

Oxidative polycyclization with rhenium(VII) oxides: application of the stereoselectivity rules in the total synthesis of rollidecins C and D

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Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Received 1 March 2001; accepted 30 March 2001

Abstract—Rollidecin C, **1**, and rollidecin D, **2**, two adjacent bis-THF Annonaceous acetogenins, were synthesized from the partially functionalized ‘naked’ carbon skeletons **14** and **15**, respectively. The retrosynthetic route to the target compounds was guided by the recently proposed rules of stereoselectivity for the tandem oxidative cyclization reaction with trifluoroacetylperhenate. Thus, the rapid transformation of compounds **14** and **15** to **1** and **2**, respectively, was achieved with a predictable stereochemistry by the oxidative bis-cyclization with Re(VII) followed by one or two simple transformations. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The tandem oxidative polycyclization reaction with rhenium(VII) reagents, first reported in 1995,¹ represents a powerful methodology by which polyenic bis-homoallylic alcohols can be converted in a single step into poly-THF products with very high diastereoselectivity. This method is particularly useful for asymmetric synthesis of polyether natural products. We have recently used trifluoroacetylperhenate for the oxidative bis-cyclization of four isomeric disubstituted dienol substrates (**1**, Scheme 1) and obtained bis-THF products with very high stereoselectivity. On the basis of these and previous results, we deduced a set of rules to predict the product's configuration in these reactions. We proposed for the single-step tandem polycyclization reactions with trifluoroacetylperhenate that the stereochemistry of the first THF ring is always *trans*. However, the stereochemistry of the subsequent rings depends on the relative configuration of the two vicinal oxygen functions that were formed in the first cyclization step (Scheme 1). When these vicinal oxygen functions have a *threo* relationship, the next cyclization will produce a *cis* THF ring.

Conversely, when they have an *erythro* relationship, the next cyclization will produce a *trans* THF ring.²

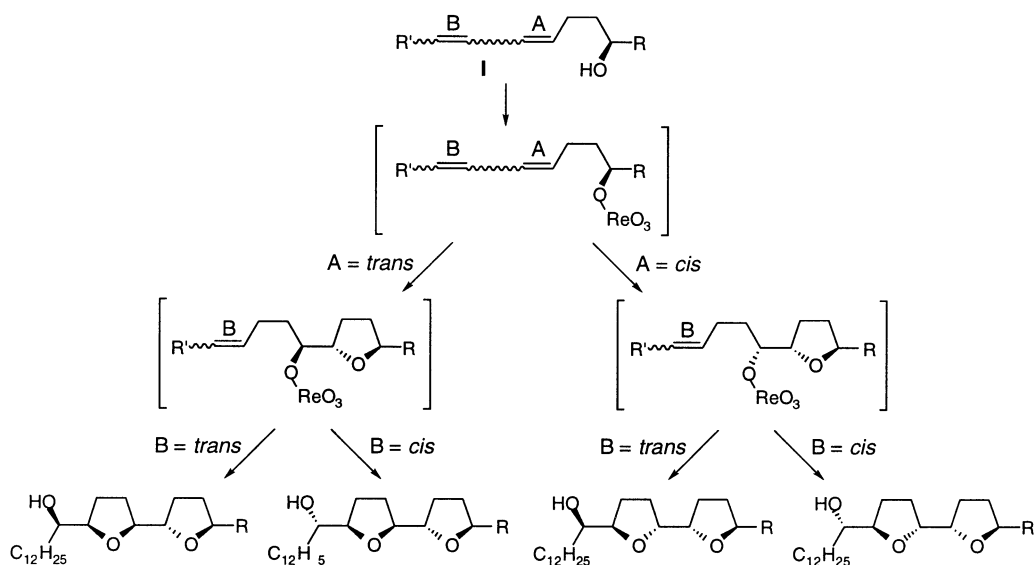
Since the two oxygen atoms add to the double bond in a syn fashion, the relative configuration of the resultant pair of vicinal carbinol centers depends on the double bond geometry: a *cis* double bond leads to an *erythro* diol and a *trans* double bond leads to a *threo* diol. Therefore, any desired absolute stereochemistry can be achieved by the appropriate choice of a double bond geometry and absolute configuration of the bis-homoallylic alcohol in the substrate.

Here we report on the application of these rules in the total synthesis of two homologous acetogenins, rollidecin C, **1**, and rollidecin D, **2**, which were discovered in the bioactive leaf extracts of *Rollinia mucosa*.³ Compounds **1** and **2** are members of a rapidly growing family of natural products, the Annonaceous acetogenins,⁴ which are known not only for their antitumor activity, but also for being potent anti-malarial, immunosuppressive, pesticidal and antifecundant agents.⁵ More than 350 acetogenins have already been isolated from 37 species in the Annonaceae, a family of tropical trees and shrubs that accommodates over 2300 species.⁶ While most of these fatty acid derivatives exhibit remarkable structural diversity, they share very similar carbon skeletons, with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. For example, a dominant structural

Keywords: Annonaceous acetogenins; rollidecin C; rollidecin D; oxidative cyclization; rhenium(VII) oxides; trifluoroacetylperhenate.

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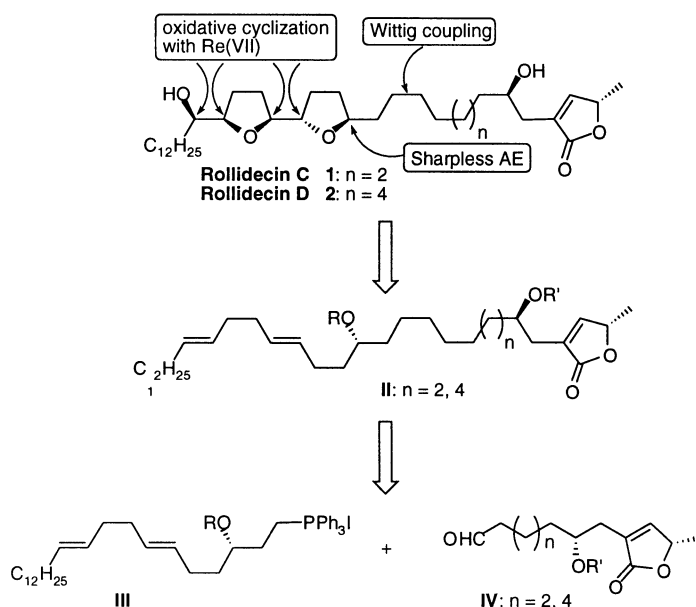
Scheme 1. Rules for predicting the stereochemistry in oxidative polycyclization with trifluoroacetylperhenate.

