[3,3]-Sigmatropic Rearrangements in the Enantioselective Synthesis of (–)-Methylenolactocin

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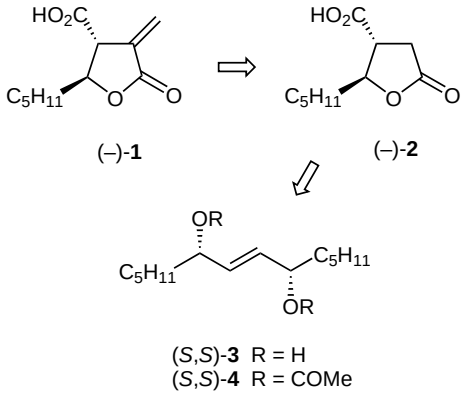
Abstract: A Pd(II)-catalyzed [3,3]-sigmatropic rearrangement is used to transfer chirality from an enantio-enriched alk-3-ene-1,2-diol to a C_2-symmetrical alk-2-ene-1,4-diol which, in turn, can be converted into a precursor of (–)-methylenolactocin through an additional [3,3]-sigmatropic rearrangement (either Johnson orthoester or Ireland–Claisen rearrangement).

Key words: rearrangement, diols, asymmetric synthesis, dihidroxylations

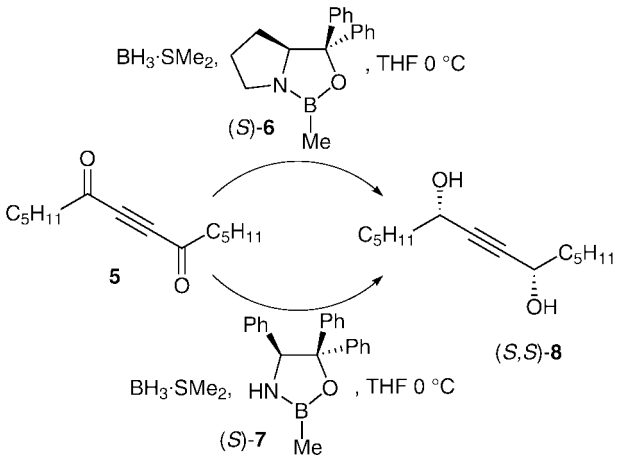
Enantio-enriched 1,4-diols have been proven to be versatile synthons for asymmetric synthesis. In particular, C_2-symmetrical 1,4-diols and their derivatives have shown to be useful building blocks for the preparation, *inter alia*, of 2,5-disubstituted pyrrolidines,[1] thiolanes,[2] and phosphine ligands.[3] In the last years, we have been interested in the conversion of these diols into natural products.[4] In this connection, we have disclosed very recently a novel route to (–)-methylenolactocin [(–)-**1**], based on a desymmetrization process (Scheme 1).[4b,5]



Scheme 1

(–)-Methylenolactocin [(–)-**1**] has attracted much attention due to its selective antibacterial activity against Gram-positive bacteria and its antitumor activity. Since its isolation from a culture filtrate of fungi of the genus *Penicillium* in 1988,[6] a number of racemic[7] or enantioselective[8] syntheses of **1** have been described. Due to the fact that conversion of lactone (–)-**2** to (–)-**1** in one step is a well-known reaction,[9] many authors have focused their attention to the synthesis of (–)-**2**.[10]

In an effort to improve the efficiency of our synthetic approach to (–)-**2**, we have looked for better routes of access to alk-2-ene-1,4-diols like (*S*,*S*)-**3**, the key intermediate in our synthesis. The initial proposal was by reduction of the parent acetylenic 1,4-diketone **5** (Scheme 2).[11] This goal was successfully accomplished by slow addition of **5** to a solution of $BH_3{\cdot}SMe_2$ (BMS) in the presence of oxazaborolidine (*S*)-**6**[12] or (*S*)-**7**[11] in THF to afford (*S*,*S*)-**8** (70%, >99% ee) along with (*R*,*S*)-**8** (*meso*-isomer). As expected, the observed diastereoselectivity depends on the amount of catalyst used (Table 1). Furthermore, in the reduction of the triple bond to allylic diol (*S*,*S*)-**3** (90%, $LiAlH_4$, THF, Δ), the undesired *meso*-isomer could be readily removed by flash chromatography and the pure allylic diol was transformed into its diacetate (*S*,*S*)-**4**.



Scheme 2

Table 1 Oxazaborolidine-Mediated Reduction of **5**

Entry	Catalyst (equiv)	(*S*,*S*)/(*R*,*S*) Ratio	ee (%)	Yield (%)
1	(*S*)-**6** (2.0)	92:8	>99	65
2	(*S*)-**6** (1.0)	85:15	>99	70
3	(*S*)-**6** (0.4)	82:18	>99	70
4	(*S*)-**7** (0.4)	82:18	>99	70
5	(*S*)-**6** (0.2)	74:26	99	60

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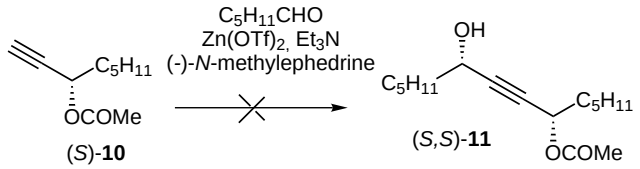
Despite the excellent stereoselectivity achieved, this approach requires a large number of steps. Thus, three steps are needed to obtain **4** starting from **5**, which is not commercially available. Preparation of **5** required three steps more: addition of hexanal to a premixed solution of oct-1-yne and BuLi to give crude tetradec-7-yn-6-ol **9** (94%) which was treated first with *t*-BuOOH/SeO_2 according to a Sharpless procedure[13] and then with $NaBH_4$ in MeOH to afford diol **8** as a mixture of stereoisomers. This mixture was finally transformed into diketone **5** by the Jones' oxidation. Thus, a more efficient stereoselective access to the pivotal intermediate **4** would be desirable.

