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 C2-symmetrical alk-2-ene-1,4-diol which, in turn, can be converted into a precursor of (−)-methyleneolactocin through an additional [3,3]-sigmatropic rearrangement (either Johnson orthoester or Ireland–Claisen rearrangement).

Key words: rearrangement, diols, asymmetric synthesis, dihydroxylation

Enantio-enriched 1,4-diols have been proven to be versatile synthons for asymmetric synthesis. In particular, C2-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 (−)-methyleneolactocin [(−)-1], based on a desymmetrization process (Scheme 1). 4b,5

Scheme 1

(−)-Methyleneolactocin [(−)-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 BH3·SMe2 (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%, LiAlH4, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (equiv)</th>
<th>(S,S)/(R,S) Ratio</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-6 (2.0)</td>
<td>92:8</td>
<td>&gt;99</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>(S)-6 (1.0)</td>
<td>85:15</td>
<td>&gt;99</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>(S)-6 (0.4)</td>
<td>82:18</td>
<td>&gt;99</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>(S)-7 (0.4)</td>
<td>82:18</td>
<td>&gt;99</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>(S)-6 (0.2)</td>
<td>74:26</td>
<td>99</td>
<td>60</td>
</tr>
</tbody>
</table>
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-yn-3-ol 9 (94%) which was treated first with t-BuOOH/SeO₂ according to a Sharpless procedure 13 and then with NaBH₄ 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-methyllephedrine and Et₃N 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

\[
\text{Scheme 3}
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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-yn 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% PdCl₂(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), 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 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 CH₃C(OEt)₁ 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.

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\text{Scheme 4 Reagents and conditions: i) AD-mix-α, MeSO₂NH₂, t-BuOH/H₂O, 0 °C; ii) Ac₂O, Et₃N, DMAP cat., CH₂Cl₂; iii) 5 mol Pd(PhCN)₂Cl₂, anhyd toluene, Δ; iv) NaOMe/MeOH, r.t.}
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\text{Scheme 5 Reagents and conditions: i) CH₃C(OEt)₁, t-BuCO₂H 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-butylidimethylsilyl enolates. When we treated (S,S)-4 with an excess of t-BuMe₂SiCl and potassium bis(trimethylsilyl)amide (KHMD) in THF at −78 °C and then heated the mixture in refluxing toluene we isolated the acid (S,S)-17 (44%) besides
its tert-butylmethyldisilyl ester (18, 44%). Since basic hydrolysis (LiOH, in refluxing 1:1 THF–H2O) 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 RuCl3/NaI2 oxidation20 of compound (S,S)-15.

Scheme 6 Reagents and conditions: i) (a) KH2PO4, t-BuMe2SiCl, THF, –78 °C to r.t., then anhyd toluene, Δ; (b) LiOH, H2O–THF, Δ; (c) aq HCl/THF, Δ; ii) cat. RuCl3, NaI2, CCl4/Methanol/H2O (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 (−)-methylenealactin [(−)-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 N2. The crude products were purified by column chromatography on silica gel of 230–400 mesh (flash chromatography). 282.2 MHz for 19F. Chemical shifts are given in ppm with respect to (S,S)-15.6.3 and (S,S)-ylephedrine and (S,S)-ylephedrine (Synthesis 2004, No. 1, 128–134 © Thieme Stuttgart · New York) and were prepared according to published procedures. (−)-86-butylidimethylsilyl ester (18, 44%). Since basic hydrolysis (LiOH, in refluxing 1:1 THF–H2O) 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 RuCl3/NaI2 oxidation20 of compound (S,S)-15.

