Tetrahedron 69 (2013) 334–340

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric synthesis of andavadoic acid via base-catalyzed 5-*exo*-tet cyclization of a β-hydroperoxy epoxide

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ARTICLE INFO

Article history:
Received 4 September 2012
Received in revised form 2 October 2012
Accepted 5 October 2012
Available online 12 October 2012

Keywords:
Andavadoic acid
Cyclization
Endoperoxides
Hydroperoxysilylation
Plakortolides

ABSTRACT

The first total synthesis of andavadoic acid, a naturally occurring five-membered ring peroxide, and its absolute configuration assignment are reported. Central to this venture was the development of an effective synthesis of a key β-hydroperoxy epoxy ester from (*R*)-epichlorohydrin via chemoselective methylenation with Nysted reagent in the presence of $Ti(Oi\text{-}Pr)_2Cl_2$ and chemo- and regioselective Mukaiyama–Isayama peroxidation. This approach also featured the construction of the 1,2-dioxolane ring system by an efficient base-promoted 5-*exo* epoxide opening by a hydroperoxy group.

1. Introduction

Marine sponges of the family Plakinidae have been reported to be a rich source of cyclic peroxides, many of which exhibit antimicrobial, antitumor, antifungal and antiparasitic activities.[1] The majority of these natural products contain six-membered peroxide rings (1,2-dioxane). Plakortolides, one of the family of secondary metabolites found in these sponges, have for most of them, an aromatic ring connected via a methylene chain to a 4,6-dimethyl peroxylactone ring.[2] They differ in absolute configuration at C_3, C_4, C_6, the substituted pattern, the level of unsaturation and the chain length. A representative sample of plakortolides is depicted in Fig. 1.

Often isolated along with plakortolides are 1,2-dioxolane carboxylates, which belong to the large family of plakinic acids.[2b,d,g–i] Thus from the extract of the sponge *Plakortis aff simplex* were isolated plakortolide I **2** and the five-membered ring peroxide: andavadoic acid 7 (Fig. 2), which showed significant activity against 13 tumor cell lines with GI_{50} values in the sub-micromolar range.[2h] In this article, only the relative stereochemistry of andavadoic acid **7** was assigned.[2h] No total synthesis of **7** has been reported. So far, only one total synthesis of a natural product bearing a 3,5-dimethyl-1,2-dioxolane-3-acetic acid system (plakinic acid A) has been published.[3,4]

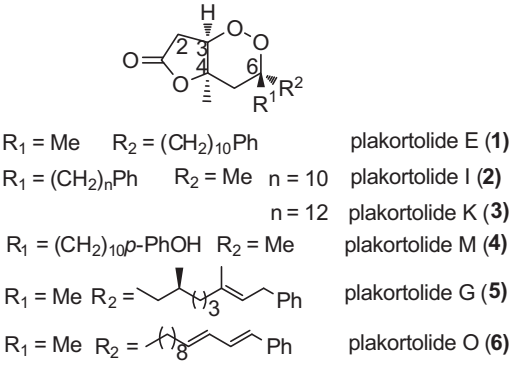

Fig. 1. Representative examples of plakortolides.

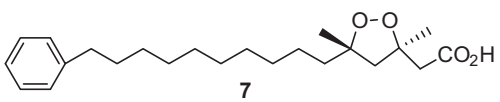

Fig. 2. Structure of andavadoic acid.

In 2002, Jung and co-workers described the first racemic total synthesis of a plakortolide: plakortolide I **2** using as key steps a [4+2] photocycloaddition of a singlet oxygen to a diene and

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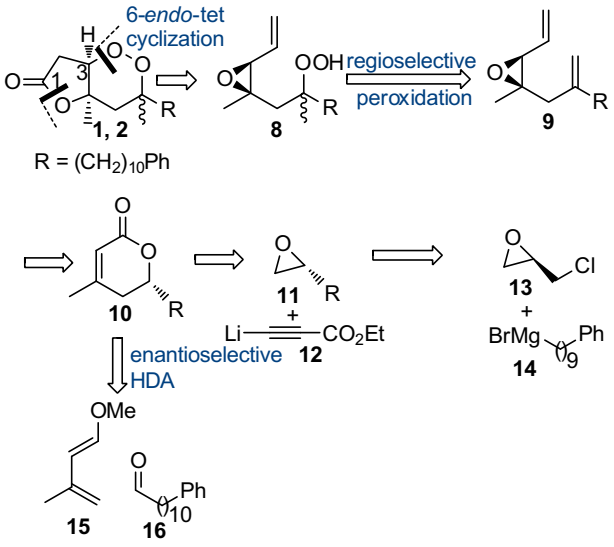
http://dx.doi.org/10.1016/j.tet.2012.10.022

iodolactonization.[5] Later on, we reported the synthesis of (−)-*ent*-plakortolide I **2** and E **1** involving the elaboration of the 1,2-dioxane ring by intramolecular Michael addition of a hydroperoxide to a butenolide.[6]

As a part of an ongoing project devoted to the directing effect of a double bond in the regiocontrol of intramolecular opening of vinyl epoxides with nucleophiles, such as alcohols and hydroperoxides via disfavored 5- or 6-*endo* modes,[7–9] we have recently reported a study concerning the application of this concept to forge the 1,2-dioxane ring system of plakortolides I **1** and E **2** from β-hydroperoxy vinyl *cis*-trisubstituted epoxides.[8] We report here the results of this investigation and the application of some of these results to the first synthesis of andavadoic acid **7** and of its configurational assignment.

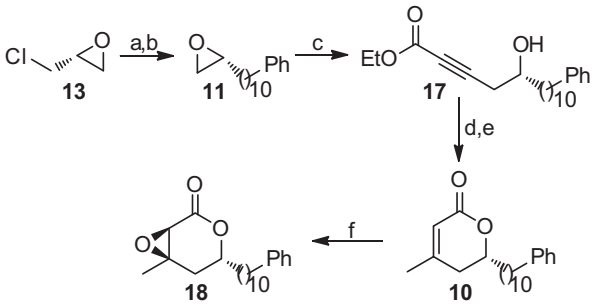
Our retrosynthetic analysis, summarized in Scheme 1, guided by our approach of 1,2-dioxane ring forming based on anti-Baldwin 6-*endo* cyclization of β-hydroperoxy vinyl epoxides, started by a disconnection of C_3—O and C_1—O bonds within **1** and **2** revealing the vinyl epoxide **8**. To introduce the hydroperoxide function, we chose the hydroperoxysilylation developed by Mukaiyama and Isayama because of its mildness and remarkable regio- and chemoselectivity.[10,11] With this method in mind, we envisioned that hydroperoxide **8** could arise from epoxy diene **9**, itself being able to originate from the unsaturated lactone **10** via diastereoselective epoxidation and standard functional manipulation. Construction of the pentenolide **10** would call upon successive addition of lithium salt of ethyl propiolate to epoxide **11**, methyl cupration of the triple bond and lactonization. Alternatively, the pentenolide **10** could be obtained via the enantioselective Jacobsen hetero Diels—Alder reaction between **15** and **16**. Finally, epoxide **11** could be accessed via epoxide-opening of (*R*)-epichlorohydrin **13** with the Grignard reagent **14** followed by base-catalyzed epoxide formation.