feature that appears in more than 40% of the Annonaceous acetogenins, including **1** and **2**, is a ten-carbon fragment containing two adjacent tetrahydrofuran rings flanked by either one or two hydroxyl groups. The Annonaceous acetogenins have attracted intense synthetic activity in recent years.^{7,8} Our contribution to this effort includes the total synthesis of solamin, reticulatacin, asimicin, bullatacin, trilobacin, trilobin, uvaricin, squamotacin, goniocin, 17,18-bis-epigoniocin, cyclogoniodenin T, and mucosin.⁹

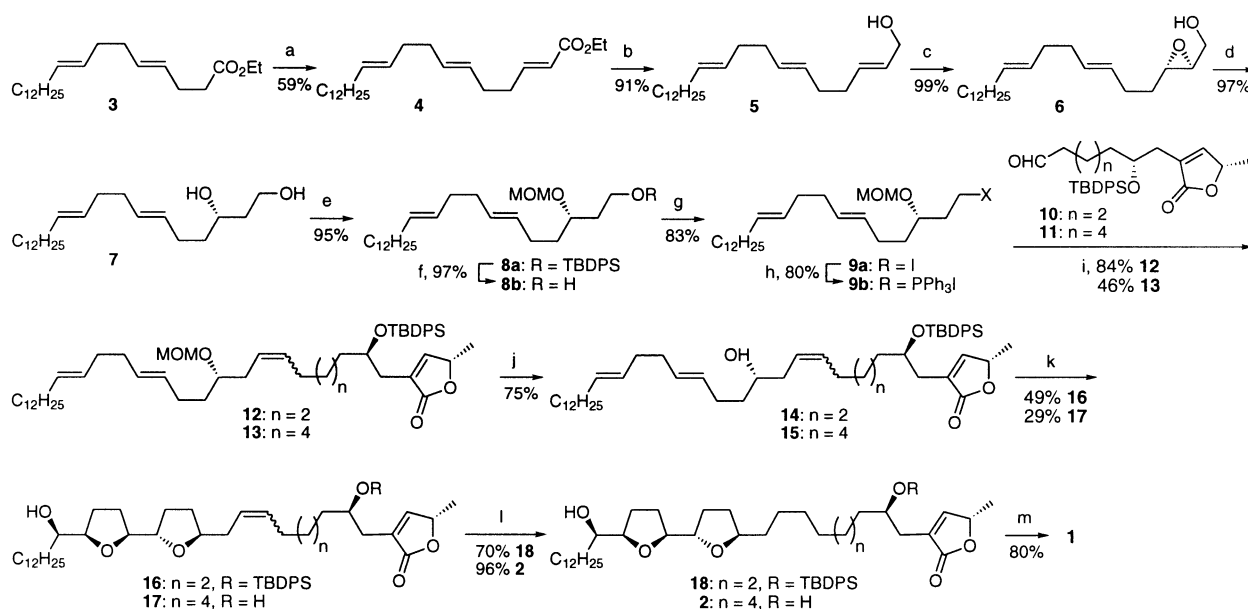
The structure of **1** and **2** was assigned mainly on the basis of ^1H (1D and 2D) and ^{13}C NMR spectroscopy and MS analysis.³ Although, no specific data have been provided to support the proposed absolute configuration of both compounds **1** and **2**, they have probably been determined using the Mosher esters methodology.¹⁰ Compounds **1** and **2**

are typical adjacent bis-THF acetogenins with an exception that they have only one hydroxyl group flanking the bis-THF moiety.

Both compounds **1** and **2** have exhibited cytotoxicity against six human tumor cell lines. Compound **1** was found to be uniformly more potent than **2** and showed selectivity toward the colon cell line HT-29, exhibiting potency that approaches that of adriamycin.³ Although the mode of action of **1** and **2** has not yet been established, studies on the primary mode of action with other, structurally similar acetogenins have established that they are powerful inhibitors of complex I (NADH-ubiquinone oxidoreductase) in mammalian and in insect mitochondrial electron transport systems.¹¹ In addition, they are potent inhibitors of NADH oxidase that is specifically active in the plasma membranes of tumors and is inactive in normal cells.¹²



Scheme 2. Retrosynthetic analysis of rollidecins C and D.



Scheme 3. Total synthesis of rollidecins C and D. Key: (a) DIBAL-H, toluene, -78°C , 2 h then $(\text{EtO})_2\text{P}(\text{O})\text{CHNaCO}_2\text{Et}$, THF, -78°C to rt, 16 h; (b) DIBAL-H, THF, -78°C , 2 h; (c) $\text{Ti}(\text{O}-i\text{-Pr})_4$, (+)-DET, TBHP, powdered molecular sieves 4A, -20°C , 4 h; (d) Red-Al, THF, 0°C , 4 h; (e) TBDPSCl, diisopropylethylamine, CH_2Cl_2 , rt, 16 h then in situ MOMCl, diisopropylethylamine, CH_2Cl_2 , 0°C to rt, 16 h; (f) TBAF, THF, 0°C to rt, 2 h; (g) I_2 , PPh_3 , imidazole, 0°C to rt, 2 h; (h) PPh_3 , NaHCO_3 , CH_3CN , 60°C , 24 h; (i) $n\text{-BuLi}$, THF, 0°C , then either aldehyde **10** or **11**, 0.5 h; (j) TMSBr , CH_2Cl_2 , -30°C , 0.5 h; (k) Re_2O_7 , TFAA, THF, rt, 1 h concentration under vacuum and washing with cold pentane, then alcohol **14**, CH_2Cl_2 , TFAA, 0°C to rt, 3 h. The same procedure was used for compound **15** with the exception that the mixture was left at rt overnight; (l) H_2 , Wilkinson's catalyst (20%, w/w), benzene-ethanol (4:1), rt, 4 h; (m) 4% AcCl in MeOH , CH_2Cl_2 (1:1), rt, 16 h.

