of pentadecyl 6-hydroxydodecanoate, a component isolated from the leaves of *Artabotrys odoratissimus*, has been achieved through a tandem cross-metathesis/hydrogenation sequence. The enantioselective synthesis required first the preparation of a homoallylic alcohol obtained by a free-metal allyl transfer from a camphor derivative to heptanal.

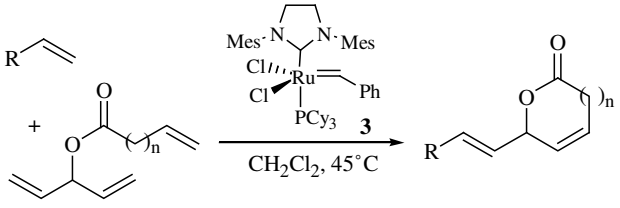
Long chain hydroxy fatty acids and esters are common frameworks in nature. Most of them exhibit important biological activities, or have found application in the cosmetic and perfume industries.[1] Pentadecyl 6-hydroxy-dodecanoate **1** has been isolated and characterized by Mehta et al. from the leaves of *Artabotrys odoratissimus* (Fig. 1).[2] Due to its potential biological activities in the treatment of cholera, the synthesis of this compound has been performed by Ballini et al. in five steps, including a nitroaldol condensation as the key-reaction.[3]

Having developed a straightforward access to substituted pyrones **4** from 3-*O*-(1,4-pentadienyl) butanoate **2a** by a tandem ring-closing/cross-coupling metathesis reaction[4,5] (Scheme 1), we have now investigated the synthesis of **1** by a similar strategy performed on the homologous ester **2b** ($n = 2$). The RCM could deliver the unsaturated caprolactone while the vinyl group could be functionalized with hexene ($R = C_4H_9$) according to a subsequent cross-metathesis. Reduction of the two double bonds and ring-opening of the lactone with pentadecanol could be performed to finally deliver the target molecule **1**.



1

Figure 1.



2a (n = 1) **4** (39-75%)
2b (n = 2) **5**

Scheme 1.

Unsaturated ester **2b**, easily prepared by esterification under DCC activation,[6] was first engaged into a ring-closing metathesis process without addition of an alkene counterpart and in the presence of catalytic amounts of Grubbs' type II catalyst **3**. Instead of the expected unsubstituted heptenolide **5**, we observed the formation of two macrodiolides **6a** and **6b** in similar amounts (Scheme 2). These symmetric compounds result from a cross-coupling/ring-closing process between two molecules of **2**, and differ only by the relative configuration of one of the two stereocenters.[7] ^{1}H NMR spectra show unambiguously that the configuration of the internal C=C bond is *E* for the two diastereoisomers ($J = 15.1$and 15.5 Hz).[8] The same reaction performed in the presence of *n*-hexene delivered an inseparable mixture of compounds.

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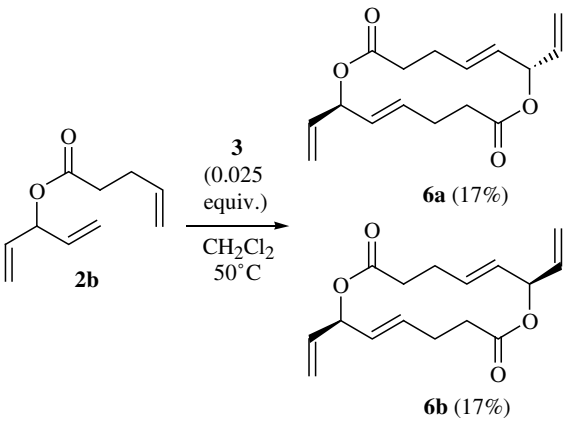
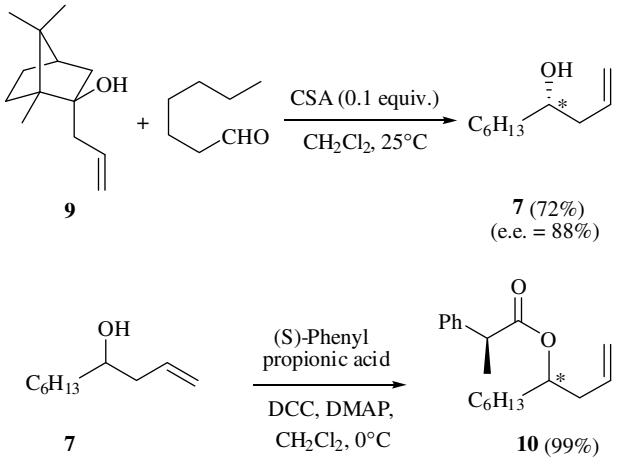