Scheme 1. Retrosynthetic analysis for **1** and **2**.

2. Results and discussion

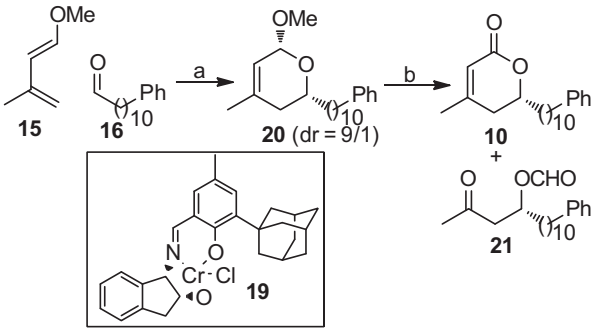
The synthesis of the key intermediate **18** started by a copper-ring opening of (*R*)-epichlorohydrin **13** with known (9-phenylnonyl) magnesium bromide **14**[12] followed by treatment of the resulting chlorohydrin with NaOH to give the (*R*)-epoxide **11** in 79% yield (Scheme 2). Regioselective ring-opening of **11** with the lithium salt of ethyl propiolate **12**, in the presence of $BF_3{\cdot}Et_2O$,[13] afforded the secondary alcohol **17** in nearly quantitative yield. Stereoselective addition of lithium dimethylcuprate[14] and subsequent lactonization



Scheme 2. Reagents and conditions: (a) $Ph(CH_2)_9MgBr$ (**14**) (1.3 equiv), CuCN (0.1 equiv), THF, −78 °C, 2 h; (b) NaOH (5 equiv), THF, rt, 4 h, 79% for two steps; (c) ethyl propiolate (3 equiv), THF, −90 °C, *n*-BuLi (3 equiv), 20 min, $BF_3{\cdot}Et_2O$ (3 equiv) then **11**, −78 °C→rt, 98%; (d) Me_2CuLi (3 equiv) then **17**, THF, −78 °C, 0.5 h; (e) *p*TsOH (0.1 equiv), MeOH, rt, 4 h, 84% for two steps; (f) H_2O_2 (30%, 3.5 equiv), NaOH (6 N, 0.6 equiv), MeOH, 0 °C→rt, 3 h, 82%.

of the resulting *Z*-enoate with *p*-toluenesulfonic acid in methanol at room temperature gave the lactone **10** in 84% overall yield. Epoxidation of **10** with alkaline hydrogen peroxide furnished the epoxy lactone **18** as a single diastereomer in 82% yield. This *trans*-selective epoxidation of pentenolides is well-precedented.[15]

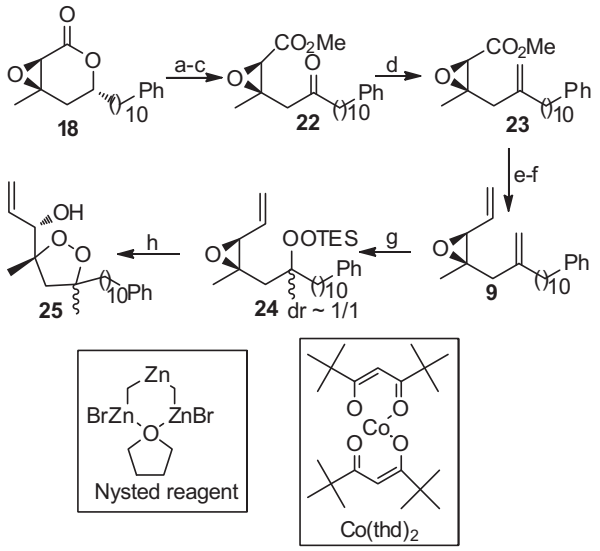
We also studied a more straightforward access to unsaturated lactone **10** using as a key step asymmetric catalytic hetero Diels—Alder (HDA) reaction developed by Jacobsen (Scheme 3).[16]



Scheme 3. Reagents and conditions: (a) MS 4 Å, **19** (5 mol %), rt, 24 h, 62% based on recovered aldehyde **16**; (b) PDC, AcOH, CH_2Cl_2, rt, 3 h, 66% (ratio **10**/**21**=88/12).

Exposure of a neat mixture of diene **15**[17] and freshly prepared aldehyde **16**[18] to catalyst (1*S*,2*R*)-**19**[16c] gave HDA adduct **20** in 62% yield and good diastereoselectivity (dr=9/1). Oxidative cleavage of the acetal of **20** with PDC in the presence of acetic acid furnished the desired lactone **10** in moderate yield accompanied by the formate **21**. Optical purity of **10** was determined by comparison of its specific rotation with that obtained from enantiopure epichlorohydrin **13** and found to be 86% ee. This route for the construction of the unsaturated lactone **10** was dismissed because of its moderate enantiomeric excess and its overall yield in comparison with that obtained from epichlorohydrin (36% vs 52%).

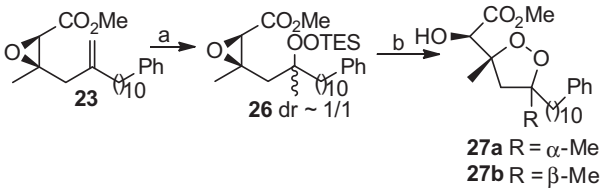
We next turned our attention to the methylenation of the C_2 and C_6 positions of epoxy lactone **18** (Scheme 4). To attain this goal we developed an efficient one-pot two-step reaction involving the saponification of lactone function of **18** followed by RuO_4 oxidation[19] of the resulting hydroxy sodium carboxylate. Treatment of the crude keto acid with diazomethane afforded the keto ester **22** in nearly quantitative yield. The regio- and chemoselective methylenation of the carbonyl function of **22** was troublesome. In the presence of Wittig, Lombardo (Zn, CH_2Br_2, $TiCl_4$),[20] Tebbe (Cp_2TiCl-CH_2AlMe_2),[21] Petasis (Cp_2TiMe_2)[22] reagents, keto ester **22** gave either decomposition products or a mixture of mono- and dimethylenation compounds. The use of Nysted reagent and $TiCl_4$[23] improved the chemoselectivity of the methylenation reaction nevertheless compound **23** was obtained in a modest yield (35%).



Scheme 4. Reagents and conditions: (a) NaOH (2 equiv), MeOH, rt, 2 h, then evaporation in vacuo; (b) $RuCl_3$ (0.05 equiv), $NaIO_4$ (3 equiv), K_2CO_3 (2 equiv), water, rt, 2–3 h; (c) CH_2N_2 (1.2 equiv), Et_2O, rt, 10 min, 96% for three steps; (d) Nysted reagent (3 equiv), $Ti(O^iPr)_2Cl_2$ (2.5 equiv), THF, 0–15 °C, 15–20 min, 70%; (e) DIBAL-H (5 equiv), toluene, −78 °C, 40 min; (f) Ph_3PMeBr (5 equiv), *n*-BuLi (4 equiv), THF, 0 °C then aldehyde, 30 min, 83% for two steps; (g) $Co(thd)_2$ (0.1 equiv), O_2 (1 atm), Et_3SiH (1.2 equiv), dichloroethane, rt, silica gel filtration, 80% conversion (% determined by ^1H NMR); (h) Amberlyst-15 (0.5 equiv), CH_2Cl_2, rt, 3 h, 51% from **9**.