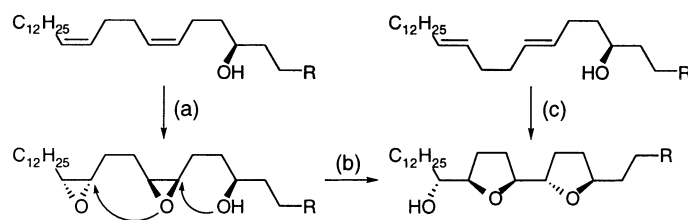
2. Results and discussion

Our retrosynthetic analysis of **1** and **2** (Scheme 2) dissects the target molecules into two major fragments, the butenolide portion, which contains two asymmetric carbinol centers, and the bis-THF fragment, which contains additional five asymmetric centers. The synthesis of this fragment with correct stereochemistry represents the main challenge in the entire synthesis. In fact, the potential diastereomeric diversity of this fragment represents the origin of diversity in the bis-THF subgroup of the Annonaceous acetogenins. To meet the challenge of structural variability we designed a general synthetic approach that is suitable for the title compounds, **1** and **2**, as well as for many of their stereoisomers. We anticipated that the introduction of both THF rings could be achieved in a single step at the final stages of the synthesis by a Re(VII) -mediated oxidative cyclization of a bis-homoallylic diene, **II**. The expected product could be only two simple steps (hydrogenation and deprotection) away from the target molecule. This strategy was based on our previous observation that the oxidative cyclization reaction is compatible with many functional groups, including a homoallylic alcohol.¹³ Therefore, the bis-cyclization could be carried out at a very late stage, after the completion of the molecular carbon skeleton. We have already demonstrated the tandem oxidative cyclization reaction with a substrate in which the secondary alcohol was both homoallylic as well as bis-homoallylic and the cyclization with trifluoroacetyl perhenate and trifluoroacetic anhydride took place exclusively at the bis-homoallylic site. The key intermediate **II** could be obtained by Wittig olefination using the phosphonium salt **III** and aldehyde **IV**. Compound **III** could be prepared by the Sharpless asymmetric epoxida-

tion¹⁴ followed by reductive cleavage of the resultant epoxide.¹³

The total synthesis of **1** and **2** is described in Scheme 3. Our starting material, **3**, was easily prepared from ethyl heptadec-4-enoate^{9b} in four steps, i.e. LAH reduction of the ester to the corresponding primary alcohol, PCC oxidation of the alcohol to produce aldehyde, Grignard reaction of the latter with vinylmagnesium bromide to give an allylic alcohol, and finally, Claisen–Johnson rearrangement¹⁵ using triethylorthoacetate. One pot two-step conversion of **3** to the unsaturated ester **4** was achieved by the low temperature, DIBAL-H reduction of the ester in **3** to the corresponding aldehyde followed by a Wittig–Horner olefination using sodium triethylphosphonoacetate. Reduction of **4** with DIBAL-H in THF produced the allylic alcohol **5** and the latter was subjected to the Sharpless asymmetric epoxidation using (+)-DET as the chiral auxiliary to yield the epoxyl alcohol **6**. Regioselective reductive opening of the epoxide to diol **7** was achieved at 0°C using Red-Al. The primary alcohol in **7** was first protected in the form of a TBDPS ether and the secondary alcohol was then converted to the MOM ether in the same pot to produce the fully protected intermediate **8a**. The primary alcohol was regenerated by desilylation using TBAF in THF and the resultant alcohol, **8b**, was first converted to the corresponding iodide, **9a**, and then to the phosphonium salt, **9b**. Compound **9b** (**III** in Scheme 1) represents a key intermediate in our synthetic strategy because it is designed to couple with aldehyde **IV** to produce the complete carbon skeletons of the target molecules.

The Wittig reactions between the ylide derived from **9b**



Scheme 4. Comparison of two routes to the *bis*-THF system of rollidecins C and D. The proposed biosynthetic pathway follows steps (a) and (b) while (c) represents a direct oxidative cyclization approach with Re(VII).

(using *n*-BuLi) and either of the two homologous butenolide aldehydes, **10** or **11**, were achieved in THF at 0°C to produce **12** or **13**, respectively, both in the form of a mixture of both *E* and *Z* isomers. The MOM ether in **12** and **13** was selectively cleaved using TMSBr at low temperature, affording **14** and **15**, respectively, setting the stage for the key step in the entire synthetic scheme, the oxidative bis-cyclization reaction.^{16,17} This reaction was carried out with either **14** or **15** using CF₃CO₂ReO₃ with trifluoroacetic anhydride (TFAA) at 0°C to room temperature, affording the desired *bis*-THF products, **16** or **17**, respectively. We found that the required subsequent cleavage of the TBDPS ether could be achieved during the cyclization step. Thus, keeping the mixture longer (overnight rather than 3 h) under the reaction conditions resulted in partial, probably acid-catalyzed, desilylation of **15** to produce alcohol **17**. The latter was converted to **2** by hydrogenation over Wilkinson's catalyst with 1 atm of hydrogen. Using a slightly different protocol, compound **16** was first hydrogenated and the product, **18**, was desilylated with 4% AcCl in MeOH at room temperature, affording **1**. Both synthetic compounds **1** and **2** were found to be identical by ¹H- and ¹³C NMR with the naturally occurring rollidecins C and D, respectively.