Consequently, we turned our attention to the stereoselective addition of alkynyl acetate (*S*)-**10**, easily obtained from commercially available (*S*)-oct-1-yn-3-ol, to hexanal using our recently described protocol (Scheme 3).[14] Unfortunately, our attempts to obtain **11** in the presence of $Zn(OTf)_2$, (–)-*N*-methylephedrine and Et_3N were unsuccessful, yielding a crude in which the desired adduct was a minor product despite several trials performed under different conditions (r.t. to 60 °C, up to two-fold reagents).[15] In fact, Carreira et al. had reported that in the case of α-unbranched aldehydes, as hexanal, these kinds of additions are less efficient.[16]

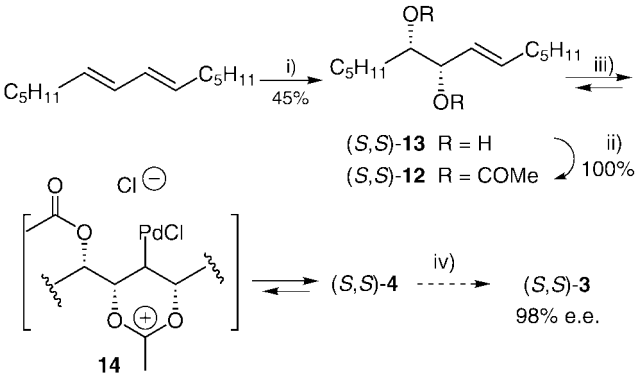


Scheme 3

Finally, looking for a more convenient way to the chiral 1,4-diol motif, we explored an alternative process based on a Pd(II)-assisted isomerization of allylic diacetate **12** to **4** as shown in Scheme 4. Tetradeca-6,8-diene, readily obtained from hept-1-yne by an one-pot process,[17] was subjected to Sharpless asymmetric dihydroxylation[18] to give highly enantio-enriched diol (*S*,*S*)-**13**. The allylic isomerization of its diacetate (*S*,*S*)-**12** was next explored in several solvents but the best results were obtained in toluene.[19] Thus, the treatment of (*S*,*S*)-**12** with 5% $PdCl_2(PhCN)_2$ as catalyst in toluene at 80 °C for 12 hours led us to obtain the desired (S,*S*)-**4** with complete transfer of chirality (63%, only one diastereomer, 98% ee),[20] besides a 27% of starting material, which can be recycled.

As far as the mechanism of the allylic rearrangements is concerned, an oxypalladation of the alkene have been proposed to give a cyclic intermediate (**14**, in Scheme 4).[21] This mechanism is in agreement with the complete transfer of the chirality observed in this [3,3]-sigmatropic rearrangement of the acetate group.[22]

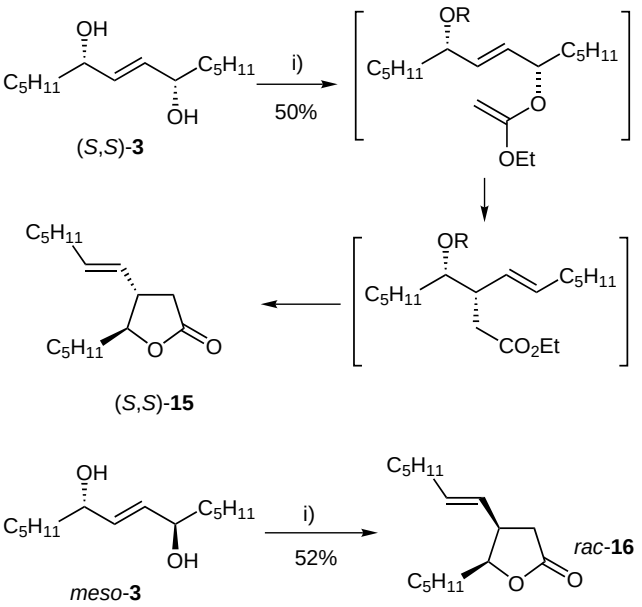
Having in hand highly enantio-enriched diol (*S*,*S*)-**3** or its diacetate (*S*,S)-**4**, the synthesis of (–)-methylenolactocin [(–)-**1**] is a straightforward process. We have developed



Scheme 4 *Reagents and conditions*: i) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C; ii) Ac_2O, Et_3N, DMAP cat., CH_2Cl_2; iii) 5% mol $Pd(PhCN)_2Cl_2$, anhyd toluene, Δ; iv) NaOMe/MeOH, r.t.

two approaches based on [3,3]-sigmatropic rearrangements starting from either **3** or **4**.

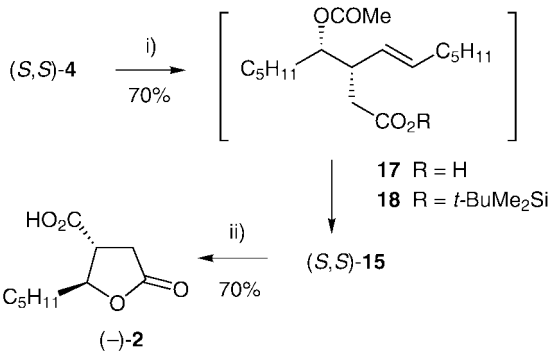
In this sense, our efforts were first focused on the study of the Johnson orthoester rearrangement of diol (*S*,*S*)-**3** (Scheme 5).[23] To our satisfaction, we found that by refluxing (*S*,*S*)-**3** in $CH_3C(OEt)_3$ with a catalytic amount of pivalic acid, the lactone (*S*,*S*)-**15** was isolated in 50% yield in a single step with complete stereoselectivity. In this connection, it is noteworthy that the same conditions when applied to *meso*-**3** led to the isomeric lactone *rac*-**16**.