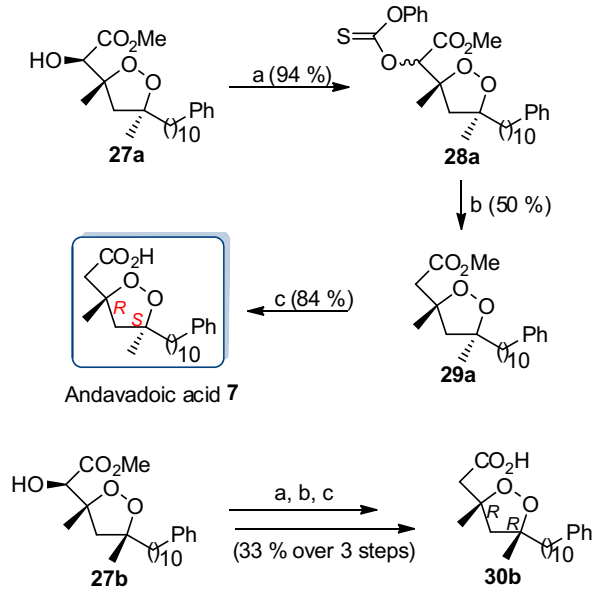
Interestingly, replacing $TiCl_4$ by a milder Lewis acid: $TiCl_2(Oi\text{-}Pr)_2$[24] improved considerably the yield (70%). DIBAL-H reduction of the ester function of **23** followed by methylenation of the resulting aldehyde with methylene triphenylphosphorane provided the epoxy diene **9** in 83% overall yield setting the stage for the chemoselective Mukaiyama–Isayama peroxidation. Among Co(II) salts used as catalysts in this reaction, from our experience[6,7b] and those of other groups,[25] bis(2,2,6,6-tetramethylheptane-3,5-dienoate Co(II)) ($Co(thd)_2$) was selected because of its large superior catalytic activity. Co(II)-catalyzed regio and chemoselective hydroperoxysilylation of diene **9** with triethylsilane and oxygen and stopping the reaction at about 80% conversion to avoid bisperoxidation gave an unseparable mixture of the starting material **9** and the TES protected hydroperoxide **24**. After filtration of the crude mixture through a pad of silica gel to remove the catalyst, the residue was treated with acidic resin Amberlyst-15, which effected cleavage of the TES group and concomitant cyclization to afford exclusively the 5-*exo*-cyclized product **25** in 51% overall yield as an unseparable 1/1 mixture of diastereomers. The structure of **25** was established by 1D and 2D NMR experiments (HSQC, HMBC). In contrast to a large number of examples, the vinyl group of compound **24** has no directing effect in the acid-catalyzed intramolecular epoxide opening and the cyclization followed Baldwin's rules providing a five-membered peroxide. Difficulties for hydroperoxy vinyl-*cis*-epoxides to assume the planar arrangement for maximum stabilization in the transition state and steric interactions may be responsible for the selectivity in favor of the Baldwin's product.[9,26]

At last, we explored a new strategy for 1,2-dioxane ring forming based on the hypothesis that a peroxy anion, derived from a β-hydroperoxy epoxide bearing an electron-withdrawing group (EWG) adjacent to the epoxide, should attack the oxirane function at the less hindered and more electrophilic position, namely in the α position of the EWG. To test this tactic, the protected hydroperoxide **26**, which fulfilled the desired structural requirement was prepared in excellent yield from unsaturated epoxy ester **23** by Mukaiyama–Isayama peroxidation (Scheme 5). Treatment of **26** with a catalytic amount of potassium carbonate gave, after TES cleavage, again the 5-*exo*-cyclized product **27**, obtained as a mixture



Scheme 5. Reagents and conditions: (a) $Co(thd)_2$ (0.1 equiv), O_2 (1 atm), Et_3SiH (2 equiv), dichloroethane, rt, 3–4 h, 86%; b) K_2CO_3 (0.3 equiv), MeOH, 0 °C, 3 h, 64%.

of 1:1 diastereomers separable by preparative TLC. The structure and relative stereochemistry of **27a**,**b** was established by 1D and 2D experiments (NOE, HSQC, HMBC). The structure of compound **27a** is closely related to natural andavadoic acid **7** (its 2-hydroxy analog) and we found interesting to transform the former to the latter in order to confirm its structure and to establish its absolute configuration. The synthesis of andavadoic acid **7** from **27a** involved a radical Barton–McCombie deoxygenation[27] from its corresponding thionocarbonate ester **28a**[28] (Scheme 6). Combination of $^nBu_3SnH$ with 2,2′-azobisisobutyronitrile (AIBN) mediated the reduction **28a** in hot toluene to afford **7** methyl ester in moderate yield. Saponification with lithium hydroperoxide in aqueous THF furnished andavadoic acid **7** in an excellent yield.[3,29] ^1H and ^{13}C NMR data are consistent with that reported for the natural product (See Supplementary data). Additionally, the optical rotation of the synthetic material is in good agreement with that of the natural product (lit. value: $[\alpha]_D^{20}$ +34.7 (*c* 0.004, $CHCl_3$)[2h]; synthetic **7**: $[\alpha]_D^{20}$ +32.7 (*c* 0.28, $CHCl_3$)). The absolute configuration of andavadoic acid **7** is 3*R*,5*S*.



Scheme 6. Reagents and conditions: (a) PhOC(S)Cl (3 equiv), pyridine, CH_2Cl_2, 0 °C→rt, 5 h, 83–94%; (b) $HSnBu_3$ (3 equiv), AIBN (1 equiv), toluene, 80 °C, 1 h, 50–53%; (c) $LiOH{\cdot}H_2O$ (3 equiv), H_2O_2 (35%, 7 equiv), rt, 24 h, 75–84%.

By the same reaction sequence than **27a**, compound **27b** was transformed to 5-*epi*-andavadoic acid **30b** in 33% yield for the three steps (Scheme 6).

3. Conclusion

In summary, during the study of plakortolide synthesis we have shown that acid-catalyzed cyclization of a β-hydroperoxy vinyl-*cis*-epoxide occurred exclusively via a 5-*exo* mode, unlike hydroxyl analogs, to give a 1,2-dioxolane. On our substrate, the vinyl group has no directing effect. We also described a modification of the

method of methylenation of Matsubara and co-workers, using Nysted reagent and a mixture of $TiCl_4$ and $Ti(iOPr)_4$, which allowed the chemoselective methylenation of a keto ester in the presence of sensitive functional groups, such as epoxides. Extension of the Mukaiyama and Isayama peroxygenation method to a functionalized diene allowed the introduction of the hydroperoxide function regio- and chemoselectively. Finally, K_2CO_3-catalyzed cyclization of a β-hydroperoxy epoxy ester furnished a 3,5-dimethyl-1,2-dioxolane ester, which was transformed to andavadoic acid in 9% overall yield from (*R*)-epichlorohydrin.

4. Experimental

4.1. Caution

Organic peroxides are potentially hazardous compounds and must be handled with great care: avoid direct exposure to strong heat or light, mechanical shock, oxidizable organic materials, or transition-metal ions. A safety shield should be used for all reactions involving large quantities of organic peroxides or H_2O_2.