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All the solvents were distilled from an appropriate drying agent and stored under N2. The crude products were purified by column chromatography on silica gel of 230–400 mesh (flash chromatography). Thin-layer chromatograms were performed on HF254 silica gel plates (using CH2Cl2, CHCl3–MeOH or hexane–EtOAc as the eluent phases were separated and the aqueous layer was extracted with CH2Cl2). 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-yn-6-ol (9)
Oil; Rf 0.35 (CH2Cl2).1H NMR (CDCl3, 300 MHz): δ = 0.89 (t, 6 H, J = 7.4 Hz, CH3), 1.25–1.33 (m, 14 H, CH2), 2.20 (m, 2 H, CH2C=C), 4.35 (t, 1 H, J = 6.0 Hz, CH2OH).13C NMR (CDCl3): δ = 14.0 (CH3), 18.2 (CH2C=C), 22.5, 22.6, 24.9, 28.5, 28.6, 31.5, 38.2, 62.7 (CH2OH), 85.9 (C=C). A solution of t-butyl hydroperoxide (TBHP) in CH2Cl2 was obtained by swirling commercial aq TBHP (70 wt% in H2O, 43.0 mL, 0.31 mol) with CH2Cl2 (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 (Na2SO4). To this solution of TBHP in CH2Cl2 was added SeO2 (4.48 g, 25.86 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 CH2Cl2 (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. NaHSO3 (280 mL) for 30 min to destroy excess of TBHP. The organic layer was separated, dried (Na2SO4) and concentrated in vacuo. The residue was purified by flash chromatography (CH2Cl2) to give 7.40 g (55%) of tetradec-7-yn-6,9-diol (8) as a mixture of stereoisomers besides 2.74 g (22%) of tetradec-7-yn-6-ol (9).

Tetradec-7-yn-6,9-dione (5)
To a stirred solution of tetradec-7-yn-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 CrO3 in 7.6 mL conc. H2SO4 and 20 mL H2O) dropwise until an orange color persisted. The reaction mixture was poured into CH2Cl2 (200 mL) and pH 7 phosphate buffer (100 mL). The aqueous phase was separated and the aqueous layer was extracted with CH2Cl2 (50 mL). The combined organic phases were washed with brine, dried (Na2SO4) and concentrated in vacuo. The residue was purified by flash chromatography (CH2Cl2) to give 7.40 g (55%) of tetradec-7-yn-6,9-dione (8) as a mixture of stereoisomers besides 2.74 g (22%) of tetradec-7-yn-6-ol (9).

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1H NMR (CDCl3, 300 MHz): δ = 0.91 (t, 6 H, J = 6.6 Hz, CH3), 1.20–1.31 (m, 12 H, CH2), 2.63 (m, 4 H, CH2CO).13C NMR (CDCl3): δ = 13.8 (CH3), 22.3, 23.4, 31.0, 40.2 (CH2CO), 84.2 (C=C), 184.4 (C=O). Anal. Calcd for C14H22O2: C, 75.63; H, 9.97. Found: C, 75.31; H, 10.05.

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 (6R,7E,9S)-tetradec-7-ene-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 19F NMR revealed a 4:6:1 dl/dlmoso 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 dlmoso ratio, >99% ee). A similar reduction using a molar ratio of (Mosher acid chloride [derived from (S)-7,8] = 0.2 led to >99% ee. When the reaction was monitored by TLC. When TLC revealed the disappearance of the starting diol (6 h), more CH2Cl2 (20 mL) was added and the solution was washed with 0.5 M aq HCl, sat. aq NaHCO3, and brine. The organic phase was dried (Na2SO4) and concentrated under vacuum. The residue was purified by flash chromatography (9:1 hexane–EtOAc) to give 119 mg (70%) of enantio-enriched (6R,7E,9S)-tetradec-7-ene-6,9-diol ([S,S]-8). Anal. Calcd for C14H26O2: C, 74.29; H, 11.58. Found: C, 74.02; H, 11.65.

(6R,7E,9S)-Tetradec-7-ene-6,9-diol ([S,S]-9) 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 LiAIH4 (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 CH2Cl2 and brine. The aqueous layer was extracted with CH2Cl2 and the combined organic layers were dried (Na2SO4) and concentrated under vacuum. The residue was purified by flash chromatography (2:1 hexane–EtOAc) to give 93 mg (77%) of (S,S)-9 and 16 mg (13%) of meso-9 (90% overall yield). An analytical sample of the isolated (S,S)-9 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 19F NMR revealed >99% ee. (δ = −70.93 for R,R isomer; δ = −71.06 for S,S isomer).

(6R,7E,9S)-Tetradec-7-ene-6,9-diol ([S,S]-9) Oil; Rf 0.20 (95:5 CH2Cl2–MeOH); [α]D20 +6.3 (c = 2.3, CHCl3). IR (film): 3300, 2920, 2235, 1440 cm⁻¹.