Scheme 5 *Reagents and conditions*: i) $CH_3C(OEt)_3$, *t*-$BuCO_2H$ cat., Δ

Since the preparation of diacetate (*S*,*S*)-**4** is more straightforward (see Scheme 4), we then turned our attention to the Ireland–Claisen rearrangement[24] of its *tert*-butyldimethylsilyl enolates. When we treated (*S*,*S*)-**4** with an excess of *t*-$BuMe_2SiCl$ and potassium bis(trimethylsilyl)amide (KHMDS) in THF at –78 °C and then heated the mixture in refluxing toluene we isolated the acid **17** (44%) besides

its *tert*-butyldimethylsilyl ester (**18**, 44%). Since basic hydrolysis (LiOH, in refluxing 1:1 THF–H_2O) of both **17** and **18** separately, followed by acidic treatment led to (*S*,*S*)-**15**, we attempted the direct transformation of (*S*,*S*)-**4** into (*S*,*S*)-**15** without isolation of any intermediate. We were gratified to obtain a 70% overall yield of (*S*,*S*)-**15** in such a transformation, as outlined in Scheme 6. Eventually, lactone (–)-**2** was readily obtained by $RuCl_3/NaIO_4$ oxidation[25] of compound (*S*,*S*)-**15**.



Scheme 6 *Reagents and conditions*: i) (a) KHMDS, *t*-$BuMe_2SiCl$, THF, –78 °C to r.t., then anhyd toluene, Δ; (b) LiOH, H_2O–THF, Δ; (c) aq HCl/THF, Δ; ii) cat. $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O (2:2:3)

In conclusion, we have described that the use of an unprecedented tandem asymmetric dihydroxylation/Pd(II)-assisted isomerization allowed us to reduce to 6 steps the stereoselective synthesis of lactone (–)-**2** from hept-1-yne. This constitutes a concise catalytic formal synthesis of (–)-methylenolactocin [(–)-**1**], which explores and exemplifies the usefulness of [3,3]-sigmatropic rearrangements in allylic diols by transferring chirality from one carbon to another.

All the solvents were distilled from an appropriate drying agent and stored under N_2. The crude products were purified by column chromatography on silica gel of 230–400 mesh (flash chromatography). Thin-layer chromatograms were performed on HF_{254} silica gel plates (using CH_2Cl_2, CH_2Cl_2–MeOH or hexane–EtOAc as the eluents, as indicated after the R_f values). NMR spectra were recorded in $CDCl_3$ at 300 MHz or 400 MHz for ^1H, 50.3 MHz for ^{13}C, and 282.2 MHz for ^{19}F. Chemical shifts are given in ppm with respect to internal TMS (^1H and ^{13}C NMR) or with respect to external CF_3CO_2H (^{19}F NMR). IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer on NaCl plates (neat); only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Optical rotations were measured at 20 ± 2 °C. Chemical ionization mass spectra (NH_3) are given in *m*/*z*. HRMS (EI or FAB+) were obtained at the CACTI (Universidad de Vigo). $Zn(OTf)_2$ was dried overnight at 120 °C under vacuum prior use. Tetradeca-6,8-diene[17b] and compounds (*S*)-**6**,[26] (*S*)-**7**,[27] (*S*)-**10**,[28] and were prepared according to published procedures. (–)-*N*-Methylephedrine and (*S*)-oct-1-yn-3-ol are commercially available.

Tetradec-7-yne-6,9-diol (8)

To a magnetically stirred solution of oct-1-yne (10 mL, 65.7 mmol) in anhyd THF (200 mL) was added a solution of BuLi in hexanes (39.4 mL, 63.04 mmol) dropwise at 0 °C under argon. After 30 min, hexanal (7.73 mL, 62.26 mmol) was added and the resulting solution was stirred for 5 min at 0 °C and 30 min at r.t. Then, the mixture was poured into CH_2Cl_2 (200 mL) and pH 7 phosphate buffer (100 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 12.47 g of the crude product. The NMR spectra of the crude revealed that it contained mainly of tetradec-7-yne-6-ol (**9**; 12.47 g, 94%) and was then used without further purification.

Tetradec-7-yne-6-ol (9)

Oil; R_f 0.35 (CH_2Cl_2).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, 6 H, *J* = 7.4 Hz, CH_3), 1.25–1.33 (m, 14 H, CH_2), 2.20 (m, 2 H, $CH_2C{\equiv}C$), 4.35 (t, 1 H, *J* = 6.0 Hz, C*H*OH).

^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 18.2 (*C*$H_2C{\equiv}C$), 22.5, 22.6, 24.9, 28.5, 28,6, 31.5, 38.2, 62.7 (*C*HOH), 85.9 (C≡C).