4.2. General experimental detail

NMR spectra were recorded at ambient probe temperature on Bruker AV 300, DRX 300, DRX 400 and AV 500 spectrometers. Multiplicity is described by the following abbreviations: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad. Chemical shifts are given in parts per million. ^{1}H NMR spectra were referenced to the residual solvent peak at δ=7.26 ($CDCl_3$) or δ=7.16 (C_6D_6). ^{13}C NMR spectra were referenced to the solvent peak at δ=77.16 ($CDCl_3$) or δ=128.06 (C_6D_6). High resolution mass spectrometry (HRMS) analyses were conducted using a Thermofinigan-MAT 95 XL instrument. IR spectra were recorded on a Perkin–Elmer spectrum. One spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer 343 apparatus at the sodium D line (598 nm). Reagents and solvents were purified by standard means. Tetrahydrofuran and diethyl ether were distilled from sodium wire/benzophenone and stored under a nitrogen atmosphere. Dichloroethane, dichloromethane, pyridine and toluene were distilled from calcium hydride. Methanol was distilled from magnesium metal. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Flash chromatography was performed on silica gel (230–400 mesh) from Macherey Nagel. Preparative thin-layer chromatography (PTLC) was performed on Silicycle plates (F-254, 1000 microns).

4.3. Experimental procedures

*4.3.1. (2R)-2-(10-Phenyldecyl)oxirane (**11**).* To a mixture of (*R*)-epichlorohydrin **13** (99% ee, 0.2 g, 0.17 mL, 2.16 mmol, 0.7 equiv), CuCN (28 mg, 0.31 mmol, 0.1 equiv), and THF (3 mL) was added dropwise at −78 °C, 9-phenylnonylmagnesium bromide **14**[12] in THF (6 mL), prepared from (9-bromononyl)benzene (0.88 g, 3.1 mmol, 1 equiv) and Mg turnings (83 mg, 3.4 mmol, 1.1 equiv). The solution was warmed up to 0 °C over 2 h and poured into a mixture of saturated NH_4Cl (10 mL) and Et_2O (10 mL) with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried and concentrated to furnish the crude chlorohydrin (0.86 g), which was used in the next step without purification. To a solution of the chlorohydrin (0.86 g) in THF (5 mL) was added crushed NaOH (0.618 g, 15.4 mmol). The mixture was stirred vigorously at room temperature for 3 h and poured into water. The product was extracted with Et_2O (4×10 mL). The combined ethereal solutions were washed with saturated NH_4Cl, dried (Na_2SO_4), and concentrated. Purification by flash chromatography of the oily residue (Et_2O/petroleum ether=5:95) afforded the epoxide **11** as an oil (0.443 g, 79% for two steps). $[\alpha]_D^{20}$ +4.2 (*c* 1.2, $CHCl_3$). IR (neat): 1604, 2854, 2926, 3027, 3061, 3085. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29–1.63 (m, 18H), 2.47 (dd, *J*=5.0, 2.7 Hz, 1H), 2.61 (t, *J*=7.5 Hz, 2H), 2.76 (dd, *J*=4.9, 4.1 Hz, 1H), 2.92 (m, 1H), 7.18–7.20 (m, 3H), 7.26–7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.1, 29.5–29.7 (6C), 31.7, 32.6, 36.1, 47.3, 52.5, 125.7, 128.3 (2C), 128.5 (2C), 143.0. HRMS (CI): calculated for $C_{18}H_{29}O$ (MH^+) 261.2218, found 261.2216.

*4.3.2. (R)-Ethyl 5-hydroxy-15-phenylpentadec-2-ynoate (**17**).* A solution of *n*-butyl lithium (2.5 M in hexanes, 9.92 mL, 24.8 mmol) cooled to −78 °C was added dropwise to a solution of ethyl propiolate (2.51 mL, 24.8 mmol) in THF (44 mL) at −90 °C. After 20 min, $BF_3\cdot Et_2O$ (3.15 mL, 24.8 mmol) was added. After a further 10 min, a solution of (2*R*)-2-(10-phenyldecyl)oxirane **11** (2.15 g, 8.27 mmol) in THF (10 mL) was added dropwise and the resulting solution allowed to warm up to room temperature, stirred for 15 min and cooled to 0 °C. The reaction mixture was then quenched with satd aqueous NH_4Cl and allowed to warm to room temperature. The layers were separated and the aqueous phase extracted five times with Et_2O (30 mL). The combined organic extracts were washed with satd aqueous $NaHCO_3$ and brine then dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/petroleum ether=1:2) to provide **17** (2.9 g, 98%) as a clear oil. $[\alpha]_D^{20}$ −3.7 (*c* 0.9, CH_2Cl_2). IR (neat): 1604, 1712, 2236, 2854, 2927, 2982, 3026, 3062, 3423. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (m, 14H), 1.31 (t, *J*=7.2 Hz, 3H), 1.52–1.64 (m, 4H), 2.02 (s, 1H, OH), 2.47 (dd, *J*=17.1, 6.5 Hz, 1H), 2.56 (dd, *J*=17.1, 6.5 Hz, 1H), 2.60 (t, *J*=7.5 Hz, 2H), 3.84 (m, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 7.17–7.19 (m, 3H), 7.25–7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2, 25.7, 27.7, 29.5–29.7 (6C), 31.7, 36.1, 36.6, 62.1, 69.7, 75.1, 86.0, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 153.7. HRMS (ESI): calculated for $C_{23}H_{34}O_3Na$ (MNa^+) 381.2400, found 381.2400.

*4.3.3. (R)-4-Methyl-6-(10-phenyldecyl)-5,6-dihydro-2H-pyran-2-one (**10**). Method A.* Methyl lithium (1.6 M in Et_2O, 31 mL, 49.6 mmol, 6 equiv) was added to a stirred suspension of CuI (5.03 g, 26.5 mmol, 3.2 equiv) in THF (40 mL) at −78 °C. Once the addition was complete, the mixture was allowed to warm up to 0 °C to help the formation of the cuprate. Once a clear solution had been obtained, the reaction mixture was cooled to −78 °C and (*R*)-ethyl 5-hydroxy-15-phenylpentadec-2-ynoate **17** (2.96 g, 8.27 mmol, 1 equiv) in THF (30 mL) was added dropwise over 10 min. The resulting solution was allowed to stir for 30 min and was then quenched with satd aqueous NH_4Cl and NH_4OH (3:1) at −78 °C. The layers were separated, and the aqueous phase extracted four times with Et_2O (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. To a stirred solution of the residue in MeOH (40 mL) was added a catalytic amount of *p*TsOH (0.157 g, 0.827 mmol, 0.1 equiv) under N_2 atmosphere. After stirring for 3 h at room temperature the reaction mixture was quenched with solid $NaHCO_3$ and filtered off. The solvent was removed at reduced pressure and the residue was chromatographed on silica gel (Et_2O/petroleum ether=1:1) to give the pentenolide **10** (2.28 g, 84%) as a colorless solid. $[\alpha]_D^{20}$ −71.1 (*c* 1.1, $CHCl_3$).