According to the Cane–Celmer–Westley hypothesis concerning the biosynthesis of microbial polyether antibiotics, initial polyepoxidation of a polyene is followed by a cascade of intramolecular nucleophilic epoxide ring openings.¹⁸ This hypothesis has been used to propose the biosynthetic pathway leading to the *bis*-THF fragment of **1** and **2** (Scheme 4).³ Here we have used an alternative, abiotic strategy of ligand-assisted¹⁹ oxygenation, featuring two major advantages: (a) high effective molarity of the oxidant; and (b) high regio- and stereochemical control over the reaction. Townsend and Basak have suggested that nature could also be using this approach for the biosynthesis of polyethers.²⁰ The key point in their hypothesis is that the oxidative cyclization route requires a polyene substrate with opposite double bond configuration. For example, in Scheme 4 the direct route requires a polyene substrate that has *E*-double bonds, whereas the stepwise, polyepoxide model requires *Z*-double bonds. Since the actual polyene intermediates in polyether antibiotics have never been observed there is no direct evidence bearing on this issue.²¹ We believe that the a hydroxyl-directed, metal-controlled oxidative polycyclization option is a less likely biosynthetic option than the polyepoxide pathway because high effective molarity and stereochemical control are already available to enzymes. Thus, in enzyme-catalyzed reactions there is no need for substrate-assisted catalysis of specificity since this control arises normally from binding specificity.

In conclusion, the rules of stereoselectivity in the tandem oxidative polycyclization with CF₃CO₂ReO₃ have been applied here in the total synthesis of **1** and **2**. The synthesis of **1** was achieved in 13 steps and 5.2% overall yield and that of **2** was achieved in 12 steps and 2.9% yield. Further studies are currently underway to gain better understanding of the origin of stereoselectivity in the oxidative polycyclization reaction and of the dependence of product stereochemistry on the oxidant and on the reaction conditions.

3. Experimental section

3.1. General methods

¹H and ¹³C NMR spectra were measured in CDCl₃. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Negative mass spectra were obtained with Sciex API 100. Optical rotations were measured in a one-decimeter (1.3 mL) cell using an Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under pressure. THF was dried and distilled over sodium ketyl.

3.1.1. (4*E*,8*E*)-Ethyl eicosa-4,8-dienoate, **3.** To a suspension of LiAlH₄ (4.7 g, 124 mmol) in dry Et₂O (150 mL), a solution of ethyl heptadec-4-enoate^{9h} (16.81 g, 57 mmol) in dry Et₂O (100 mL) was added dropwise at 0°C (ice-water bath). The mixture was warmed to room temperature and stirred for 2.5 h. Upon completion, as judged by TLC, the reaction mixture was diluted with ether and quenched by careful addition of water. The mixture was stirred for another 0.5 h, dried over anhydrous Na₂SO₄ and filtered over Celite to remove inorganic materials. Solvents were removed under reduced pressure to afford heptadec-4-en-1-ol (14.15 g, 98%) in the form of a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 5.41 (m, 2H), 3.62 (t, *J*=6.5 Hz, 2H), 2.05 (m, 2H), 1.95 (m, 2H), 1.60 (m, 3H), 1.35–1.20 (m and br s, 20H), 0.86 (t, *J*=7.0 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): 131.3, 129.3, 62.5, 32.5, 32.4, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.9, 22.7, 14.1.

Celite (26 g) and PCC (26 g, 121 mmol) were added to a solution of heptadec-4-en-1-ol (14.12 g, 55 mmol) in anhydrous CH₂Cl₂ (250 mL) and the mixture was stirred at room temperature for 2.5 h, then filtered over a short

silica gel column using CH_2Cl_2 to give the corresponding aldehyde (12.18 g, 87%), which was taken to next step without further purification. ^1H NMR (CDCl_3 , 300 MHz): δ 9.75 (t, $J=1.6$ Hz, 1H), 5.41 (m, 2H), 2.47 (t, $J=7.4$ Hz, 2H), 2.32 (q, $J=6.5$ Hz, 2H), 1.95 (q, $J=6.8$ Hz, 2H), 1.40–1.20 (m and br s, 20H), 0.86 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 202.5, 132.1, 127.5, 43.5, 32.5, 31.9, 29.7, 29.5, 29.3, 25.2, 22.7, 14.1.

Vinylmagnesium bromide (1.0 M in THF, 64.4 mL, 64.4 mmol) was added dropwise to a solution of the above mentioned aldehyde (12.10 g, 48 mmol) in dry THF (100 mL) at 0°C (ice-water bath). The mixture was stirred at the same temperature for 1 h and then quenched by slow addition of a saturated aqueous NH_4Cl . The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4 , concentrated and filtered through a short column of silica gel using hexane-ethyl acetate, 4:1, to produce the corresponding allylic alcohol (13.36 g, 99%) in the form of a light yellow oil, which was taken to next step without further purification. ^1H NMR (CDCl_3 , 300 MHz): δ 5.85 (ddd, $J=16.8$, 10.2, 6.2 Hz, 1H), 5.41 (m, 2H), 5.21 (dt, $J=16.8$, 1.4 Hz, 1H), 5.09 (dt, $J=10.2$, 1.6 Hz, 1H), 4.11 (q, $J=6.3$ Hz, 1H), 2.08 (m, 2H), 1.96 (q, $J=7.2$ Hz, 2H), 1.58 (m, 3H), 1.40–1.20 (m and br s, 20H), 0.87 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 141.1, 131.3, 129.3, 72.7, 36.7, 32.6, 31.9, 29.7, 29.5, 29.3, 29.2, 28.5, 22.7, 14.1.

A solution of the above-mentioned allylic alcohol (13.36 g, 48 mmol), triethylorthoacetate (20 mL, 110 mmol) and propionic acid (0.068 mL, 0.9 mmol) in xylene (20 mL) was refluxed for 2 h using an azeotropic distillation condenser. The volatile components were removed under reduced pressure and the residue was purified by flash chromatography (hexane-ethyl acetate, 24:1) to give **3** (8.52 g, 51% yield from aldehyde) in the form of a light yellow oil. ^1H NMR (CDCl_3 , 500 MHz): δ 5.50–5.36 (m, 4H), 4.13 (q, $J=7.0$ Hz, 2H), 2.38–2.30 (m, 4H), 2.08–1.95 (m, 6H), 1.36–1.24 (m, 23H), 0.89 (t, $J=6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 173.4, 131.4, 131.1, 129.6, 128.5, 60.4, 34.6, 32.9, 32.8, 32.7, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.4, 28.1, 22.9, 14.4, 14.3; MS (ESI): 373 ($\text{M}+\text{Na}^+$).