A solution of *t*-butyl hydroperoxide (TBHP) in CH_2Cl_2 was obtained by swirling commercial aq TBHP (70 wt% in H_2O, 43.0 mL, 0.31 mol) with CH_2Cl_2 (50 mL) in a separatory funnel. The milky mixture was allowed to stand until complete separation of the layers had occurred. The organic layer was separated and dried (Na_2SO_4). To this solution of TBHP in CH_2Cl_2 was added SeO_2 (4.48 g, 39.56 mmol). The mixture was magnetically stirred for 15 min at r.t. and the crude compound **9** (12.47 g) was added dropwise. The reaction mixture was stirred for 24 h at r.t. Then, aq KOH (90 mL) and CH_2Cl_2 (50 mL) were slowly added to the reaction mixture cooled in an ice bath. After 25 min, the organic layer, cooled in an ice bath, was stirred with aq sat. $NaHSO_3$ (280 mL) for 30 min to destroy excess of TBHP. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to a pale-yellow oil. This oil was dissolved in MeOH (100 mL), and the resulting solution was cooled in an ice bath. Then, $NaBH_4$ (2.04 g, 53.9 mmol) was cautiously added over a period of 5–10 min. After 15 min, the reaction mixture was poured into a cold mixture of pH 7 phosphate buffer (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was decanted and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2) to give 7.40 g (55%) of tetradec-7-yne-6,9-diol (**8**) as a mixture of stereoisomers besides 2.74 g (22%) of tetradec-7-yne-6-ol (**9**).

Tetradec-7-yne-6,9-dione (5)

To a stirred solution of tetradec-7-yne-6,9-diol (**8**; 1.12 g, 4.96 mmol) in acetone (25 mL) in an ice bath was added a solution of Jones' reagent (8.0 g of CrO_3 in 7.6 mL conc. H_2SO_4 and 20 mL H_2O) dropwise until an orange color persisted. The reaction mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (50 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2) to give 825 mg (75%) of **5** as a pale yellow oil; R_f 0.87 (CH_2Cl_2–MeOH, 95:5).

IR (film): 2985, 1690, 1140 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (t, 6 H, *J* = 6.6 Hz, CH_3), 1.20–1.31 (m, 12 H, CH_2), 2.63 (m, 4 H, CH_2CO).

^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 22.3, 23.4, 31.0, 40.2 (*C*H_2CO), 84.2 (C≡C), 184.4 (C=O).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.31; H, 10.05.

Stereoselective Reduction of Diketone 5; (6*S*,9*S*)-Tetradec-7-yne-6,9-diol [(*S*,*S*)-8]

A solution of diketone **5** (161 mg, 0.72 mmol) in THF (2 mL) was added slowly to a solution of oxazaborolidine (*S*)-**6** (0.29 mmol) and $BH_3{\cdot}SMe_2$ (156 μL, 1.56 mmol) in THF (1 mL) at 0 °C under

argon. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. The reaction was cautiously quenched by slow addition of MeOH (0.5 mL) at 0 °C. The solution was stirred for 15 min at r.t. and then concentrated under vacuum. The residue was purified by flash chromatography (9:1 hexane–EtOAc) to yield 114 mg (70%) of enantio-enriched (6*S*,9*S*)-tetradec-7-yne-6,9-diol [(*S*,*S*)-**8**]. An analytical sample of the crude was treated with an excess of (*S*)-Mosher acid chloride [derived from (*R*)-acid] to give a mixture of Mosher diesters. A careful analysis by ^{19}F NMR revealed a 4.6:1 *dl*/*meso* ratio and >99% ee. When the same reaction was carried out using (*S*)-**7** as chiral auxiliary, a similar result was obtained (70% yield, 4.5:1 *dl*/*meso* ratio, >99% e.e). A similar reduction using a molar ratio of (*S*)-**6**/diketone = 1 led to (*S*,*S*)-**8** in 70% yield, with a *dl*/*meso* ratio of 5.7:1 and >99% ee. Similarly, when a molar ratio of 2 was used, compound (*S*,*S*)-**8** was obtained in 65% yield with *dl*/*meso* ratio of 12:1 and >99% ee. In the same way, the reduction using a molar ratio (*S*)-**6**/diketone = 0.2 led to (*S*,*S*)-**8** in 60% yield, with a *dl*/*meso* ratio of 2.8:1 and 99% ee.

Oil; R_f 0.20 (95:5 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ –11.5 (*c* = 0.9, $CHCl_3$).

IR (film): 3300, 2920, 2235, 1440 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.27–1.75 (m, 16 H, CH_2), 3.01 (br s, 2 H, OH), 4.39 (t, 2 H, *J* = 6.2 Hz, C*H*OH).

^{13}C NMR ($CDCl_3$): δ = 15.0 [*C*H$_3$(CH$_2$)$_4$], 22.5, 24.9, 31.4 and 37.6 (CH_2), 62.3 (CHOH), 85.9 (C≡*C*).

HRMS: *m*/*z* calcd for $C_{14}H_{26}O_2$: 226.1933; found: 226.1930.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.02; H, 11.65.

(6*S*,7*E*,9*S*)-Tetradec-7-ene-6,9-diol [(*S*,*S*)-3]

To a solution of (*S*,*S*)-**8** (120 mg, 0.53 mmol, containing 18% of the *meso* isomer) in anhyd THF (10 mL) was added $LiAlH_4$ (57 mg, 1.5 mmol) and the resulting mixture was heated to reflux. The progress of the reaction was monitored by TLC. After 3 h, the mixture was cooled to 0 °C and then cautiously quenched by dropwise addition of EtOAc (1 mL) followed by a 2 M aq solution of sodium potassium tartrate (5 mL). The mixture was stirred at r.t. overnight and then poured into CH_2Cl_2 and brine. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuo. The residue was purified by flash chromatography (2:1 hexane–EtOAc) to give 93 mg (77%) of (*S*,*S*)-**3** and 16 mg (13%) of *meso*-**3** (90% overall yield). An analytical sample of the isolated (*S*,*S*)-**3** was treated with an excess of (*S*)-Mosher acid chloride [derived from (*R*)-acid] to give a mixture of Mosher diesters. A careful analysis by ^{19}F NMR revealed >99% ee. (δ = –70.93 for *R*,*R* isomer; δ = –71.06 for *S*,*S* isomer).