Method B. Pyridinium dichromate (72 mg, 0.19 mmol, 2 equiv) was added to a solution of (2*R*,6*R*)-6-methoxy-4-methyl-2-(10-phenyldecyl)-3,6-dihydro-2*H*-pyran **20** (33 mg, 95.7 μmol, 1 equiv) and AcOH (0.2 mL) in CH_2Cl_2 (1.2 mL). The reaction mixture was stirred at room temperature for 3 h, then 1.5 mL of Et_2O/petroleum ether (1:1) was added and the resulting mixture was filtered through a pad of Na_2SO_4 (upper layer) and silica gel (lower layer). The combined organic layers were evaporated and the residue was chromatographed on preparative TLC (MeOH/petroleum ether=1:20) to give first the formate **21** (2.5 mg, 8%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.25 (m, 12H), 1.6 (m, 6H), 2.17 (s,

3H), 2.6 (t, J=7.7 Hz, 2H), 2.63 (m, 1H), 2.8 (dd, J=16.7, 7.4 Hz, 1H), 5.34 (m, 1H), 7.14–7.19 (m, 3H), 7.25–7.3 (m, 2H), 8.04 (s, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.2, 29.4–29.7 (6C), 30.6, 31.7, 34.2, 36.1, 47.8, 70.5, 125.7, 128.4 (2C), 128.5 (2C), 143.1, 160.8, 205.5. HRMS (CI): calculated for $C_{21}H_{32}O_3Na$ (MNa^+) 355.2244, found 355.2253. The next fraction was constituted of compound **10** (18.2 mg, 58%) obtained as a colorless oil. $[\alpha]_D^{20}$ −61.4 (c 0.94, $CHCl_3$). IR (neat): 1720, 2853, 2925, 3026. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28–1.84 (m, 18H), 1.97 (s, 3H), 2.17 (dd, J=17.8, 4.1 Hz, 1H), 2.31 (dd, J=17.8, 11.6 Hz, 1H), 2.60 (t, J=7.8 Hz, 2H), 4.36 (m, 1H), 5.80 (m, 1H), 7.16–7.19 (m, 3H), 7.25–7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.1, 25.0, 29.4, 29.5, 29.56, 29.58, 29.61, 29.63, 31.6, 34.8, 34.9, 36.1, 77.4, 116.6, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 157.2, 165.5. HRMS (CI): calculated for $C_{22}H_{33}O_2$ (MH^+) 329.2481, found 329.2487.

*4.3.4. (1R,4R,6R)-6-Methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo [4.1.0]heptan-2-one (**18**).* To a solution of pentenolide **10** (2.28 g, 6.95 mmol, 1 equiv) in MeOH (100 mL) was added H_2O_2 (35%, 2.13 mL, 24.3 mmol, 3.5 equiv) and 6 N NaOH (0.7 mL, 4.17 mmol, 0.6 equiv) at 0 °C. After 10 min, a precipitate was formed. The reaction mixture was stirred for 30 min at 0 °C, then warmed to room temperature and stirred until the solution became clear (~3 h). Et_2O (100 mL) and H_2O (100 mL) were added and the solution was acidified with HCl (35%) to pH ~3. Water phase was extracted with Et_2O (5×20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether=1:1) to furnish **18** (1.96 g, 82%) as an amorphous powder. $[\alpha]_D^{20}$ +33.0 (c 0.9, CH_2Cl_2). IR (neat): 1735, 2851, 2919, 2947. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (m, 14H), 1.50 (s, 3H), 1.60 (m, 4H), 1.91 (dd, J=11.7, 15 Hz, 1H), 2.18 (dd, J=3, 15 Hz, 1H), 2.60 (t, J=7.5 Hz, 2H), 3.39 (s, 1H), 4.48 (m, 1H), 7.17–7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.3, 25.0, 29.4–29.6 (6C), 31.7, 34.7, 34.8, 36.1, 55.6, 59.4, 75.0, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 168.5. HRMS (ESI): calculated for $C_{22}H_{33}O_3$ (MH^+) 345.2424, found 345.2422.

*4.3.5. (2R,6R)-6-Methoxy-4-methyl-2-(10-phenyldecyl)-3,6-dihydro-2H-pyran (**20**).* 1-Methoxy-3-methylbuta-1,3-diene **15**[17] (80% in pentane, 238 mg, 1.95 mmol, 1.5 equiv) was added to a stirred mixture of 11-phenylundecanal **16**[18] (314 mg, 1.28 mmol, 1 equiv), [Cr(salen)]Cl **19** (18 mg, 38 μmol, 0.03 equiv), and 4 Å molecular sieves (240 mg) under N_2 at ambient temperature. The mixture was stirred for 24 h and chromatographed on silica gel (Et_2O/petroleum ether/Et_3N=8:91:1) to furnish the aldehyde **16** (35 mg, 11%) and **20** (241 mg, 55%) (mixture of 9/1 diastereomers) as a slight-yellow oil. IR (neat): 1604, 1681, 2852, 2923, 3025, 3061. ^{1}H NMR (300 MHz, C_6D_6): δ=1.26 (m, 12H), 1.47 (s, 3H), 1.38–1.82 (m, 8H), 2.51 (t, J=7.6 Hz, 2H), 3.42 (s, 3H), 3.50 (tdd, J=9.6, 6.5, 4.0 Hz, 1H), 5.05 (m, 1H), 5.45 (m, 1H), 7.05–7.11 (m, 3H), 7.16–7.21 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6): δ=22.7, 26.1, 29.7, 30.0–30.2 (5C), 32.0, 35.9, 36.1, 36.4, 54.5, 72.1, 99.1, 122.6, 126.0, 128.6 (2C), 128.8 (2C), 136.7, 143.0. HRMS (ESI): calculated for $C_{23}H_{36}NaO_2$ (MNa^+) 367.2608, found 367.2611.

*4.3.6. (2R,3R)-Methyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate (**22**).* To a solution of the epoxy lactone **18** (110 mg, 0.32 mmol, 1 equiv) in MeOH (6 mL) was added NaOH (6 M, 0.1 mL, 0.64 mmol, 2 equiv) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H_2O (7 mL) and $RuCl_3$ (4 mg, 16 μmol, 0.05 equiv) and K_2CO_3 (88 mg, 0.64 mmol, 2 equiv) were added sequentially followed by addition of an aqueous $NaIO_4$ solution (10%, 2.01 mL, 0.96 mmol, 3 equiv) by portions (0.3 mL). When the reaction was finished (~3–4 h) the reaction mixture was acidified with HCl (2 M) to pH 3–4, and extracted with EtOAc (6×3 mL). The combined organic extracts were treated with a solution of CH_2N_2 in Et_2O until persistent slightly yellow color, and then dried (Na_2SO_4). Solvents were evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether=1:9) to give **22** (114 mg, 96%) as a colorless oil. $[\alpha]_D^{20}$ −39.5 (c 1.2, $CHCl_3$). IR (neat): 1604, 1715, 1751, 2854, 2927, 3026, 3062. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.25 (m, 12H), 1.43 (s, 3H), 1.56 (m, 4H), 2.37 (t, J=7.5 Hz, 2H), 2.59 (t, J=7.5 Hz, 2H), 2.94 (s, 2H), 3.42 (s, 1H), 3.74 (s, 3H), 7.16–7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.9, 23.7, 29.2–29.6 (6C), 31.6, 36.1, 43.4, 46.0, 52.5, 58.2, 59.8, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 169.1, 207.6. HRMS (ESI): calculated for $C_{23}H_{34}NaO_4$ (MNa^+) 397.2349, found 397.2344.