(1H NMR (DCl3, 300 MHz): δ = 0.88 (t, 6 H, J = 6.6 Hz, CH2CH3), 1.28–1.56 (m, 14 H, CH2), 3.01 (br s, 2 H, OH), 4.39 (t, 2 H, J = 6.2 Hz, CHOH), 6.28 (CHOH), 85.9 (C≡H), 122.8 (COOAc), 171.6 (CO). HRMS: m/z calcd for C14H26O2: 226.1933; found: 226.1930. IR (film): 3320, 2920, 1450 cm⁻¹.

Synthesis of (−)-Methylenolactonin

Typical Procedure

AcO2 (150 μL, 1.59 mmol) was added to a stirred solution of (S,S)-9 (39 mg, 0.41 mmol), EtN (128 μL, 0.92 mmol) and a catalytic amount of 2-(N,N-dimethylamino)pyridine (DMAP) in anhyd CH2Cl2 (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 CH2Cl2 (20 mL) was added and the solution was washed with 0.5 M aq HCl, sat. aq NaHCO3, and brine. The organic phase was dried (Na2SO4) and concentrated under vacuum. The residue was purified by flash chromatography (9:1 hexane–EtOAc) to give 119 mg (70%) of enantio-enriched (6R,7E,9S)-tetradec-7-ene-6,9-diol ([S,S]-9). Anal. Calcd for C14H26O2: C, 74.02; H, 11.65. Found: C, 74.02; H, 11.58.

Attempts at Stereoselective Alkynylation of Hexanal with (S)-1-Pentylprop-2-ynyl Acetate ([S]-10) A slurry of dry Zn(OtBu)2 (408 mg, 1.1 mmol), (−)-N-methylphe- drine (220 mg, 1.2 mmol), alkynyl (S)-10 (168 mg, 1 mmol) in anhyd toluene (300 mL), and Et3N (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 alkynyl 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(OtBu)2 (−)-N-methylphedrine and Et3N at 60 °C or r.t. for 1–3 d were also unsuccessful.

Asymmetric Dihydroxylation of Tetradeca-6,8-diene

(6S,7E,9S)-Tetrade-6,8-diene-6,7-diol ([S,S]-13) Tetradeca-6,8-diene (0.630 g, 3.24 mmol) was added to a mixture of AD-mix-α (4.60 g) and CH2SO4NH2 (0.320 g, 3.26 mmol) in 1:1 tert-butyl alcohol–H2O (15 mL of each) at 0 °C and the mixture was stirred at this temperature overnight. The reaction was quenched by slow addition of Na2SO4 (5 g) and the suspension was warmed to r.t. while stirring vigorously. After 30 min, CH2Cl2 (30 mL) was added and the aqueous layer was further extracted with more CH2Cl2 (3 × 10 mL). The combined organic layers were washed with 2 N aq KOH (10 mL) and dried (MgSO4). The crude was purified by flash chromatography (hexane–EtOAc, 9:5) to give 333 mg (45%) of (S,S)-13; oil; Rf 0.38 (hexane–EtOAc, 2:1); [α]D20 −11.5 (c = 1.0, CHCl3). IR (film): 3230, 2925, 1442 cm⁻¹.
1H NMR (CDCl₃, 300 MHz): δ = 0.89 (t, 6 H, J = 6.6 Hz, CH₂(CH₃)), 1.26–1.40 (14 H, CH₂(CH₃)), 2.04 (2 H, CH₂=CH₂), 2.87 (br s, 2 H, OH), 3.42 (m, 1 H, CHOCH(CH₃)), 3.83 (m, 1 H, CHOCH₂CH₃), 5.43 (m, 1 H, CH₂=CHCH₃), 5.74 (m, 1 H, CH₃CH=CH₂). IR (film): 2930, 1750, 1729, 1220 cm⁻¹.

IR (film): 2931, 1748, 1372, 1243 cm⁻¹.

IR (film): 2930, 1748, 1729, 1220 cm⁻¹.

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Thick oil; Rₜ = 0.01 (hexane–EtOAc, 9:1); [α]₂₀ⁿ = +2.4 (c = 2.1, CHCl₃).

IR (film): 2930, 1750, 1729, 1220 cm⁻¹.

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

Pale-yellow oil; Rf 0.55 (hexane–EtOAc, 9:1); [α]D20 24.4 (c = 0.9, CHCl3).