(6*S*,7*E*,9*S*)-Tetradec-7-ene-6,9-diol [(*S*,*S*)-3]

Oil; R_f 0.33 (95:5 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +6.3 (*c* = 2.3, $CHCl_3$).

IR (film): 3320, 2934, 1440 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.28–1.56 (m, 14 H, CH_2), 3.25 (br s, 2 H, OH), 4.05 (m, 2 H, C*H*OH), 5.59 (m, 2 H, CH=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 [*C*H$_3$(CH$_2$)$_4$], 22.6, 25.1, 31.7 and 37.0 (CH_2), 72.3 (CHOH), 134.4 (CH=*C*H).

HRMS: *m*/*z* calcd for $C_{14}H_{28}O_2$: 228.2089; found: 228.2088.

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: 73.63; H, 12.53.

(6*R*,7*E*,9*S*)-Tetradec-7-ene-6,9-diol [*meso*-3][29]

Mp 74–75 °C (Lit.[29] mp 69–70 °C); R_f 0.41 (CH_2Cl_2–MeOH, 95:5).

IR (film): 3320, 2920, 1450 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.29–1.52 (m, 14 H, CH_2), 2.55 (br s, 2 H, OH), 4.10 (m, 2 H, C*H*OH), 5.68 (m, 2 H, CH=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 [*C*H$_3$(CH$_2$)$_4$], 22.6, 25.1, 31.7 and 37.1 (CH_2), 66.3 (CHOH), 133.3 (CH=*C*H).

HRMS: *m*/*z* calcd for $C_{14}H_{28}O_2$: 228.2089; found: 228.2091.

(1*S*,2*E*,4*S*)-4-Acetoxy-1-pentylnon-2-enyl Acetate [(*S*,*S*)-4]; Typical Procedure

Ac_2O (150 μL, 1.59 mmol) was added to a stirred solution of (*S*,*S*)-**3** (93 mg, 0.41 mmol), Et_3N (128 μL, 0.92 mmol) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in anhyd CH_2Cl_2 (3 mL) at r.t. The progress of the reaction was monitored by TLC. When TLC had revealed the disappearance of the starting diol (6 h), more CH_2Cl_2 (20 mL) was added and the solution was washed with 0.5 M aq HCl, sat. aq $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated under vacuo. The residue was purified by flash chromatography (9:1 hexane–EtOAc) to give 119 mg (93%) of (*S*,*S*)-**4** as an oil; R_f 0.33 (hexane–EtOAc, 2:1); $[\alpha]_D^{20}$ –48.0 (*c* = 2.4, $CHCl_3$).

IR (film): 2934, 1740 (C=O), 1371, 1238, 1020 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (t, 6 H, *J* = 6.9 Hz, C*H*$_3$CH$_2$), 1.55 (m, 12 H, CH_2), 1.61 (m, 4 H, CH_2), 2.06 (s, 6 H, $COCH_3$), 5.19 (m, 2 H, C*H*OAc), 5.81 (m, 2 H, CH=CH).

^{13}C NMR ($CDCl_3$): δ = 13.9 [*C*H$_3$(CH$_2$)$_4$], 22.4 (CO*C*H$_3$), 24.6, 24.7, 31.4 and 34.2 (CH_2), 73.7 (*C*HOAc), 130.8 (CH=*C*H), 171.6 (C=O).

HRMS: *m*/*z* calcd for $C_{18}H_{32}O_4$: 312.2301; found: 312.2298.

Attempts at Stereoselective Alkynylation of Hexanal with (*S*)-1-Pentylprop-2-ynyl Acetate [(*S*)-10]

A slurry of dry $Zn(OTf)_2$ (408 mg, 1.1 mmol), (–)-*N*-methylephedrine (220 mg, 1.2 mmol), alkyne (*S*)-**10** (168 mg, 1 mmol) in anhyd toluene (300 μL), and Et_3N (167 μL, 1.2 mmol) was vigorously stirred under argon at r.t. After 30 min, hexanal (132 μL, 1.1 mmol) was added dropwise by syringe to the mixture at 60 °C. After 24 h, TLC revealed a complex crude in which the starting alkyne had almost disappeared. The mixture was poured directly into a silica gel column and purified by flash chromatography (hexane–EtOAc, 9:1). None of the collected fractions revealed the presence of a significant amount of the desired adduct. Other attempts with two-fold excess of $Zn(OTf)_2$, (–)-*N*-methylephedrine and Et_3N at 60 °C or r.t. for 1–3 d were also unsuccessful.

Asymmetric Dihydroxylation of Tetradeca-6,8-diene; (6*S*,7*S*,8*E*)-Tetradec-8-ene-6,7-diol [(*S*,*S*)-13]

Tetradeca-6,8-diene[17b] (0.630 g, 3.24 mmol) was added to a mixture of AD-mix-α (4.60 g) and $CH_3SO_2NH_2$ (0.320 g, 3.26 mmol) in 1:1 *tert*-butyl alcohol–H_2O (15 mL of each) at 0 °C and the mixture was stirred at this temperature overnight. The reaction was quenched by slow addition of Na_2SO_3 (5 g) and the suspension was warmed to r.t. while stirring vigorously. After 30 min, CH_2Cl_2 (30 mL) was added and the aqueous layer was further extracted with more CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 2 N aq KOH (10 mL) and dried ($MgSO_4$). The crude was purified by flash chromatography (hexane–EtOAc, 95:5) to give 333 mg (45%) of (*S*,*S*)-**13**; oil; R_f 0.38 (hexane–EtOAc, 2:1); $[\alpha]_D^{20}$ –11.5 (*c* = 1.0, $CHCl_3$).