*4.3.7. (2R,3R)-Methyl 3-methyl-3-(2-methylene-12-phenyldodecyl)-oxirane-2-carboxylate (**23**).* To a stirred solution of the keto ester **22** (0.219 g, 0.585 mmol) in dry THF (8 mL) was added at 0 °C Nysted reagent (20% in THF, 3.51 mL, 1.83 mmol) followed by dropwise addition of $TiCl_2(O^iPr)_2$, prepared from $TiCl_4$ (1 M in dichloromethane, 0.73 mL, 0.73 mmol) and $Ti(O^iPr)_4$ (0.217 mL, 0.73 mmol).[24] The reaction mixture was then allowed to reach 15 °C and stirred for 15 min. The reaction mixture was cooled to 0 °C, treated carefully with water (1 mL) and extracted with ether (5×8 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and brine. The ethereal solution was filtered through a small pad of silica gel to remove metal species, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (Et_2O/petroleum ether=1:5) to provide **23** (0.153 g, 70%) as a colorless oil. $[\alpha]_D^{20}$ −29.2 (c 1, CH_2Cl_2). IR (neat): 1646, 1736, 1757, 2854, 2927, 3026. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (m, 14H), 1.38 (s, 3H), 1.60 (m, 2H), 1.95 (m, 2H), 2.35 (d, J=15 Hz, 1H), 2.41 (d, J=15 Hz, 1H), 2.59 (t, J=7.6 Hz, 2H), 3.37 (s, 1H), 3.76 (s, 3H), 4.79 (s, 1H), 4.85 (s, 1H), 7.16–7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.8, 27.6, 29.4–29.7 (6C), 31.6, 36.1, 36.3, 39.0, 52.3, 59.0, 62.2, 112.2, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 145.3, 169.0. HRMS (ESI): calculated for $C_{24}H_{36}NaO_3$ (MNa^+) 395.2557, found 395.2557.

*4.3.8. (2R,3S)-2-Methyl-2-(2-methylene-12-phenyldodecyl)-3-vinyloxirane (**9**).* To a cooled (−90 °C) solution of epoxy ester **23** (26 mg, 0.07 mmol, 1 equiv) in toluene (1 mL) was added slowly a solution of DIBAL (1 M in hexanes, 0.35 mL, 0.35 mmol, 5 equiv). After stirring for 30–40 min at −78 °C, the reaction mixture was treated with MeOH (0.2 mL) and saturated aqueous Rochelle salt solution (1 mL). The mixture was warmed up to room temperature, stirred for 20 min and extracted with Et_2O (5×2 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to yield crude aldehyde. n-BuLi (2.4 M, 0.12 mL, 0.28 mmol, 4 equiv) was added dropwise to the suspension of Ph_3PMeBr (125 mg, 34.9 mmol, 5 equiv) in THF (1.3 mL) cooled to −78 °C. After the temperature had raised to 0 °C the mixture was stirred for 30 min and the solution of aldehyde in THF (2 mL) was added dropwise. After 30 min, H_2O (3 mL) was added and the mixture was extracted with Et_2O/petroleum ether=1:2 (5×4 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography on silica gel (Et_2O/petroleum ether=3:97) gave **9** (19.6 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ −3.2 (c 0.7, CH_2Cl_2). IR (neat): 1643, 2854, 2927, 3026, 3070. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26–1.43 (br m, 14H), 1.31 (s, 3H), 1.60 (m, 2H), 1.99 (m, 2H), 2.18 (d, J=15 Hz, 1H), 2.31 (d, J=15 Hz, 1H), 2.59 (t, J=7.5 Hz, 2H), 3.23 (d, J=7.2 Hz, 1H), 4.78 (s, 1H, H), 4.83 (s, 1H), 5.33 (d, J=10.5 Hz, 1H), 5.45 (d, J=17.1 Hz, 1H), 5.78 (ddd, J=7.2 Hz, 10.5 Hz, 17.1 Hz, 1H), 7.16–7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.1, 27.8, 29.5–29.7 (6C), 31.7, 36.1, 36.5, 39.5, 62.2, 64.2, 112.1, 120.1, 125.7, 128.3 (2C), 128.5 (2C), 133.6, 143.1, 146.1. HRMS (ESI): calculated for $C_{24}H_{36}NaO$ (MNa^+) 363.2658, found 363.2656.

*4.3.9. Triethyl((2-methyl-1-((2R,3S)-2-methyl-3-vinyloxiran-2-yl)-12-phenyldodecan-2-yl)peroxy)silane (**24**).* To a solution of dienyloxirane **9** (13 mg, 38 μmol) in dichloroethane (0.5 mL) was added

Co(II) bis(2,2,6,6-tetramethylheptane-3,5-dienoate) [$Co(thd)_2$] (1.6 mg, 3.8 μmol). The flask was charged with O_2 and Et_3SiH (7.3 μL, 45.8 μmol) was added. The reaction mixture was stirred under O_2 atmosphere for 4 h, filtered through a pad of silica gel and evaporated. As determined by ^1H NMR, the crude mixture was composed of diene **9** and peroxy ether **24** in a ratio: 1:4, unseparable by chromatography on silica gel.

*4.3.10. (1S)-1-((3R)-3,5-Dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)prop-2-en-1-ol (**25**).* The crude TES hydroperoxy ether **24** was dissolved in dichloromethane (1 mL) and Amberlyst-15 (4.7 mequiv/g, 8.1 mg) was added. After stirring for 2 h at room temperature, the reaction mixture was filtered and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether=1:3) to provide **25** (mixture of 1/1 diastereomers) (7.3 mg, 51%) as a colorless oil. IR (neat): 1722, 2854, 2927, 3026, 3521. ^1H NMR (400 MHz, $CDCl_3$): δ=1.26–1.43 (br m, 20H), 1.57 (br m, 4H), 2.00 (d, *J*=12.2 Hz, 0.5H), 2.12 (d, *J*=12.3 Hz, 0.5H), 2.32 (d, *J*=12.3 Hz, 0.5H), 2.38 (d, *J*=12.2 Hz, 0.5H), 2.53 (d, *J*=2.7 Hz, 0.5H), 2.54 (d, *J*=2.7 Hz, 0.5H), 2.60 (t, *J*=6 Hz, 2H), 4.19 (m, 1H), 5.27 (d, *J*=10.5 Hz, 1H), 5.39 (dd, *J*=17.2, 1.5 Hz, 0.5H), 5.40 (dd, *J*=17.2, 1.5 Hz, 0.5H), 5.81 (m, 1H), 7.17–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.2, 22.4, 24.6, 25.2, 25.2, 29.5–29.7 (6C), 31.7, 36.1, 38.3, 39.9, 52.8, 53.2, 76.3, 76.4, 87.0, 87.3, 87.9, 88.2, 118.3, 125.7, 128.4 (2C), 128.5 (2C), 135.2, 135.3, 143.1. HRMS (ESI): calculated for $C_{24}H_{38}NaO_3$ (MNa^+) 397.2713, found 397.2707.