IR (film): 2930, 1750, 1729, 1220 cm−1.

1H NMR (CDCl3, 300 MHz): δ = 0.23 (s, 3 H, CH3Si), 0.24 (s, 3 H, CH3Si), 0.87 (t, 6 H, CH3CH2), 0.97 (s, 9 H, (CH3)2C), 1.25 (m, 14 H, CH2), 1.97 (dt, 2 H, J = 6.6, 6.6 Hz, CH2CH3CH), 2.04 (s, 3 H, CH3CO), 2.20 (dd, 1 H, J = 15.0, 4.5 Hz, HCHCO3), 2.42 (dd, 1 H, J = 15.0, 4.5 Hz, HCHCO3), 2.69 (m, 1 H, CH2CH=CH), 4.79 (m, 1 H, CHOAc), 5.23 (dd, 1 H, J = 15.3, 8.7 Hz, CH2CH=CH), 5.50 (td, 1 H, J = 15.3, 6.6 Hz, CH2CH=CH).

13C NMR (CDCl3): δ = 4.84 (CH3Si), 13.9 and 14.0 (CH2CH3), 17.5 [(CH3)2C], 21.0, 22.5 and 25.4 (CH2), 25.5 (CH2CO), 34.7 [(CH3)2C], 31.3, 31.6, 31.9 and 32.5 (CH2), 38.1 (CH2CH=CH), 57.8 (CHO), 128.4 (CH=CHCH2), 133.7 (CH=CHCH2), 170.7 (C=O), 172.7 (C=O).

HRMS: FAB+ m/z calcd for C13H2O3Si (M+ + 1): 427.3244; found: 427.3243.

A similar experiment was carried out with (S,S)-4 (120 mg, 0.38 mmol), BuMe3SiCl (239 mg, 1.53 mmol) and a toluene solution of KHMD (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 was vigorously stirred for 2 h. The reaction was quenched by the addition of CH2Cl2 (20 mL), the phases were decanted and the aqueous layer was further extracted with more CH2Cl2 (10 mL). The combined organic layers were dried over Na2SO4 and the solvent was removed under vacuum. The crude was purified by flash chromatography (CH2Cl2 – MeOH, 98:2) to give 33 mg of the known acid (–)-5-Oxo-2-pentyl-3-tetrahydrofurancarboxylic Acid (98:2) with 2 M aq HCl (6 mL), additional THF (3 mL) was added 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 ºC for 6 h. CH2Cl2 (50 mL) was added and the organic layer was separated and dried (Na2SO4).

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 yellow oil.

IR (film): 3500, 2960, 2930, 1748, 1722, 1220 cm−1.

1H NMR (CDCl3, 300 MHz): δ = 0.90 (t, 3 H, J = 6.6 Hz, CH3CH2), 1.25–1.83 (m, 8 H, CH2CH3), 1.97 (dt, 2 H, J = 6.6, 6.6 Hz, CH2CH=CH), 2.04 (s, 3 H, CH3CO), 2.82 (dd, 1 H, J = 17.8, 9.9 Hz, HCHCO3), 2.94 (dd, 1 H, J = 17.8, 8.2 Hz, HCHCO3), 3.10 (m, 1 H, CH2CH2O), 4.56–4.68 (m, 1 H, CHOOCO), 8.35 (br s, 1 H, CO2H).

13C NMR (CDCl3): δ = 14.0 [(CH3)2C], 22.6, 25.0, 31.5, 32.1 and 35.5 (CH2), 45.5 (CH2CO2H), 81.9 (CHO), 174.8 (C=O), 176.7 (C=O).

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

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References

(15) An attempt to obtain (S,S)-5 by double addition of acetylene to hexanal under similar conditions also failed, see: Sasaki,


(20) In order to assess the stereochemical purity of the product, an analytical sample of diacetate (S,S)-4, was hydrolyzed (NaOMe/MeOH) to diol (S,S)-3. The analysis of the corresponding Mosher diester revealed a 98% ee. Since the analysis of the Mosher diester derived from (S,S)-13 was unclear (signal overlap in 19F NMR and HPLC), we assumed that its optical purity should be ≥98% ee on the basis of that found for (S,S)-3. Absolute configuration of diol 3 revealed it to be identical to that obtained from reduction of diketone 5.