IR (film): 3230, 2925, 1442 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.26–1.40 (m, 14 H, CH_2), 2.04 (m, 2 H, C*H*$_2$CH=), 2.87 (br s, 2 H, OH), 3.42 (m, 1 H, C*H*OHCH$_2$), 3.83 (m, 1 H, C*H*OHCH=), 5.43 (m, 1 H, CH$_2$CH=C*H*), 5.74 (m, 1 H, CH$_2$C*H*=CH).

^{13}C NMR ($CDCl_3$): δ = 13.9 and 14.0 (CH_3), 22.4, 22.5, 25.2, 28.6, 31.3, 31.8, 32.3 and 32.9 (CH_2), 74.6 and 76.4 (CHOH), 129.2 and 134.9 (CH=*C*H).

HRMS: *m*/*z* calcd for $C_{14}H_{28}O_2$: 228.2089; found: 228.2097.

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.85; H, 12.22.

(1*S*,2*S*,3*E*)-2-Acetoxy-1-pentylnon-3-enyl Acetate [(*S*,*S*)-12]

Acetylation of (*S*,*S*)-**13** was carried out as described for diol (*S*,*S*)-**3**; yield: ca. 100%.; pale-yellow oil; R_f 0.57 (hexane–EtOAc, 2:1); $[\alpha]_D^{20}$ –3.5 (*c* = 2.1, $CHCl_3$).

IR (film): 2931, 1748 (C=O), 1372, 1243 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.27–1.40 (m, 16 H, CH_2), 2.05 (s, 6 H, COC*H*$_3$), 5.01 (m, 1 H, C*H*OAc), 5.29 (m, 1 H, C=CH), 5.36 (m, 1 H, C=CH), 5.77 (m, 1 H, =CC*H*OAc).

^{13}C NMR ($CDCl_3$): δ = 13.8 and 13.9 (CH_3), 20.9 and 21.0 (CH_2), 22.4 (CO*C*H$_3$), 24.6, 28.4, 30.4, 31.2, 31.5 and 32.2 (CH_2), 73.7 and 75.0 (*C*HOAc), 124.2 and 136.9 (CH=*C*H), 169.9 and 170.4 (C=O).

HRMS: *m*/*z* calcd for $C_{18}H_{32}O_4$: 312.2301; found: 312.2299.

Isomerization of (*S*,*S*)-12

A solution of diacetate (*S*,*S*)-**12 (**80 mg, 0.26 mmol) in anhyd toluene (3 mL) was added to a solution of $PdCl_2(PhCN)_2$ (5.0 mg) in anhyd toluene (7 mL) under argon at r.t. The mixture was heated under argon in an oil bath at 80 °C. The progress of the isomerization was monitored by TLC. When TLC revealed that the composition of the mixture apparently did not change (ca. 12 h), the solvent was removed under vacuo and the crude was purified by flash chromatography (hexane–EtOAc, 2:1) to afford 51 mg (63%) of (*S*,*S*)-**4** and 22 mg (27%) of starting diacetate (*S*,*S*)-**12**. An analytical sample (ca. 5–7 mg) of (*S*,*S*)-**4** was stirred with a 10% solution of NaOMe in MeOH at r.t. overnight. The reaction was quenched by addition of strongly acidic resin Dowex® 50W, filtered and the solvent was eliminated under vacuo. The crude (ca. 5 mg) was treated with an excess of (*S*)-Mosher acid chloride [derived from (*R*)-acid] to give a mixture of Mosher diesters. A careful analysis by ^{19}F NMR revealed 98% ee.

Johnson Orthoester Rearrangements; (4*S*,5*S*)-4-[(*E*)-Hept-1-enyl)]-5-pentyl-4,5-dihydro-(3*H*)-furan-2-one [(*S*,*S*)-15]; Typical Procedure

A solution of (*S*,*S*)-**3** (149 mg, 0.65 mmol) and pivalic acid (7 mg, 0.07 mmol) in triethyl orthoformate (1.5 mL) was heated in a round-bottom flask connected to a short-path distillation apparatus until most of the formed EtOH was removed. The distillation apparatus was changed for a reflux condenser and the mixture was refluxed for 1 h. Then, it was allowed to cool to r.t., toluene (10 mL) was added and the volatiles were removed under vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and the solution was washed with sat. aq $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated under vacuo. The residue was purified by flash chromatography (9:1 hexane–EtOAc) to give 83 mg (50%) of lactone (*S*,*S*)-**15**.

Yellowish oil; R_f 0.73 (hexane–EtOAc, 65:35); $[\alpha]_D^{20}$ –52.9 (*c* = 1.8, $CHCl_3$).

IR (film): 2930, 1785, 1466, 1204 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (t, 6 H, *J* = 7.0 Hz, C*H*$_3$CH$_2$), 1.27–1.65 (m, 14 H, CH_2), 2.00 (m, 2 H, C*H*$_2$CH=CH), 2.41 (dd, 1 H, *J* = 16.5, 10.0 Hz, *H*CHCO$_2$), 2.69 (m, 2 H, HC*H*CO$_2$ and C*H*CH=CH), 4.10 (td, 1 H, *J* = 8.2, 3.4 Hz, CHO), 5.25 (dd, 1 H, *J* = 15.3, 8.7 Hz, CH$_2$CH=C*H*), 5.55 (dt, 1 H, *J* = 15.3, 6.9 Hz, CH$_2$C*H*=CH).

