

An Efficient Stereoselective Approach for the Synthesis of (+)-(4*S*,5*S*)-Muricatacin

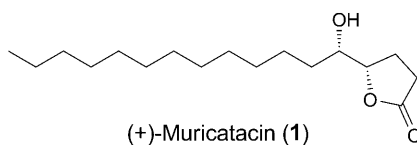
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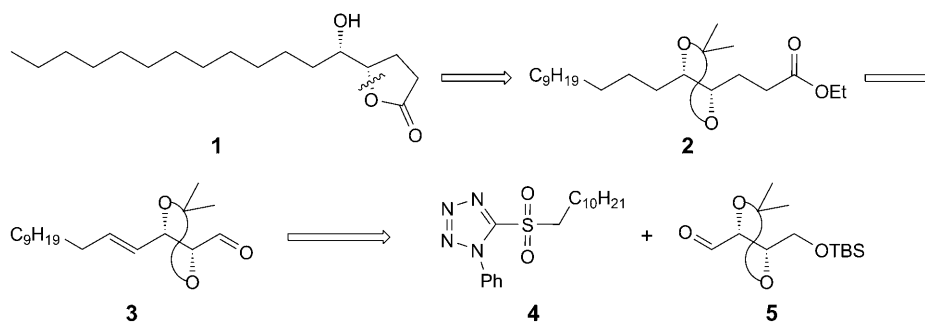
An efficient stereoselective total synthesis of (+)-(4*S*,5*S*)-muricatacin was accomplished in good yields from inexpensive, commercially available chemicals ((+)-diethyl tartrate (DET) and undecan-1-ol) by utilizing *Mitsunobu* and *Julia–Kocienski* reactions, *Wittig* homologation, *Swern* oxidation, and lactonization.

Introduction. – Acetogenins are natural products isolated from tropical plants *Annonaceae*, and they have potential biological activities such as antitumor, antimicrobial, immunosuppressive, and pesticidal effects [1]. Muricatacin (**1**) is an acetogenin, [2] isolated from the seeds of *Annona muricata* (*Annonaceae*) and related to γ -butyrolactone, with antiproliferative activity against certain cell lines. Several syntheses of muricatacin and its congeners [3–6] have been developed in recent years due to their chemical and biological properties. However, a general method for the synthesis of functionalized muricatacin is still warranted. In continuation of our interest on the synthesis of heterocycles with potential biological activities [7], here, we report an alternative way for the synthesis of (+)-(4*S*,5*S*)-muricatacin (**1**) from inexpensive, commercially available (+)-diethyl tartrate (DET) and undecan-1-ol in a convergent manner.

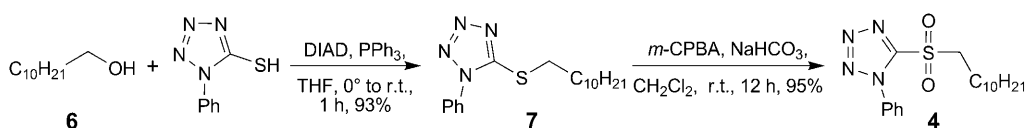


Results and Discussion. – The retro-synthesis for (+)-(4*S*,5*S*)-muricatacin (**1**) is depicted in *Scheme 1*. The reaction of 1-phenyl-1*H*-tetrazole-5-thiol with undecan-1-ol (**6**) under *Mitsunobu* conditions [8] in the presence of Ph_3P and diisopropyl azodicarboxylate (DIAD) afforded sulfide **7**. The sulfide **7**, upon oxidation with *m*-CPBA (*meta*-chloroperbenzoic acid) provided sulfone **4** [9] (*Scheme 2*). The acetone ester **9** was prepared starting from the commercially available diethyl L-