*4.3.11. (2R,3R)-Methyl 3-methyl-3-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl) oxirane-2-carboxylate (**26**).* To a solution of the epoxy ester **23** (118 mg, 0.32 mmol) in dichloroethane (3 mL) was added $Co(thd)_2$ (13.5 mg, 32 μmol) and the flask was charged with O_2. Et_3SiH (101 μL, 0.63 mmol) was added and the reaction mixture was stirred for 2 h under O_2 atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et_2O/petroleum ether=1:10) afforded **26** (mixture of 1/1 diastereomers) (142 mg, 86%) as a colorless oil. IR (neat): 1737, 1756, 2854, 2926, 3026. ^1H NMR (300 MHz, $CDCl_3$): δ=0.67 (q, *J*=7.8 Hz, 6H), 0.98 (t, *J*=7.8 Hz, 9H), 1.07 (s, 1.5H), 1.26 (m, 15.5H), 1.51 (s, 1.5H), 1.52 (s, 1.5H), 1.61 (m, 4H), 1.98 (s, 1H), 2.00 (s, 1H), 2.59 (t, *J*=7.5 Hz, 2H), 3.24 (s, 0.5H), 3.27 (s, 0.5H), 3.76 (s, 3H), 7.16–7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=3.9, 6.9, 21.7, 22.2, 23.4, 23.5, 23.8, 29.5–29.7 (6C), 30.28, 30.30, 31.7, 36.1, 37.2, 37.7, 38.1, 38.5, 52.26, 52.27, 59.6, 59.7, 61.9, 62.1, 84.1, 84.3, 125.63, 125.65, 128.3 (2C), 128.5 (2C), 143.02, 143.05, 169, 169.3. HRMS (ESI): calculated for $C_{30}H_{52}NaO_5Si$ (MNa^+) 543.3476, found 543.3492.

*4.3.12. (R)-Methyl 2-((3R,5R,S)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)-2-hydroxyacetate (**27a**,**b**).* To an ice-cooled solution of the peroxy **26** (140 mg, 0.269 mmol) in MeOH (5 mL) was added K_2CO_3 (11 mg, 80.7 μmol). The reaction mixture was stirred at 0 °C for 5 h, water (10 mL) was added and the resulting mixture was extracted with Et_2O (5×5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude mixture was purified by preparative TLC (Et_2O/petroleum ether=1:2, two elutions) to give first the *cis*-isomer (5*R*) **27b** (40 mg, 36%) as a colorless oil. $[\alpha]_D^{20}$ +51.3 (*c* 1.65, $CHCl_3$). IR (neat): 1733, 1738, 2854, 2927, 3498. ^1H NMR (400 MHz, $CDCl_3$): δ=1.26 (m, 14H), 1.34 (s, 3H), 1.37 (s, 3H), 1.55 (br m, 4H), 2.03 (d, *J*=12.3 Hz, 1H), 2.59 (t, *J*=7.5 Hz, 2H), 2.78 (d, *J*=12.3 Hz, 1H), 3.01 (d, *J*=5.7 Hz, 1H), 3.79 (s, 3H), 4.23 (d, *J*=5.7 Hz, 1H), 7.16–7.29 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ=20.2, 24.8, 25.2, 29.4–29.6 (5C), 30.2, 31.6, 36.1, 37.9, 52.4, 52.7, 74.7, 86.9, 87.3, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 172.5. HRMS (ESI): calculated for $C_{24}H_{38}NaO_5$ (MNa^+) 429.2611, found 429.2623. The next fraction was constituted by the *trans*-isomer **27a** (42 mg, 39%) obtained as a colorless oil. $[\alpha]_D^{20}$ +46.8 (*c* 2.3, $CHCl_3$). IR (neat): 1736, 2854, 2926, 3498. ^1H NMR (400 MHz, $CDCl_3$): δ=1.25 (s, 3H), 1.27 (br s, 14H), 1.34 (s, 3H), 1.50–1.76 (br m, 4H), 2.13 (d, *J*=12.6 Hz, 1H), 2.59 (t, *J*=7.7 Hz, 2H), 2.72 (d, *J*=12.6 Hz, 1H), 3.00 (br s, 1H), 3.80 (s, 3H), 4.24 (s, 1H), 7.16–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.3, 21.8, 24.5, 29.4–29.7 (5C), 30.1, 31.6, 36.1, 39.8, 52.6, 52.8, 74.8, 87.0, 87.2, 125.7, 128.3 (2C), 128.5 (2C), 143.0, 172.6. HRMS (ESI): calculated for $C_{24}H_{38}NaO_5$ (MNa^+) 429.2611, found 429.2609.

4.4. General procedure for the preparation of thionocarbonate esters 28a,b

To a solution of alcohols **27a**,**b** (20 mg, 0.050 mmol) in dichloromethane (3 mL) was added at 0 °C, *O*-phenyl thionochloroformate (28 μL, 4 equiv) followed by pyridine (21 μL, 5 equiv). After being stirred at room temperature for 5 h, the mixture was diluted with ether, washed with 2 N HCl followed by water. The combined organic extracts were dried with Na_2SO_4 and evaporated. Flash chromatography (Et_2O/petroleum ether=1:10) of the residue afforded desired thionocarbonate esters **28a**,**b** as a mixture of epimers.

*4.4.1. Methyl-2-((3R,5S)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)-2-((phenoxycarbonothioxyl)oxy)acetate (**28a**).* Obtained as a colorless oil (94% yield). IR (neat): 2924, 2862, 1749. ^1H NMR (400 MHz, $CDCl_3$): δ=1.20–1.38 (m, 12H), 1.31 (s, 3H), 1.48 (s, 2.1H), 1.49 (s, 0.9H), 1.52–1.67 (m, 3H), 1.69–1.82 (m, 1H), 2.19 (d, *J*=12.8 Hz, 1H), 2.61 (t, *J*=7.7 Hz, 2H), 2.86 (d, *J*=12.9 Hz, 0.3H), 2.91 (d, *J*=12.9 Hz, 0.7H), 3.82 (s, 3H), 5.1 (s, 0.3H), 5.47 (s, 0.7H), 7.12–7.23 (m, 2H), 7.23–7.31 (m, 3H), 7.31–7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.7 (0.3C), 21.1 (0.7C), 21.7, 24.4, 29.0–30.1 (8C), 31.6, 36.1, 39.7, 52.4, 52.9, 82.8, 85.47 (0.3C), 85.57 (0.7C), 87, 121.1–129.7 (8C), 143.0, 153.5, 167.9, 194.2. HRMS (ESI): calculated for $C_{31}H_{42}NaO_6S$ (MNa^+) 565.2594, found 565.2605.