3.1.2. (2E,6E,10E)-Ethyl tricoso-2,6,10-trienoate, 4. DIBAL-H (1.5 M in toluene, 17.6 mL, 26 mmol) was added dropwise to a solution of **5** (8.38 g, 24 mmol) in dry toluene (100 mL) at -78°C , and the mixture was stirred at the same temperature for 2.5 h. In a separate flask, triethyl phosphonoacetate (5.8 mL, 29 mmol) was added dropwise to a mixture of NaH (60% in mineral oil, 1.16 g, 29 mmol) in dry THF (50 mL) at 0°C , the mixture was stirred at 0°C for 0.5 h and then was added dropwise to the first mixture at -78°C . The combined mixture was stirred overnight with gradual warming to the room temperature, then it was then quenched by dropwise addition of water (9 mL). Celite (9 g) and ether (45 mL) were added and the mixture was stirred at 0°C for 0.5 h, filtered over Celite, concentrated and the residue was purified by flash chromatography (gradient from 2 to 30% ethyl acetate in hexanes) to afford **4** (5.33 g, 59%) in the form of a light yellow oil. ^1H NMR (CDCl_3 , 500 MHz):

δ 6.97 (dt, $J=15.8$, 6.6 Hz, 1H), 5.83 (dt, $J=15.4$, 1.5 Hz, 1H), 5.49–5.37 (m, 4H), 4.20 (q, $J=7.4$ Hz, 2H), 2.30–2.25 (m, 2H), 2.18–2.14 (m, 2H), 2.09–2.02 (m, 4H), 2.00–1.96 (m, 2H), 1.36–1.25 (m, 20H), 1.30 (t, $J=7.3$ Hz, 3H), 0.90 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 166.9, 148.8, 131.1, 129.7, 128.9, 121.7, 60.3, 32.9, 32.8, 32.5, 32.1, 31.2, 29.9, 29.9, 29.8, 29.6, 29.4, 22.9, 14.5, 14.3; MS (ESI): 399 ($\text{M}+\text{Na}^+$).

3.1.3. (2E,6E,10E)-Trico-2,6,10-trien-1-ol, 5. DIBAL-H (1.5 M in toluene, 22 mL, 33 mmol) was added dropwise to a solution of **4** (5.25 g, 14 mmol) in dry THF (54 mL) at -78°C . The mixture was stirred at -78°C for 1.5 h and then quenched with dropwise addition of H_2O (12 mL). Celite (12 g) and ether (100 mL) were added to the mixture and stirred at 0°C for 1 h. After clear separation of layers the mixture was filtered through Celite, concentrated and purified by flash chromatography (gradient from 10 to 20% ethyl acetate in hexanes) to afford **5** (4.23 g, 91%) in the form of a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 5.70–5.67 (m, 2H), 5.43–5.41 (m, 4H), 4.12–4.10 (m, 2H), 2.10–1.99 (m, 10H), 1.27 (br s, 20H), 0.90 (t, $J=6.6$ Hz, 3H); MS (ESI): 357 ($\text{M}+\text{Na}^+$).

3.1.4. (2S,3S,6E,10E)-2,3-Epoxytricoso-6,10-dien-1-ol, 6. To a mixture of **5** (3.26 g, 9.8 mmol), molecular sieves (4A, 1.0 g) in dry CH_2Cl_2 (100 mL) and (+)-DET (2.4 g, 11.5 mmol), $\text{Ti}(\text{O}-i\text{-Pr})_4$ (2.6 mL, 9.63 mmol) were added at -20°C and the mixture was stirred at the same temperature for 0.5 h. TBHP (9.7 mL) was added dropwise at -20°C and the mixture was stirred for 4 h. Upon completion, as judged by TLC, 10% aqueous NaOH (21 mL) was added, the mixture was stirred at room temperature for 1 h, and then filtered over Celite using ethyl acetate. The organic solution was washed with water, dried over anhydrous Na_2SO_4 , solvents were removed under reduced pressure and the residue was purified by flash chromatography (gradient 10–20% ethyl acetate in hexanes), affording **6** (2.745 g, 99% based on recovered starting material) in the form of a white solid. $[\alpha]_D^{25}=-15.1$ (CHCl_3 , $c=0.6$); ^1H NMR (CDCl_3 , 500 MHz): δ 5.44–5.32 (m, 4H), 3.87 (ddd, $J=12.5$, 5.1, 2.6 Hz, 1H), 3.59 (ddd, $J=12.1$, 7.0, 4.0 Hz, 1H), 2.95–2.92 and 2.90–2.88 (m each, 2H), 2.17–2.07 (m, 2H), 2.01 (br s, 4H), 1.95–1.91 (m, 2H), 1.66–1.55 (m, 2H), 1.31–1.23 (m, 20H), 0.85 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 131.2, 131.1, 129.7, 129.2, 61.9, 58.7, 55.7, 32.9, 32.8, 32.2, 31.8, 29.9, 29.9, 29.8, 29.8, 29.6, 29.4, 29.2, 22.9, 14.3; MS (ESI): 373 ($\text{M}+\text{Na}^+$).

3.1.5. (3S,6E,10E)-Trico-6,10-dien-1,3-diol, 7. Red-Al (65% in toluene, 10 mL, 33.3 mmol) was added dropwise to a solution of **6** (3.289 g, 9.3 mmol) in dry THF (50 mL) at 0°C . The mixture was stirred at 0°C for 4 h, then quenched with H_2O (7 mL), stirred for additional 20 min at room temperature and filtered over Celite using ethyl acetate. The organic solution was washed with brine, dried over anhydrous Na_2SO_4 , concentrated and purified by flash chromatography (silica gel, gradient from 20 to 40% ethyl acetate in hexanes), affording **7** (3.21 g, 97%) in the form of a white solid. $[\alpha]_D^{25}=-2.5$ (CHCl_3 , $c=0.6$); ^1H NMR (CDCl_3 , 500 MHz): δ 5.47–5.36 (m, 4H), 3.91–3.81 (m, 3H), 2.57–2.51 (m, 2H), 2.17–2.09 (m, 2H), 2.08–2.05

(m, 4H), 2.00–1.96 (m, 2H), 1.75–1.52 (m, 4H), 1.35–1.27 (m, 18H), 0.90 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 131.1, 130.9, 130.0, 129.7, 72.2, 62.0, 38.5, 37.6, 32.9, 32.8, 32.8, 32.1, 29.9, 29.9, 29.8, 28.8, 29.6, 29.4, 29.0, 22.9, 14.3; MS (ESI): 375 ($\text{M}+\text{Na}^+$).