Scheme 1

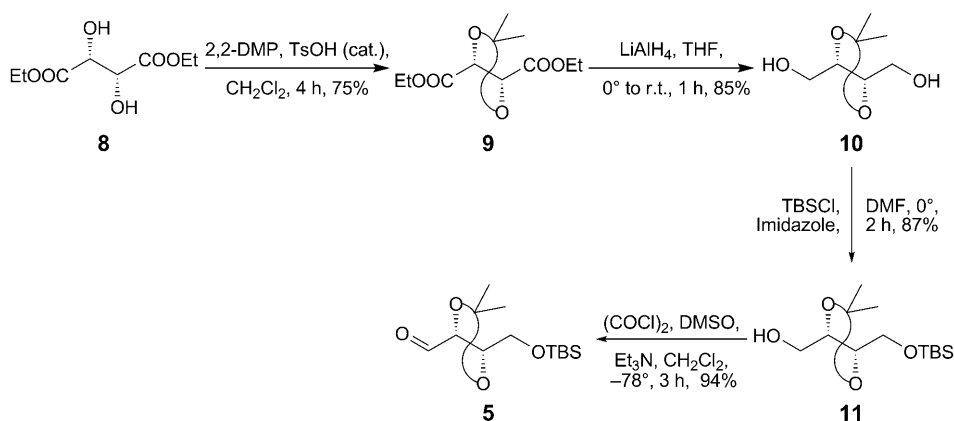


Scheme 2

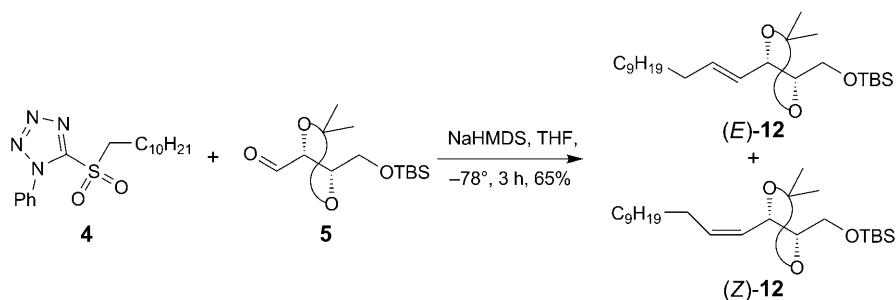


tartrate (**8**) by using 2,2-dimethoxypropane (2,2-DMP) and TsOH. The ester **9** was reduced with LiAlH₄ to give the corresponding diol **10**; the selective monoprotection of **10** with 1 equiv. of (*tert*-butyl)(dimethyl)silyl chloride (TBSCl) in the presence of 1*H*-imidazole afforded the alcohol **11** in 87% yield. The alcohol **11** was converted to the corresponding aldehyde **5** by *Swern* oxidation [10] (Scheme 3). The coupling reaction of sulfone **4** and aldehyde **5** was performed by the *Julia–Kocienski* olefination protocol [9] using NaHMDS as base (Scheme 4). The geometrical isomers (*E*)-**12** (major) and (*Z*)-**12** (minor) (¹H-NMR) were obtained in 65% yield. The mixture of stereoisomers was subjected to deprotection to give alcohol **13** by using Bu₄NF (TBAF) [11]. The alcohol **13** was oxidized to aldehyde **14** with TEMPO (= 2,2,6,6-tetramethylpiperidin-1-yl)oxyl [12], followed by C₂-Wittig olefination to furnish the unsaturated ester **15** in

