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Synthesis of (4*R*,15*R*,16*R*,21*S*)-Rollicosin and Its 4*S* Epimer

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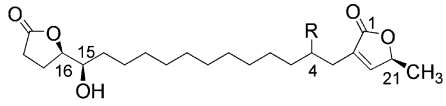
(4*R*,15*R*,16*R*,21*S*)-Rollicosin (**2**) was synthesized by palladium-catalyzed coupling of two building blocks **4** and **5**. Lactone **4** was synthesized from 1-heptyne and terminal acetylene **5** was prepared from lactone **6** and allyl iodide or (*S*)-epichlorohydrin. (4*S*,15*R*,16*R*,21*S*)-Rollicosin (**3**) was also synthesized from (*R*)-epichlorohydrin by the same synthetic pathway.

Introduction

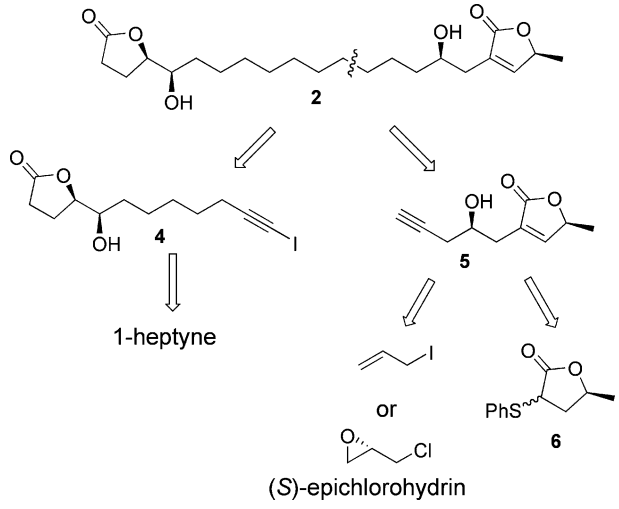
Numerous naturally occurring components have been isolated from subtropical or tropical plant genus *Annonaceae*. Among them, the annonaceous acetogenins show remarkable biological activities, such as antifeedant, antimalarial, antibiotic, antiparastic, and anticancer activities.[1] More than 400 acetogenins have been discovered in the past two decades since the first acetogenin, uvaricin,[2] was isolated. Recently, two new acetogenins, squamostolide (**1**)[3] and rollicosin (**2**),[4] were isolated from *Annona squamosa* and *Rollina mucosa*, respectively. These compounds have received much attention from synthetic organic chemists[5] due to their special features and unique biological responses. Quinn[5c] and Makabe[5d] and their co-workers independently reported the total synthesis of rollicosin. Although both papers claimed to derive the same stereoisomer of the natural product, the reported specific rotations were incompatible with each other. Also, one of the syntheses suffers from a low-yielding alkylation step. The determination of the absolute configuration of rollicosin by Wu and co-workers[4] was based on CD spectral data[6] and comparison of the optical rotation with that of muricatacin.[7] These methods may not be reliable enough to determine the stereochemistry of acetogenins. To elucidate the absolute configuration of rollicosin and improve the overall yield of the syntheses, we report herein the efficient synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**2**) and its analogue **3**.



1 Squamostolide (R = H)
2 Rollicosin (4*R*, R = OH)
3 (4*S*)-Rollicosin (R = OH)

Results and Discussion

The retrosynthetic analysis of rollicosin (**2**) is shown in Scheme 1. A key step involves the palladium-catalyzed coupling[8] of iodoalkyne **4** and terminal acetylene **5**. Compound **4** could be prepared from 1-heptyne and compound **5** could be accomplished by the reaction of allyl iodide or (*S*)-epichlorohydrin with lactone **6**.[5b] We believe that the use of allyl iodide or epichlorohydrin as the alkylating agent could solve the problem of the low-yielding alkylation step.



Scheme 1.