3.1.6. (3S,6E,10E)-1-tert-Butyldiphenylsilyloxy-3-(methoxy)methoxy-tricosa-6,10-dien, 8a. TBDPSCl (3.5 mL, 13.4 mmol) was added dropwise to a solution of **7** (3.13 g, 8.9 mmol), $i\text{-Pr}_2\text{NEt}$ (4.3 mL, 26 mmol) and DMAP (100 mg) in dry CH_2Cl_2 (50 mL), at 0°C and the mixture was stirred at room temperature for 18 h. Upon completion, as judged by TLC, the mixture was cooled to 0°C , and more $i\text{-Pr}_2\text{NEt}$ (19 mL, 108 mmol) was added dropwise followed by MOMCl (9 mL, 119 mmol). The mixture was stirred at room temperature for 22 h, then worked-up with CH_2Cl_2 and H_2O , the combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (silica gel, hexanes-ethyl acetate, 49:1), affording **8a** (5.80 g) in the form of a colorless oil. $[\alpha]_D^{25}+3.0$ (CHCl_3 , $c=2.0$); ^1H NMR (CDCl_3 , 500 MHz): δ 7.73–7.68 (m, 4H), 7.46–7.39 (m, 6H), 5.47–5.39 (m, 4H), 4.63 (dd, $J=11.8$, 7.0 Hz, 2H), 3.82–3.74 (m, 3H), 3.34 (s, 3H), 2.09–2.03 (m, 6H), 2.01–1.98 (m, 2H), 1.79–1.76 (m, 2H), 1.64–1.56 (m, 2H), 1.37–1.29 (m, 20H), 1.08 (s, 9H), 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 136.0, 134.3, 131.2, 130.6, 130.4, 130.0, 128.0, 96.2, 74.9, 61.0, 55.9, 37.8, 35.2, 33.2, 33.1, 33.0, 32.3, 30.1, 30.0, 29.8, 29.6, 28.8, 27.3, 23.1, 19.6, 14.5; MS (ESI): 657 ($\text{M}+\text{Na}^+$).

3.1.7. (3S,6E,10E)-3-(Methoxy)methoxy-tricosa-6,10-dien-1-ol, 8b. To a solution of **8a** (5.698 g, 8.97 mmol) in dry THF (100 mL), a solution of TBAF (1 M in THF, 34 mL, 34 mmol) was added at 0°C and the mixture was warmed at 40°C for 2.5 h. Solvents were removed under reduced pressure and the residue was purified by flash chromatography (silica gel, gradient from 10 to 20% ethyl acetate in hexanes), affording **8b** (3.34 g, 94%) in the form of a colorless oil. ^1H NMR (CDCl_3 , 500 MHz): δ 5.54–5.44 (m, 4H), 4.74 (dd, $J=8.8$, 6.6 Hz, 2H), 3.72–3.67 (m, 1H), 3.47 (s, 3H), 2.41 (m, 1H), 2.14–2.10 (m, 8H), 2.06–2.02 (m, 2H), 1.74–1.58 (m, 4H), 1.42–1.34 (m, 18H), 0.96 (t, $J=7.0$ Hz, 3H); MS (ESI): 419 ($\text{M}+\text{Na}^+$).

3.1.8. (3S,6E,10E)-1-Iodo-3-(methoxy)methoxy-tricosa-6,10-dien, 9a. Iodine (1.66 g, 6.6 mmol) was added in portions to a cold (0°C) solution of **8b** (1.5 g, 3.78 mmol), Ph_3P (2.5 g, 9.5 mmol) and imidazole (0.53 g, 7.9 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at the same temperature for 3 h, aqueous NaHCO_3 was added followed by iodine until the color of iodine persisted. The mixture was extracted with CH_2Cl_2 , the combined organic layer was washed several times with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and water, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (silica gel, hexanes-ethyl acetate, 99:1) to afford **9a** (1.60 g, 83%) in the form of a colorless oil. $[\alpha]_D^{25}+18.7$ (CHCl_3 , $c=0.9$); ^1H NMR (CDCl_3 , 500 MHz): δ 5.54–5.44 (m, 4H), 4.74 (dd, $J=8.8$, 6.6 Hz, 2H), 3.72–3.67 (m, 1H), 3.47 (s, 3H), 3.36–3.29 (m, 2H), 2.14–2.10 (m, 8H), 2.06–2.02 (m, 2H), 1.74–1.58 (m, 2H), 1.42–1.34 (m, 20H), 0.96 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 131.3,

131.0, 129.9, 129.9, 96.3, 77.8, 56.1, 39.2, 34.3, 33.1, 33.0, 32.3, 30.1, 30.0, 29.8, 29.6, 28.6, 23.1, 14.5, 2.5; MS (ESI): 529 ($\text{M}+\text{Na}^+$).

3.1.9. (3S,6E,10E)-3-(Methoxy)methoxy-tricosa-6,10-dien-1-yl triphenylphosphoniumiodide, 9b. A mixture of **9a** (1.52 g, 3.0 mmol), NaHCO_3 (1.0 g, 12 mmol) and Ph_3P (6.0 g, 23 mmol) in dry CH_3CN (10 mL) was stirred at 65°C for 24 h. Solvents were removed under reduced pressure, the residue was diluted with CH_2Cl_2 , filtered (to remove NaHCO_3), the organic layer was concentrated and the residue was purified by flash chromatography (silica gel, from hexanes-ethyl acetate, 3:1 to $\text{CH}_2\text{Cl}_2\text{--MeOH}$, 1:1) to afford **9b** (1.84 g, 80%); ^1H NMR (CDCl_3 , 300 MHz): δ 7.70–7.82 (m, 15H), 5.42–5.46 (m, 4H), 4.60v4.72 (m, 2H), 3.85–3.95 (m, 2H), 3.52–3.62 (m, 1H), 3.35 (s, 3H), 1.85–1.95 (m, 8H), 1.55–1.72 (m, 4H), 1.32–1.40 (m, 20H), 0.95 (t, $J=7.0$, 3H).