Scheme 3

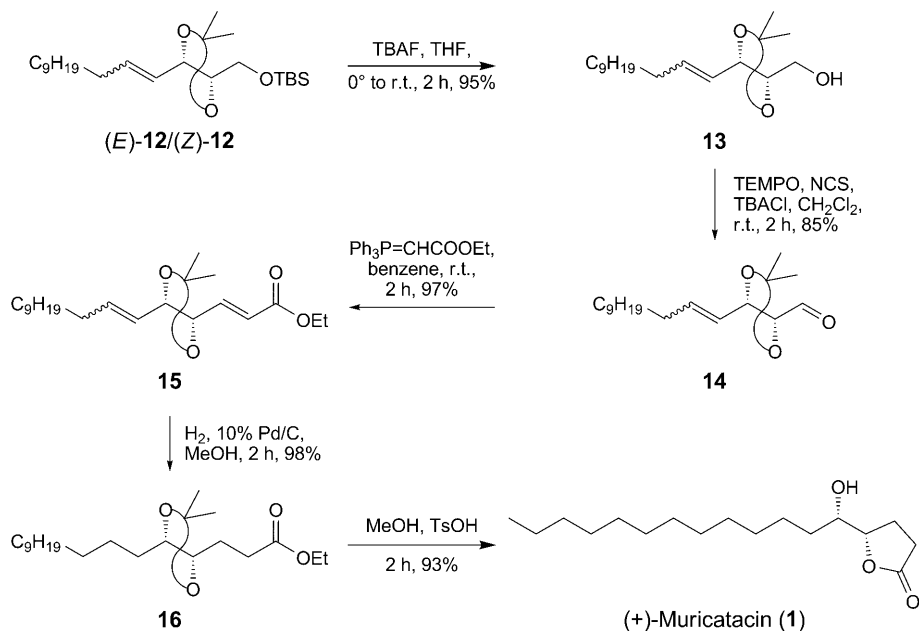


Scheme 4



97% yield. This ester was converted to the corresponding saturated ester **16** upon hydrogenation in the presence of 10% Pd/C. The deprotection of the acetonide and subsequent *in situ* lactonization of ester **16** with TsOH in MeOH afforded (+)-(4*S*,5*S*)-muricatacin (**1**; Scheme 5) as white crystalline solid in 98% yield [13]. Compound **1** was characterized by its spectral data (^1H - and ^{13}C -NMR, IR, MS, specific rotation), which were in agreement with the data of **1** reported in [4].

Scheme 5



Conclusions. – In conclusion, we developed an efficient method for the asymmetric synthesis of (+)-(4*S*,5*S*)-muricatacin (**1**) by using *Mitsunobu* and *Julia–Kocienski* reactions, *Wittig* homologation, *Swern* oxidation, and lactonization.

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Experimental Part

General. All chemicals were of reagent grade and were used as obtained from local suppliers, *Aldrich* and *Fluka*. Anal. TLC: *E. Merck* silica gel 60F glass plates. Flash chromatography (FC): *E. Merck* silica gel (SiO₂; 60–120 mesh). M.p.: *MEL-TEMP II* melting point apparatus; uncorrected. ¹H-NMR spectra: *Gemini 200 MHz Varian* instrument and *Avance 300 MHz Bruker UX 300 FT* NMR; in CDCl₃, chemical shifts in ppm rel. to TMS, coupling constants *J* in Hz; the data were compared with the reported literature values. MS: *VG Micromass 7070 H* (EI), *VG Autospec* (FAB) using a Cs⁺ ion gun, *m*-NBA (3-nitrobenzyl alcohol) as a matrix, *Applied Biosystems QSTAR XL* high-resolution (HR) mass spectrometer, *Thermo-Finnigan ESI* ion trap mass spectrometer, and GC/MS instruments.

1-Phenyl-5-(undecylsulfanyl)-1H-tetrazole (7). To a soln. of *undecan-1-ol* **6** (2.0 g, 11.62 mmol), PPh₃ (3.65 g, 13.95 mmol), and 1-phenyl-1H-tetrazole-5-thiol (2.48 g, 13.95 mmol) in THF (40 ml) was added a soln. of DIAD (2.81 g, 13.95 mmol) in 10 ml THF dropwise at 0°. After 2 h at 0°, the reaction was quenched by addition of sat. aq. NH₄Cl (10 ml), the org. layer was separated, washed with brine (10 ml), dried (Na₂SO₄), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 95:5) to afford sulfide **7** (3.59 g, 93%). Colorless solid. M.p. 40–41°. IR (neat): 2961, 2919, 2850, 1592, 1497, 1471, 1419, 1390, 1244, 757, 687. ¹H-NMR (200 MHz): 0.88 (*t*, *J* = 6.6, 3 H); 1.25–1.47 (*m*, 16 H); 1.75–1.90 (*m*, 2 H); 3.39 (*t*, *J* = 6.6, 2 H); 7.53–7.60 (*m*, 5 H). ESI-MS: 333 ([*M* + H]⁺).