^{13}C NMR ($CDCl_3$): δ = 13.8 [*C*H$_3$(CH$_2$)$_4$], 13.9 [*C*H$_3$(CH$_2$)$_4$], 22.4, 25.4, 28.7, 30.8, 31,2, 31.4, 32.3, 33.4 and 36.0 (CH_2), 45.5 (*C*HCH=CH), 85.3 (CHO), 127.3 (*C*H=CHCH$_2$), 134.3 (CH=*C*HCH$_2$), 176.0 (C=O).

HRMS: *m*/*z* calcd for $C_{16}H_{28}O_2$: 252.2089; found: 252.2080.

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.31; H, 11.22.

(4*R*,5*S*)-4-[(*E*)-Hept-1-enyl)]-5-pentyl-4,5-dihydro-(3*H*)-furan-2-one (*rac*-16)

In a similar way, a sample of *meso*-**3** (98 mg) and pivalic acid (4 mg, 0.04 mmol) in triethyl orthoformate (1.5 mL) was transformed into lactone *rac*-**16** in 52% yield; yellowish oil; R_f 0.35 (hexane–EtOAc, 9:1).

IR (film): 2940, 1780, 1458, 1210 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, 6 H, *J* = 6.9 Hz, C*H*$_3$CH$_2$), 1.27–1.57 (m, 14 H, CH_2), 2.01 (m, 2 H, C*H*$_2$CH=CH), 2.38 (dd, 1 H, *J* = 17.4, 5.5 Hz, *H*CHCO$_2$), 2.68 (dd, 1 H, *J* = 17.4, 7.9 Hz, HC*H*CO$_2$), 3.10 (m, 1 H, C*H*CH=CH), 4.46 (m, 1 H, CHO), 5.33 (dd, 1 H, *J* = 15.6, 8.7 Hz, CH$_2$CH=C*H*), 5.54 (td, 1 H, *J* = 15.6, 6.6 Hz, CH$_2$C*H*=CH).

^{13}C NMR ($CDCl_3$): δ = 14.0 [*C*H$_3$(CH$_2$)$_4$], 14.1 [*C*H$_3$(CH$_2$)$_4$], 22.5, 25.3, 28.8, 30.8, 31,3, 31.6, 32.4, 33.4 and 35.4 (CH_2), 42.3 (*C*HCH=CH), 83.7 (CHO), 125.4 (*C*H=CHCH$_2$), 134.4 (CH=*C*HCH$_2$), 176.6 (C=O).

HRMS: *m*/*z* calcd for $C_{16}H_{28}O_2$: 252.2089; found: 252.2096.

Ireland–Claisen Rearrangement of (*S*,*S*)-4; (*S*,*S*)-4-Acetoxy-3-[(*E*)-hept-1-enyl]nonanoic Acid (17); Typical Procedure

To a solution of (*S*,*S*)-**4** (98 mg, 0.31 mmol) and *t*-BuMe$_2$SiCl (195 mg, 1.25 mmol) in anhyd THF (2 mL) at –78 °C under argon was added a toluene solution of KHMDS (0.5 M, 1.88 mL, 0.94 mmol) dropwise, and the mixture was stirred overnight at r.t.. Then, most of solvent was eliminated under vacuum, anhyd toluene (3 mL) was added and the mixture was heated (130 °C bath temperature) for 6 h. The mixture was partitioned between Et_2O (40 mL) and brine (6 mL). The aqueous layer was washed with additional Et_2O (10 mL) and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude was purified by flash chromatography (hexane–EtOAc, 4:1) to give 42 mg (44%) of acid **17** and 59 mg (44%) of its silyl ester **18.**

Thick oil; R_f 0.01 (hexane–EtOAc, 9:1); $[\alpha]_D^{20}$ +2.4 (*c* = 2.1, $CHCl_3$).

IR (film): 2930, 1750, 1729, 1220 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (t, 6 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.27 (m, 14 H, CH_2), 1.99 (dt, 2 H, *J* = 6.6, 6.3 Hz, C*H*$_2$CH=CH), 2.04 (s, 3 H, CH_3CO), 2.26 (dd, 1 H, *J* = 15.0, 9.2 Hz, *H*CHCO$_2$), 2.44 (dd, 1 H, *J* = 15.0, 5.1 Hz, HC*H*CO$_2$), 2.74 (m, 1 H, C*H*CH=CH), 4.81 (m, 1 H, C*H*OAc), 5.23 (dd, 1 H, *J* = 15.3, 8.7 Hz, CH$_2$CH=C*H*), 5.54 (td, 1 H, *J* = 15.3, 6.6 Hz, CH$_2$C*H*=CH).

^{13}C NMR ($CDCl_3$): δ = 13.9 and 14.0 [*C*H$_3$(CH$_2$)$_4$], 22.4 and 24.0 (CH_2), 25.5 (*C*H$_3$CO), 28.8, 31.2, 31,3, 32.0 and 32.4 (CH_2), 36.3 (*C*HCH$_2$CO), 43.1 (CO*C*H$_2$), 75.8 (CHO), 127.9 (*C*H=CHCH$_2$), 134.2 (CH=*C*HCH$_2$), 170.7 (C=O), 177.7 (C=O).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 68.99; H, 10.22.