3.1.10. Compound 12. $n\text{-BuLi}$ (1.5 M in hexane, 0.38 mL, 0.57 mmol) was added to a solution of the Wittig salt **9b** (450 mg, 0.59 mmol) in dry THF (5 mL) at 0°C . After stirring for 15 min, a solution of aldehyde **10**¹³ (320 mg, 0.70 mmol) in dry THF (1 mL) was added and the mixture was stirred at same temperature for additional 15 min. Workup with aqueous NH_4Cl and ether followed by column chromatography (silica gel, 50% ethyl acetate in hexanes) afforded **12** (360 mg, 84%) in the form of an oil. ^1H NMR (CDCl_3 , 300 MHz): δ 7.66–7.60 (m, 4H), 7.39–7.30 (m, 6H), 6.90 (s, 1H), 5.35–5.40 (m, 6H), 4.80 (m, 1H), 4.60 (m, 2H), 4.00 (quintet, $J=8$ Hz, 1H), 3.57 (quintet, $J=8$ Hz, 1H), 3.35 (s, 3H), 2.42 (m, 2H), 2.26 (m, 2H), 2.10–1.85 (m, 9H), 1.52–1.30 (m, 5H), 1.29 (d, $J=6.4$ Hz, 3H), 1.25–1.10 (m, 22H), 1.15 (m, 2H), 1.05 (s, 9H), 0.85 (t, $J=6.4$ Hz, 3H); MS (ESI): 849 ($\text{M}+\text{Na}^+$).

3.1.11. Compound 13. Using the above described procedure with the Wittig salt **9b** (215 mg, 0.28 mmol), $n\text{-BuLi}$ (1.5 M in hexanes, 0.19 mL, 0.30 mmol) and aldehyde **11**^{9c} (100 mg, 0.22 mmol) in dry THF (6 mL) at 0°C and purification over silica gel afforded **13** (85 mg, 46%) in the form of an oil. ^1H NMR (CDCl_3 , 300 MHz): δ 7.66–7.61 (m, 4H), 7.42–7.33 (m, 6H), 6.9 (s, 1H), 5.43–5.35 (m, 6H), 4.87 (m, 1H), 4.67 (m, 1H), 4.61 (m, 1H), 4.00 (quintet, $J=8$ Hz, 1H), 3.57 (quintet, $J=8$ Hz, 1H), 3.36 (s, 3H), 2.4 (m, 2H), 2.25 (m, 2H), 2.13–1.94 (m, 8H), 1.53 (m, 3H), 1.42–1.24 (m and br s, 32H), 1.30 (t, $J=8.0$ Hz, 3H), 1.02 (s, 9H), 0.86 (t, $J=6.4$ Hz, 3H); MS (ESI): 877 ($\text{M}+\text{Na}^+$).

3.1.12. Compound 14. TMSBr (0.096 mL, 0.726 mmol) was added dropwise to a solution of **12** (300 mg, 0.363 mmol) in CH_2Cl_2 (5 mL) at -30°C , the mixture was stirred at the same temperature for 0.5 h and then quenched with water and extracted with CH_2Cl_2 . The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, ethyl acetate-hexanes, 1:1) to afford **14** (230 mg, 83%) in the form of an oil. ^1H NMR (CDCl_3 , 500 MHz): δ 7.60 (m, 4H), 7.36 (m, 6H), 6.90 (s, 1H), 5.56–5.42 (m, 6H), 4.88 (m, 1H), 4.00 (quintet, $J=5.6$ Hz, 1H), 3.62 (quintet, $J=5.55$ Hz, 1H), 2.42 (br s, 2H), 2.15–2.12 (m, 2H), 2.01–1.88 (m, 8H), 1.59–1.50 (m,

2H), 1.49–1.40 (m, 2H), 1.39–1.36 (m, 2H), 1.30 (d, $J=6.9$ Hz, 3H), 1.29–1.20 (m, 23H), 1.19–1.10 (m, 2H), 1.016 (s, 9H), 0.85 (t, $J=6.5$ Hz, 3H); MS (ESI): 805 ($M+Na^+$).

3.1.13. Alcohol 15. Using the above-described procedure compound **13** (85 mg, 0.1 mmol) and TMSBr (0.017 mL, 0.129 mmol) were reacted in CH_2Cl_2 (2 mL) at $-30^\circ C$ followed by column chromatography to produce **15** (49 mg, 61%). 1H NMR ($CDCl_3$, 400 MHz): 7.64 (dd, $J=13.0$, 6.5 Hz, 4H), 7.36 (m, 6H), 6.90 (s, 1H), 5.48–5.37 (m, 6H), 4.88 (m, 1H), 4.00 (quintet, $J=5.5$ Hz, 1H), 3.62 (quintet, $J=5.5$ Hz, 1H), 2.42 (br s, 2H), 2.19–1.96 (m and br s, 8H), 1.58–1.25 (m and br s, 36H), 1.30 (t, $J=6.5$ Hz, 3H), 1.03 (s, 9H), 0.87 (t, $J=6.5$ Hz, 3H); MS (ESI): 833 ($M+Na^+$).

3.1.14. (9E,10Z)-9,10-Dehydro-rollidecin D-4-tert-butyl-diphenylsilyl ether, 16. Re_2O_7 (300 mg, 0.69 mmol) was placed in a dry flask under argon, dry THF (5 mL) was added followed by TFAA (0.123 mL, 0.87 mmol) and the mixture was stirred at room temperature for 1 h. Solvents were removed under reduced pressure at $0^\circ C$ and the residue was washed twice with cold, dry pentane. Dry CH_2Cl_2 (5 mL), TFAA (0.123 mL, 0.87 mmol) and **14** (200 mg, 0.256 mmol) in CH_2Cl_2 (2 mL) were added sequentially at $0^\circ C$, the mixture was stirred at the same temperature for 3 h and then worked up by slow addition of saturated aqueous $NaHCO_3$ (5 mL) followed by H_2O_2 (0.5 mL) and extraction with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . The solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to afford **16** (110 mg, 49 %). 1H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.54 (m, 4H), 7.35–7.40 (m, 6H), 6.90 (s, 1H), 5.35–5.40 (m, 2H), 4.80–4.85 (m, 1H), 4.00–3.85 (m, 5H), 3.40–3.31 (m, 1H), 2.45–2.40 (m, 2H), 2.00–1.75 (m, 15H), 1.52–1.39 (m, 6H), 1.29–1.25 (d, $J=7.0$ Hz, 3H), 1.20–1.15 (m, 20H), 1.08 (s, 9H), 0.95 (t, $J=6.4$ Hz, 3H). MS (ESI): 815 ($M+H^+$).