1-Phenyl-5-(undecylsulfonyl)-1H-tetrazole (4). To a stirred soln. of **7** (2.0 g, 6.02 mmol) in CH₂Cl₂ (100 ml), NaHCO₃ (1.26 g, 15.06 mmol) was added, followed by *m*-CPBA (5.18 g, 15.06 mmol) at 0°. The mixture was slowly brought to r.t., and stirring was continued for 12 h. After quenching the reaction with sat. aq. Na₂S₂O₃ (10 ml), the org. layer was separated, washed with brine (10 ml), dried (Na₂SO₄), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 95:5) to give pure **4** (2.08 g, 95%). Colorless solid. M.p. 47–48°. ¹H-NMR (200 MHz): 0.88 (*t*, *J* = 6.6, 3 H); 1.26–1.55 (*m*, 16 H overlapped); 1.88–2.01 (*m*, 2 H); 3.72 (*t*, *J* = 8.0, 2 H); 7.58–7.64 (*m*, 3 H); 7.69–7.73 (*m*, 2 H). IR (neat): 3070, 2952, 2919, 2852, 1592, 1498, 1473, 1354, 1148, 762, 720, 692, 542. ESI-MS: 365 ([*M* + H]⁺).

Diethyl (4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarboxylate (9). To a stirred soln. of (+)-diethyl tartrate (**8**; 10 g, 48.54 mmol) in CH₂Cl₂ (100 ml), TsOH (100 mg) was added, followed by 2,2-dimethoxypropane (2,2-DMP; 12 ml, 97.08 mmol) at r.t. The mixture was stirred for 4 h, then solid NaHCO₃ (5 g) was added. The mixture was filtered, the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 98:2) to afford **9** (8.95 g, 75%). Colorless liquid. IR (neat): 1757. ¹H-NMR (200 MHz): 1.33 (*t*, *J* = 7.1, 6 H); 1.47 (*s*, 6 H); 4.26 (*q*, *J* = 7.1, 4 H); 4.69 (*s*, 2 H). ESI-MS: 247 ([*M* + H]⁺), 269 ([*M* + Na]⁺).

[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol (10). To a suspension of LiAlH₄ (3.7 g, 97.5 mmol) in THF (100 ml), **9** (6 g, 24.4 mmol) in THF (20 ml) was added slowly at 0°, and the mixture was stirred for 2 h at same temp. After completion of the reaction (TLC), the mixture was hydrolyzed with sat. aq. NH₄Cl (20 ml), filtered through *Celite*, dried (Na₂SO₄), and the solvent was removed under reduced pressure. The crude product was subjected to FC (AcOEt) to afford **10** (3.35 g, 85%). Colorless liquid. [*α*]_D²⁵ = –8.16 (*c* = 1, CHCl₃). IR (neat): 3386. ¹H-NMR (200 MHz): 1.40 (*s*, 6 H); 2.45 (*br. s*, 2 OH); 3.63–3.78 (*m*, 4 H); 3.91–3.98 (*m*, 2 H). EI-MS: 162.

[(4S,5S)-5-((tert-Butyl)(dimethyl)silyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (11). To a cooled soln. of **10** (3.0 g, 18.51 mmol) in dry DMF (30 ml) at 0°, 1H-imidazole (3.14 g, 46.25 mmol) and (*tert*-butyl)(dimethyl)silyl chloride (2.77 g, 18.51 mmol) were added, and stirring was continued for 2 h at same temp. After completion of the reaction, the mixture was hydrolyzed with sat. aq. NH₄Cl (15 ml), the layers were separated, dried (Na₂SO₄), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 9:1) to afford **11** (4.44 g, 87%). Colorless liquid. IR (neat): 3469. ¹H-NMR (300 MHz): 0.08 (*s*, 6 H); 0.90 (*s*, 9 H); 1.37 (*s*, 3 H); 1.38 (*s*, 3 H); 3.60–3.75 (*m*, 4 H); 3.80–3.86 (*m*, 1 H); 3.89–3.95 (*m*, 1 H). ESI-MS: 277 ([*M* + H]⁺).