***tert*-Butyldimethylsilyl (*S*,*S*)-4-Acetoxy-3-[(*E*)-hept-1-enyl]-nonanoate (18)**

Pale-yellow oil; R_f 0.55 (hexane–EtOAc, 9:1); $[\alpha]_D^{20}$ –4.4 (*c* = 0.9, $CHCl_3$).

IR (film): 2930, 1750, 1729, 1220 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.23 (s, 3 H, C*H*$_3$Si), 0.24 (s, 3 H, C*H*$_3$Si), 0.87 (t, 6 H, *J* = 6.7 Hz, C*H*$_3$CH$_2$), 0.97 [s, 9 H, (C*H*$_3$)$_3$C], 1.25 (m, 14 H, CH_2), 1.97 (dt, 2 H, *J* = 6.6, 6.6 Hz, C*H*$_2$CH=CH), 2.04 (s, 3 H, CH_3CO), 2.20 (dd, 1 H, *J* = 15.0, 9.6 Hz, *H*CHCO$_2$), 2.42 (dd, 1 H, *J* = 15.0, 4.5 Hz, HC*H*CO$_2$), 2.69 (m, 1 H, C*H*CH=CH), 4.79 (m, 1 H, C*H*OAc), 5.23 (dd, 1 H, *J* = 15.3, 8.7 Hz, CH$_2$CH=C*H*), 5.50 (td, 1 H, *J* = 15.3, 6.6 Hz, CH$_2$C*H*=CH).

^{13}C NMR ($CDCl_3$): δ = –4.8 (CH_3Si), 13.9 and 14.0 [$CH_3(CH_2)_4$], 17.5 [(CH$_3$)$_3$*C*], 21.0, 22.5 and 24.7 (CH_2), 25.5 (*C*H$_3$CO), 25.7 [(CH$_3$)$_3$*C*], 31.3, 31,6, 31.9 and 32.5 (CH_2), 38.1 (*C*HCH$_2$CO), 43.4 (COCH$_2$), 75.8 (CHO), 128.4 (*C*H=CHCH$_2$), 133.7 (CH=*C*HCH$_2$), 170.7 (C=O), 172.7 (C=O).

HRMS: FAB+ *m*/*z* calcd for $C_{24}H_{47}O_4Si$ (M^+ + 1): 427.3244; found: 427.3243.

A similar experiment was carried out with (*S*,*S*)-**4** (120 mg, 0.38 mmol), *t*-BuMe$_2$SiCl (239 mg, 1.53 mmol) and a toluene solution of KHMDS (0.5 M, 2.30 mL, 1.15 mmol) in anhyd THF (4 mL). In this case, the residue was filtered through a pad of silica gel and the mixture of the acid **17** and its silyl ester **18** was treated with THF (2 mL) and aq LiOH (8 M, 1 mL) at 70 °C for 9 h. The solution was then acidified with 2 M aq HCl (6 mL), additional THF (3 mL) was added and the mixture was heated at 50 °C for 6 h. CH_2Cl_2 (50 mL) was added and the organic layer was separated and dried ($MgSO_4$). Evaporation of solvents and purification by flash chromatography on silica gel (hexane–EtOAc, 95:5) gave 68 mg (70%) of lactone (*S*,*S*)-**15** as a yellowish oil.

(2*S*,3*R*)-5-Oxo-2-pentyl-3-tetrahydrofurancarboxylic Acid [(–)-2]

To a stirred solution of (*S*,*S*)-**15** (60 mg, 0.23 mmol) in CCl_4 (0.5 mL), MeCN (0.5 mL) and H_2O (0.75 mL) were added $RuCl_3$ (2 mg, 0.009 mmol) and $NaIO_4$ (209 mg, 0.97 mmol) at r.t. After 4 h, an additional amount of $NaIO_4$ (100 mg, 0.47 mmol) was added and the mixture was vigorously stirred for 2 h. The reaction was quenched by the addition of CH_2Cl_2 (20 mL), the phases were decanted and the aqueous layer was further extracted with more CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under vacuo. The crude was purified by flash chromatography (CH_2Cl_2 –MeOH, 98:2) to give 33 mg of the known acid (–)-**2**; mp 102–103 °C (Lit.[9a] mp 105–107 °C); R_f 0.16 (hexane–EtOAc, 2:1); $[\alpha]_D^{20}$ –53.3 (*c* = 0.25, $CHCl_3$) {Lit.[9a] $[\alpha]_D^{20}$ –54 (*c* = 0.5, $CHCl_3$)}.

IR (film): 3500, 2960, 2930, 1748, 1722, 1220 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (t, 3 H, *J* = 6.6 Hz, C*H*$_3$CH$_2$), 1.25–1.83 (m, 8 H, CH_2), 1.97 (dt, 2 H, *J* = 6.6, 6.6 Hz, C*H*$_2$CH=CH), 2.04 (s, 3 H, CH_3CO), 2.82 (dd, 1 H, *J* = 17.8, 9.9 Hz, HC*H*CO$_2$), 2.94 (dd, 1 H, *J* = 17.8, 8.2 Hz, *H*CHCO$_2$), 3.10 (m, 1 H, C*H*CO$_2$H), 4.56–4.68 (m, 1 H, CHOCO), 8.35 (br s, 1 H, CO_2H).

^{13}C NMR ($CDCl_3$): δ = 14.0 [$CH_3(CH_2)_4$], 22.6, 25.0, 31.5, 32.1 and 35.5 (CH_2), 45.5 (*C*HCO$_2$H), 81.9 (CHO), 174.8 (C=O), 176.7 (C=O).

MS (CI): *m*/*z* (%) = 218 (M + 18, 100).

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