*4.4.2. Methyl-2-((3R,5R)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)-2-((phenoxycarbonothioxyl)oxy)acetate (**28b**).* Obtained as a colorless oil (83% yield). IR (neat): 2922, 2865, 1747. ^1H NMR (400 MHz, $CDCl_3$): δ=1.2–1.42 (m, 11H), 1.38 (s, 3H), 1.5 (s, 3H), 1.53–1.65 (5H), 2.07 (d, *J*=12.8 Hz, 1H), 2.59 (t, *J*=7.8 Hz, 2H), 2. 92 (d, *J*=12.8 Hz, 0.15H), 2.96 (d, *J*=12.8 Hz, 0.85H), 3.81 (s, 3H), 5.07 (s, 0.15H), 5.44 (s, 0.85H), 7.11–7.23 (m, 5H), 7.23–7.33 (m, 3H), 7.36–7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.1, 24.9, 25.5, 29.4–30.2 (8C), 31.6, 36.1, 37.8, 52.2, 52.9, 82.9, 85.4, 87.3, 121.9–129.6 (8C), 143.1, 153.6, 167.9, 194.3. HRMS (ESI): calculated for $C_{31}H_{42}NaO_6S$ (MNa^+) 565.2594, found 565.2584.

4.5. General procedure for the deoxygenation of 28a,b

To a solution of **28a**,**b** (20 mg, 0.037 mmol) in toluene (3 mL) was added $HSnBu_3$ (30 μL, 3 equiv) and AIBN (6 mg, 1 equiv). The solution was stirred at 80 °C for 1 h and evaporated. Flash chromatography (Et_2O/petroleum ether=1:9) of the residue afforded **29a**,**b**.

*4.5.1. Methyl 2-((3R,5S)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl) acetate (**29a**).* Obtained as a colorless oil (50% yield). $[\alpha]_D^{20}$ +30.1 (*c* 0.5, $CHCl_3$). IR (neat): 2926, 2854, 1736. ^1H NMR (400 MHz, $CDCl_3$): δ=1.2–1.38 (m, 12H), 1.28 (s, 3H), 1.43 (s, 3H), 1.48–1.75 (m, 6H), 2.23 (d, *J*=12.4 Hz, 1H), 2.47 (d, *J*=12.4 Hz, 1H), 2.6 (t, *J*=7.9 Hz, 2H), 2.65 (d, *J*=14.5 Hz, 1H), 2.77 (d, *J*=14.5 Hz, 1H), 3.69 (s, 3H), 7.14–7.22 (m, 2H), 7.23–7.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.2, 24.1, 24.5, 29.3, 29.47, 29.53 (3C), 29.9, 31.5, 36.0, 39.6, 44.0, 51.7, 55.3, 83.9, 86.5, 125.5, 128.2 (2C), 128.4 (2C), 143.0, 171.1. HRMS (ESI): calculated for $C_{24}H_{38}NaO_4$ (MNa^+) 413.2662, found 413.2662.

*4.5.2. Methyl 2-((3R,5R)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)acetate (**29b**).* Obtained as a colorless oil (53%

yield). $[\alpha]_D^{20}$ +21.1 (*c* 0.4, $CHCl_3$). IR (neat): 2854, 2927, 1733. ^1H NMR (400 MHz, $CDCl_3$): δ=1.24–1.32 (m, 12H), 1.33 (s, 3H), 1.45 (s, 3H), 1.49–1.64 (m, 6H), 2.12 (d, *J*=12.4 Hz, 1H), 2.55 (d, *J*=12.4 Hz, 1H), 2.6 (t, *J*=7.9 Hz, 2H), 2.63 (d, *J*=14.6 Hz, 1H), 2.76 (d, *J*=14 6 Hz, 1H), 3.69 (s, 3H), 7.12–7.23 (m, 2H), 7.24–7.32 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.0, 24.6, 24.9, 29.3, 29.48, 29.50, 29.53 (2C), 30.0, 31.5, 36.0, 38.8, 44.1, 51.7, 55.3, 83.8, 86.7, 125.5, 128.2 (2C), 128.4 (2C), 143.0, 171.2. HRMS (ESI): calculated for $C_{42}H_{38}Na04$ (MNa^+) 413.2662, found 413.2663.

4.6. General procedure for the saponification of 29a,b

To a solution of **29a,b** (10 mg, 0.025 mmol) in THF–H_2O (2 mL, 4/1) were added at 0 °C H_2O_2 (35%, 16 μL, 7 equiv) followed by $LiOH \cdot H_2O$ (3.2 mg, 3 equiv). The reaction mixture was stirred at room temperature for 24 h. Aqueous Na_2SO_3 (10%) was added and the solution was acidified to pH 2 with HCl 2 N and diluted with water. The resulting solution was extracted twice with ether, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on silica gel (petroleum ether–AcOEt–AcOH=79:20:1) to provide pure andavadoic acid **7** or is 5-epimer **30b**.

*4.6.1. 2-((3R,5S)-3,5-Dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)acetic acid (andavadoic acid) (**7**).* Obtained as a colorless oil (84% yield). $[\alpha]_D^{20}$ +32.7 (*c* 0.27, $CHCl_3$). IR (neat): 1720. ^1H NMR (500 MHz, $CHCl_3$): δ=1.23–1.36 (m, H), 1.29 (s, 3H), 1.47 (s, 3H), 1.54 (m, 1H), 1.57–1.66 (m, 2H), 1.7 (m, 1H), 2.25 (d, *J*=12.4 Hz, 1H), 2.44 (d, *J*=12.4 Hz, 1H), 2.60 (t, *J*=7.9 Hz, 2H), 2.73 (d, *J*=14.9 Hz, 1H), 2.8 (d, *J*=1H), 7.14–7.20 (m, 2H), 7.23–7.31 (m, 3H). ^{13}C NMR (125 MHz, $CHCl_3$): δ=23.1, 23.8, 24.5, 29.32, 29.48, 29.54 (3C), 30.0, 31.5, 36.0, 39.7, 43.7, 55.6, 83.8, 86.6, 125.4, 128.2 (2C), 128.4 (2C), 142.9, 174.6. HRMS (ESI): calculated for $C_{23}H_{36}NaO_4$ 399.2506, found 399.2502.

*4.6.2. 2-((3R,5R)-3,5-Dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)acetic acid (**30b**).* Obtained as a colorless oil (75% yield). $[\alpha]_D^{20}$ +16.7 (*c* 0.15, $CHCl_3$). IR (neat): 1715. ^1H NMR (500 MHz, $CHCl_3$): δ=1.19–1.37 (m, 12H), 1.34 (s, 3H), 1.49 (s, 3H), 1.571–1.66 (m, 6H), 2.15 (d, *J*=12.4 Hz, 1H), 2.51 (d, *J*=12.4 Hz, 1H), 2.60 (t, *J*=7.9 Hz, 2H), 2.72 (d, *J*=14.9 Hz, 1H), 2.78 (d, *J*=14.9 Hz, 1H), 7.13–7.20 (m, 2H), 7.23–7.30 (m, 3H). ^{13}C NMR (125 MHz, $CHCl_3$): δ=23.7, 24.7, 24.9, 29.3, 29.47 (2C), 29.52 (2C), 30.0, 31.5, 36.0, 38.7, 43.9, 55.5, 83.7, 86.9, 125.5, 128.2 (2C), 128.4 (2C), 143.0, 174.2. HRMS (ESI): calculated for $C_{23}H_{36}NaO_4$ 399.2506, found 399.2501.

Acknowledgements

B.B. thanks the « French Ministère de la Recherche et de l'Enseignement Supérieur »for a PhD grant.

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.10.022.

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