(4R,5S)-5-((tert-Butyl)(dimethyl)silyloxy)methyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**5**). The alcohol **11** (2.8 g, 10.14 mmol) in CH_2Cl_2 (10 ml) was added to the mixture of oxalyl chloride (1.77 ml, 20.28 mmol) in CH_2Cl_2 and dry DMSO (2.38 ml, 40.57 mmol) held at -78° slowly over a period of 30 min, and the mixture was stirred for 3 h at the same temp. Then, NEt_3 (7.3 ml, 50.72 mmol) was added in one portion, stirring was continued for 30 min, and the mixture was slowly brought to r.t. The org. layer was washed with a sat. aq. soln. of NH_4Cl (5 ml) and brine (2×15 ml), dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 9:1) to afford **5** (2.6 g, 94%). Colorless oil. $[\alpha]_D^{25} = +25.36$ ($c = 0.5$, CHCl_3). IR (neat): 1735. $^1\text{H-NMR}$ (300 MHz): 0.08 (s, 6 H); 0.90 (s, 9 H); 1.40 (s, 3 H); 1.46 (s, 3 H); 3.76–3.79 (m, 2 H); 4.04–4.10 (m, 1 H); 4.26 (dd, $J = 7.5$, 1.5, 1 H); 9.75 (d, $J = 1.5$). ESI-MS: 275 ($[M + \text{H}]^+$).

(tert-Butyl)((4S,5S)-5-[(1E)-dodec-1-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy(dimethyl)silane and (tert-Butyl)((4S,5S)-5-[(1Z)-dodec-1-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy(dimethyl)silane ((E)- and (Z)-**12**, resp.). To a stirred soln. of **4** (2.2 g, 8.03 mmol) in THF (40 ml), NaHMDS (8.83 ml of a 1.0M soln. in THF; 8.83 mmol) was added slowly dropwise at -78° , and stirring was continued for another hour, then **5** (2.81 g, 8.03 mmol) in CH_2Cl_2 was added at the same temp. The resulting yellow mixture was allowed to reach r.t., and stirring was continued for additional 2 h. The reaction was quenched with sat. aq. NaCl (10 ml), and the mixture was extracted with AcOEt (2×25 ml). The org. layer was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 95:5) to afford the mixture (E)-**12**/(Z)-**12** in 65% yield. Colorless liquid. $[\alpha]_D^{25} = -8.70$ ($c = 1.55$, CHCl_3). IR (neat): 2926, 2858, 1462, 1373. $^1\text{H-NMR}$ (300 MHz): 0.05 (s, 6 H); 0.86–0.92 (m, 12 H, Me group overlapped with 9 H); 1.24–1.27 (m, 16 H); 1.38 (s, 3 H); 1.40 (s, 3 H); 1.97–2.13 (m, 2 H); 3.57–3.81 (m, 3 H); 4.68–4.77 (m, 1 H); 5.30–5.48 (m, 1 H); 5.56–5.83 (m, 1 H). ESI-MS: 435 ($[M + \text{Na}]^+$).

((4S,5S)-5-[(Dodec-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (**13**). To a soln. of (E)-**12**/(Z)-**12** (1.2 g, 2.91 mmol) in THF (20 ml) was added TBAF (4.36 ml of 1.0M soln. in THF; 4.36 mmol) at r.t. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (5 ml), the org. layer was separated, washed with brine (5 ml), dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 95:5) to give **13** (0.82 g, 95%). Colorless liquid. $[\alpha]_D^{25} = -14.13$ ($c = 1.45$, CHCl_3). IR (neat): 3444, 1460, 1375. $^1\text{H-NMR}$ (300 MHz): 0.88 (t, $J = 6.7$, 3 H); 1.23–1.32 (m, 16 H, overlapped); 1.43 (s, 6 H); 1.72 (br. s, OH); 2.01–2.18 (m, 2 H); 3.48–3.56 (m, 1 H); 3.65–3.74 (m, 1 H); 3.76–3.83 (m, 1 H); 4.69 (t, $J = 8.3$, 1 H); 5.31–5.46 (m, 1 H); 5.62–5.85 (m, 1 H). ESI-MS: 321 ($[M + \text{Na}]^+$).

(4R,5S)-5-[Dodec-1-en-1-yl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**14**). To a soln. of **13** (0.56 g, 1.87 mmol), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO; 0.03 g, 0.18 mmol), Bu_4NCl (TBACl; 0.062 g, 0.18 mmol) in 10 ml of CH_2Cl_2 , 10 ml of an aq. soln. of NaHCO_3 (0.42 g, 0.5M) and K_2CO_3 (0.069 g, 0.05M) were added, and the mixture was vigorously stirred at r.t. The solid NCS (0.37 g, 2.8 mmol) was added, stirring was continued, and the reaction was monitored by TLC. After completion of the reaction, the org. layer was separated, washed with brine (10 ml), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was directly used for the next step without further purification.