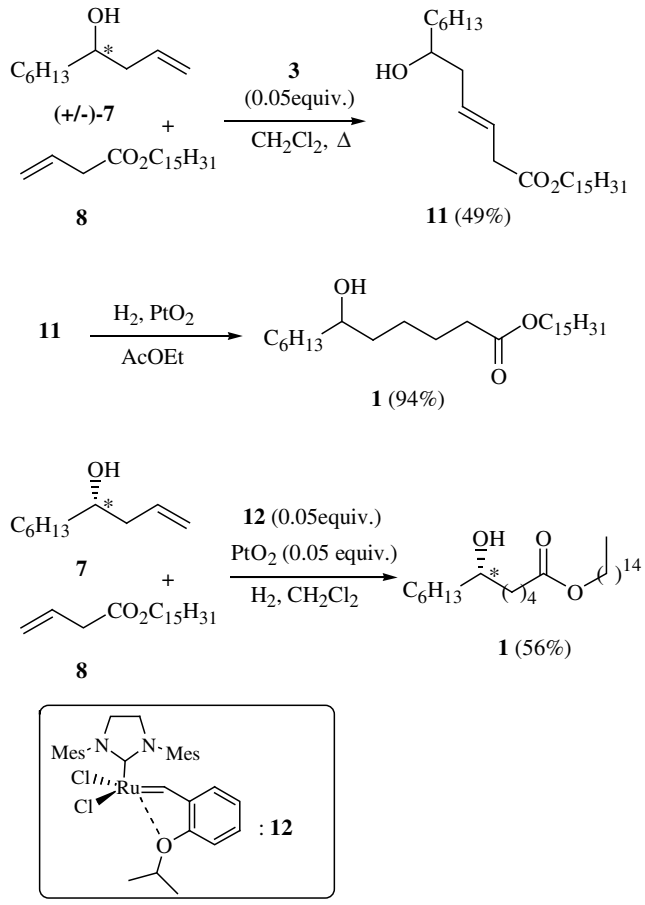
Scheme 2.

While the tandem RCM/CM appeared unefficient, we turned to another strategy based on a tandem cross-metathesis/hydrogenation,[9,10] which could directly afford the expected structure in a single step from readily available homoallylic alcohol **7** and pentadecanyl but-2-enoate **8**. Moreover, in order to develop an enantioselective synthesis of **1**, we synthesized **7** by the allyltransfer method reported by Loh and co-workers[11] and we previously used for the synthesis of the hermitamides.[12] Thus, heptanal was treated with the allyl isoborneol **9** in the presence of catalytic amounts of camphorsulfonic acid at rt to deliver **7** in 72% yield and in 88% ee (Scheme 3).

The enantiomeric excess was determined by derivatization of the alcohol **7** with homochiral (*S*)-2-phenylpropionic acid.[13] It should be noted that **7** in racemic form was also esterified with the same acid to give a 1:1 mixture of the two diastereoisomers **10**, which denotes no kinetic resolution during this process. The cross-metathesis was first performed between racemic alcohol **7** and **8**. Compound **11** was obtained apparently as a single isomer in 49% yield and according to previous results, the *E* configuration has been assigned to the new C=C bond. Hydrogenation over PtO_2 gave (+/−)-**1** in 94% yield. Starting from enantiomeric enriched **7**, the tandem cross-metathesis/hydrogenation was achieved under a hydrogen atmosphere in the presence of Grubbs-Hoveyda reagent **12**[14] and catalytic amounts of PtO_2. By this way, **1** was directly isolated in 56% yield (Scheme 4).[15,16]



Scheme 3.



Scheme 4.

In conclusion, the synthesis of (6*S*)-pentadecyl 6-hydroxydodecanoate **1** has been performed in only two steps from heptanal. This strategy can be favorably compared to the previous synthesis, which required up to five steps, and was performed on racemic form.

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7. Data for **6a** and **6b**: ^{1}H NMR ($CDCl_3$): δ 2.37–2.43 (4H, m); 5.19 (1H, d, J = 10.3 Hz); 5.27 (1H, d, J = 16.9 Hz); 5.46 (1H, dd, J = 7.7, 15.1 Hz); 5.66–5.75 (2H, m); 5.85 (1H, ddd, J = 16.9, 10.3, 5.9 Hz). ^{1}H NMR ($CDCl_3$): δ 2.37–2.56 (4 H, m); 5.19 (1H, d, J = 10.4 Hz); 5.27 (1H, d, J = 17.2 Hz); 5.43 (1H, dd, J = 8.1, 15.5 Hz); 5.65–5.77 (2H, m); 5.88 (1H, ddd, J = 17.2, 10.4, 5.5 Hz).