3.1.15. (11E,12Z) 11,12-Dehydro-rollidecin C 4-tert-butyl-diphenylsilyl ether, 17. Following the above-described procedure compound **15** (49 mg, 61%) was reacted with $CF_3CO_2ReO_3$ (prepared from Re_2O_7 (100 mg, 0.20 mmol) and TFAA (0.038 mL, 0.26 mmol) in dry THF (5 mL) at room temperature) and TFAA (0.037 mL, 0.26 mmol) in CH_2Cl_2 at $0^\circ C$ for 16 h. Workup followed by extraction with ether and purification by column chromatography (silica gel, hexane-ethyl acetate, 3:7) afforded **17** (10 mg, 29 %) in the form of an oil. 1H NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, $J=4.0$ Hz, 1H), 5.46–5.28 (m, 2H), 5.04 (m, 1H), 4.00–3.83 (m, 4H), 3.35 (m, 1H), 2.49 (m, 1H), 2.37 (m, 2H), 2.17 (m, 1H), 2.01–1.24 (m and br s, 40H), 1.43 (t, $J=6.8$ Hz, 3H), 0.86 (t, $J=6.4$ Hz, 3H); MS: 605 ($M+H^+$).

3.1.16. Compound 18. Compound **16** (80 mg, 0.1 mmol) was dissolved in ethanol-benzene (1:1, 2 mL) and purged with argon for 10 min. Wilkinson's catalyst (20 mg) was added and the mixture was stirred at room temperature under hydrogen (balloon) for 4 h. Solvents were removed under reduced pressure and the residue was filtered through

silica gel to give **18** (56 mg, 70%). 1H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.54 (m, 4H), 7.35–7.40 (m, 6H), 6.90 (s, 1H), 4.85 (m, 1H), 3.95–3.80 (m, 5H), 3.30 (m, 1H), 2.42 (m, 2H), 2.20–1.85 (m, 15H), 1.52–1.39 (m, 10H), 1.29 (d, $J=6.9$ Hz, 3H), 1.25–1.20 (m, 20H), 1.03 (s, 9H), 0.90 (t, $J=6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.4, 151.6, 136.3, 136.2, 134.5, 131.1, 130.0, 128.1, 127.9, 82.9, 82.0, 81.6, 77.7, 72.2, 36.3, 34.9, 33.2, 32.6, 32.3, 30.2, 30.1, 30.0, 29.8, 29.5, 28.9, 28.8, 27.4, 26.5, 26.4, 26.3, 23.1, 19.8, 19.3, 14.5; MS (ESI): 817 ($M+H^+$).

3.1.17. Rollidecin C, 1. A solution of 4% $AcCl$ in MeOH (2 mL) was added to a solution of the **18** (45 mg, 0.056 mmol) in dry CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and filtered. Removal of solvents under reduced pressure followed by column chromatography (silica gel, 20–30% ethyl acetate in hexanes) afforded **1** (38 mg, 94%) in the form of a white solid. Mp. $39-41^\circ C$; $[\alpha]_D^{25} +5.9$ ($CHCl_3$, $c=0.15$); 1H NMR ($CDCl_3$, 600 MHz): δ 7.10 (s, 1H), 5.05 (m, 1H), 3.95–3.82 (m, 4H), 3.34 (m, 1H), 2.53 (m, 1H), 2.40 (m, 1H), 2.03–1.80 (m, 7H), 1.56–1.34 (m and br s, 15H), 1.43 (d, $J=6.9$ Hz, 3H), 1.25–1.20 (m, 28H), 0.86 (t, $J=6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 174.6, 151.7, 131.1, 82.4, 81.5, 80.6, 80.0, 78.0, 77.9, 69.8, 37.3, 35.7, 34.4, 33.3, 32.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 20.0, 28.4, 26.1, 25.8, 25.4, 22.6, 19.1, 14.0; MS (ESI): 579 ($M+H^+$).

3.1.18. Rollidecin D, 2. Compound **17** (10 mg, 0.016 mmol) was dissolved in ethanol-benzene (1:1, 2 mL) and purged with argon for 10 min. Wilkinson's catalyst (6 mg) was added and the mixture was stirred at rt under hydrogen (1 atm) for 4 h. Solvents were removed under reduced pressure and the residue was filtered through silica gel to give **2** (9.6 mg, 96%) in the form of a low melting solid. Mp. $41-42^\circ C$; $[\alpha]_D^{25} +1.5$ ($CHCl_3$, $c=0.003$); 1H NMR ($CDCl_3$, 500 MHz): δ 7.10 (s, 1H), 5.05 (m, 1H), 3.95–3.82 (m, 4H), 3.34 (m, 1H), 2.53 (m, 1H), 2.40 (m, 1H), 2.03–1.73 (m, 1H), 1.56–1.24 (m and br s, 39H), 1.42 (t, $J=6.5$ Hz, 3H), 0.86 (t, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz): 179.0, 151.7, 131.2, 82.5, 81.6, 80.7, 80.2, 78.0, 74.6, 70.0, 37.4, 35.8, 34.5, 33.4, 32.2, 31.9, 29.7, 29.1, 28.8, 26.2, 25.8, 25.5, 22.7, 19.1, 14.1; MS (ESI): 607 ($M+H^+$).

Acknowledgements

We thank the Skaggs Institute for Chemical Biology, US-Israel Binational Science Foundation, the Israel Cancer Research Fund and the CaP CURE Foundation for financial support.

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