Ethyl (2E)-3-((4S,5S)-5-[Dodec-1-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-enoate (**15**). To a soln. of $\text{Ph}_3\text{P}=\text{CHCOOEt}$ (0.423 g, 1.21 mmol) in benzene (10 ml) at r.t. was added dropwise a soln. of **14** (0.3 g, 1.01 mmol) in benzene (3 ml). The mixture was stirred for 2 h at r.t., the solvent was removed under reduced pressure, the crude product was subjected to FC (hexane/AcOEt 97:3) to furnish **15** (0.36 g, 97%). Colorless liquid. $[\alpha]_D^{25} = +25.2$ ($c = 1.45$, CHCl_3). IR (neat): 1725, 1662, 1461. $^1\text{H-NMR}$ (300 MHz): 0.88 (t, $J = 6.7$, 3 H); 1.23–1.34 (m, 21 H, Me); 1.40–1.45 (m, 6 H); 1.98–2.11 (m, 2 H); 4.08–4.23 (m, 2 H); 5.32–5.51 (m, 1 H); 5.64–5.88 (m, 1 H); 6.06 (dd, $J = 15.8$, 1.5, 1 H); 6.79 (dd, $J = 15.8$, 4.5, 1 H). GC/MS: 351 ($[M - 15]^+$).

Ethyl 3-[(4S,5S)-5-Dodecyl-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate (**16**). A soln. of **15** (0.3 g) in MeOH (10 ml) was hydrogenated on 10% of Pd/C for 2 h at r.t. The suspension was filtered through Celite and washed with MeOH. The combined filtrates were evaporated, and the crude product was subjected to FC (hexane/AcOEt 95:5) to afford pure **16** (0.297 g, 95%). Colorless liquid. $[\alpha]_D^{25} = -18.66$ ($c = 1.5$, CHCl_3). IR (neat): 1738, 1461, 1373. $^1\text{H-NMR}$ (200 MHz): 0.88 (t, $J = 7.0$, 3 H); 1.23–1.31 (m,

23 H, Me); 1.34 (s, 6 H); 1.47–1.53 (m, 2 H); 1.61–2.04 (m, 2 H); 2.20–2.60 (m, 2 H); 3.55–3.58 (m, 2 H); 4.08–4.18 (q, $J = 7.0$, 2 H). ^{13}C -NMR (75 MHz): 14.2; 14.3; 22.7; 26.1; 27.3; 27.4; 27.9; 29.4; 29.5–29.8; 30.7; 31.9; 32.9; 60.2; 79.9; 80.7; 108.0; 172.9. GC/MS: 355 ($[M - 15]^+$).

(5*S*)-4,5-Dihydro-5-[(1*S*)-1-hydroxytridecyl]furan-2(3*H*)-one (**1**). To a soln. of **16** (0.25 g, 0.675 mmol) in MeOH (10 ml) was added a cat. amount of TsOH at r.t., and stirring was continued for 4 h. After completion of the reaction, MeOH was removed under reduced pressure, and the crude product was subjected to FC (hexane/AcOEt 1:1) to afford **1** (0.176 g, 93%). Colorless solid. M.p. 69–71°. $[\alpha]_D^{25} = +25.33$ ($c = 1.5$, CHCl_3); [4]: $+23.6$ ($c = 1.6$, CHCl_3). IR (neat): 3399, 1744, 1472. ^1H -NMR (300 MHz): 0.88 (t, $J = 6.5$, 3 H); 1.25–1.29 (m, 20 H); 1.47–1.58 (m, 2 H); 2.07–2.29 (m, 2 H); 2.45–2.65 (m, 2 H); 3.51–3.55 (m, 1 H); 4.36–4.41 (m, 1 H). ^{13}C -NMR (75 MHz): 14.0; 22.6; 24.0; 25.4; 28.6; 29.2; 29.6 (6 C); 31.8; 32.9; 73.5; 82.9; 177.2. ESI-MS: 307 ($[M + \text{Na}]^+$). HR-MS: 307.2249 ($\text{C}_{17}\text{H}_{32}\text{NaO}_3^+$, $[M + \text{Na}]^+$; calc. 307.2249).

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