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15. *Experimental procedures and data*: Homoallylic alcohol **7**: CSA (70 mg, 0.30 mmol, 0.1 equiv) was added to a solution of heptanal (1.14 g, 3.00 mmol, 1 equiv) and allylated camphor (1.75 g, 9.00 mmol, 3 equiv) in DCM (6 M, 0.5 mL). The resulting mixture was stirred at room temperature for 5 days. Then $NaHCO_3$ (5 mL) and DCM (5 mL) were added and the aqueous phase was separated, and extracted with DCM (3×5 mL). The combined organic extracts were washed with brine (10 mL), and then dried over magnesium sulfate, and concentrated. Purification of the residue by flash chromatography (5% ethyl acetate–petroleum ether) afforded alcohol **7** as a colorless oil (337 mg, 72% yield). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz); 1.29–1.59 (10H, m), 2.08–2.18 (1H, m), 2.26–2.35 (1H, m), 3.60–3.68 (1H, m), 5.11–5.16 (2H, m), 5.83 (1H, ddt, J = 16.2, 9.8, 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.7, 29.4, 31.9, 36.9, 42.0, 70.8, 117.9, 135.1. IR: ν = 3368, 3077, 2930, 2859, 1459, 993, 912 cm^{-1}. $[\alpha]_D$ −8.7 (c 1.06, $CHCl_3$). Ester **8**: DMAP (367 mg, 3.0 mmol, 0.3 equiv) and DCC (2.27 g, 11.0 mmol, 1.1 equiv) were added successively at room temperature to a solution of pentadecan-1-ol (2.28 g, 10.0 mmol, 1 equiv) and vinylacetic acid (947 mg, 11.0 mmol, 1.1 equiv) in DCM (50 mL). The resulting mixture was stirred at room temperature for 6 h. DCM was then removed under vacuum, and the residue was dissolved in Et_2O. Then urea was filtered off, and rinsed with Et_2O. The filtrate was then concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (5% ethyl acetate–hexanes) to afford ester **8** as a colorless oil (2.96 g, 99% yield). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, H_{19}), 1.25–1.30 (24H, m), 1.60–1.65 (2H, m), 3.08 (2H, d, J = 7.0 Hz), 4.08 (2H, t, J = 6.8 Hz), 5.13–5.20 (2H, m), 5.93 (1H, ddt, J = 17.3, 9.8, 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.2, 22.8, 26.0, 28.7, 29.3, 29.5, 29.6, 29.7, 29.8, 32.0, 39.3, 64.9, 118.4, 130.5, 171.6. IR (neat): ν = 3072, 2925, 2854, 1742, 1467, 1171 cm^{-1}. Formation of **11**: Nitrogen was bubbled through a solution of homoallylic alcohol **7** (156 mg, 1.0 mmol) and ester **8** (593 mg, 2.0 mmol) in DCM (0.2 M, 5 mL) for 10 min. Then, Grubbs' second generation catalyst (21 mg, 0.025 mmol) was added, and the resulting mixture was heated to reflux and stirred for 15 h. After cooling to room temperature, DCM was evaporated. The residue was then purified by flash chromatography on silica gel (10% ethyl acetate–hexanes) to give alkene **11** (210 mg, 49% yield). ^{1}H NMR ($CDCl_3$): δ 0.86–0.90 (6H, m); 1.26–1.30 (34H, m); 1.57–1.62 (4H, m); 3.06 (2H, d, J = 5.7 Hz); 3.58–3.65 (1H, m); 4.07 (2H, t, J = 6.8 Hz); 5.53–5.75 (2H, m). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.1, 22.7, 22.8, 25.7, 25.9, 28.6, 29.3, 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 31.9, 31.9, 36.9, 38.1, 40.6, 64.9, 70.8, 125.2, 130.8, 172.1 IR: ν = 3434, 2956, 2920, 2851, 1734, 1468, 1078 cm^{-1}. MS: (ESI) m/z = 447 (M+Na$^+$, 100). HRMS: (ESI) 447.3815 (M+Na$^+$, $C_{27}H_{52}O_3Na$ requires 447.3814).
16. *Tandem cross-metathesis/hydrogenation procedure*: A solution of homoallylic alcohol **7** (78 mg, 0.50 mmol, 1 equiv) and ester **8** (297 mg, 1.00 mmol, 2 equiv) in DCM (0.2 M, 2.5 mL) was placed under vacuum, purged with H_2. Grubbs-Hoveyda catalyst (16 mg, 0.025 mmol, 0.05 equiv) and PtO_2 (7.1 mg, 0.025 mmol, 0.05 equiv) were introduced at once. The reaction mixture was degassed again under vacuum and then vigorously stirred under one atmosphere of hydrogen. After 15 h at room temperature, the solvent was evaporated, and the residue was purified by flash chromatography (10% ethyl acetate–hexanes) to give pentadecyl 6-hydroxydodecanoate **1** (120 mg, 56% yield). ^{1}H NMR ($CDCl_3$): δ 0.86–0.90 (6H, m); 1.24–1.68 (42H, m); 2.31 (2H, d, J = 7.4 Hz); 3.58–3.61 (1H, m); 4.05 (2H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.2, 22.7, 22.8, 25.1, 25.3, 25.7, 26.0, 28.7, 29.4, 29.5, 29.6, 29.7, 29.8, 29.8, 31.9, 32.0, 34.4, 37.1, 37.6, 64.6, 71.7 173.9. IR neat: ν = 3348, 2918, 2850, 1728, 1460, 1191 cm^{-1}. MS: (ESI) m/z = 449 (M+Na$^+$, 100). HRMS: (ESI) 449.3971 (M+Na$^+$, $C_{27}H_{54}O_3Na$ requires 447.3971). $[\alpha]_D$ +0.4 (c 1.6, $CHCl_3$).