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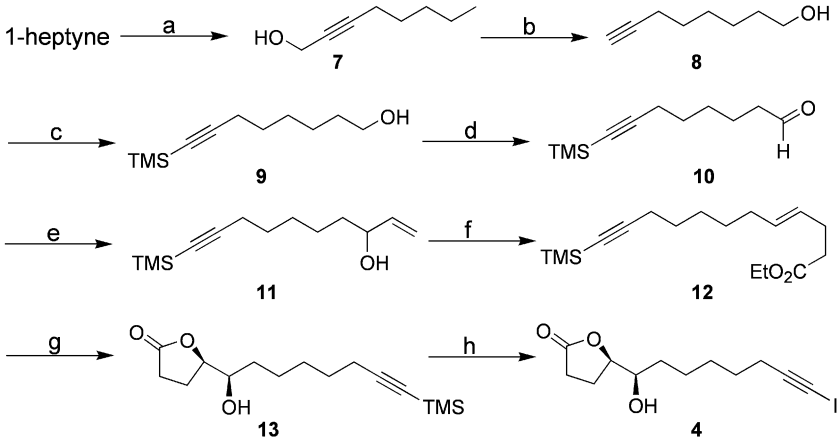
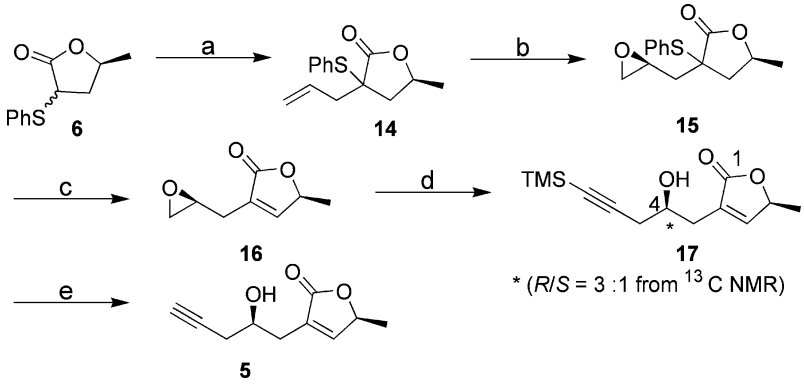


Scheme 2. Reagents and conditions: (a) *n*BuLi, THF, –78 °C, 1 h, then paraformaldehyde, 24 h, 99%; (b) KH, 1,3-diaminopropane, 1 h, then **7**, 15 °C, 30 min, 65%; (c) i. *n*BuLi, THF, 0 °C, 40 min; ii. TMSCl, 0 °C to room temp., 2 h, 80%; (d) PCC, CH_2Cl_2, room temp., 4 h, 60%; (e) vinylmagnesium bromide, THF, –78 °C, 1 h, 70%; (f) CH_3CH_2COOH, $CH_3C(OEt)_3$, reflux, 2 h, 99%; (g) AD-MiX-b, $CH_3SO_2NH_2$, *t*BuOH/H_2O, 0 °C, 24 h, 65%; (h) $AgNO_3$, NIS, DMF, room temp., 15 min, 99%.

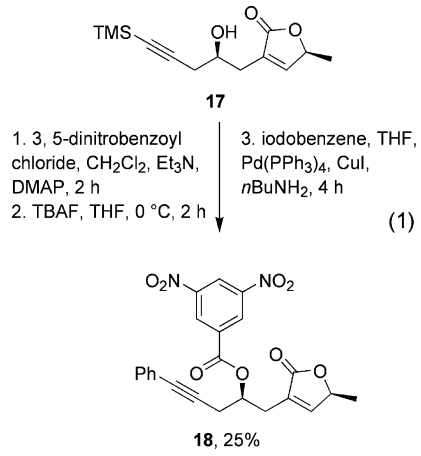
The construction of fragment **4** is shown in Scheme 2. Treatment of 1-heptyne with *n*-butyllithium in dry THF followed by paraformaldehyde gave propargyl alcohol **7** in 99% yield. The internal alkyne **7** was isomerized to the terminal acetylene **8** in 65% yield by potassium hydride in 1,3-diaminopropane. Reaction of **8** with trimethylsilyl chloride produced alcohol **9** in 80% yield. Alcohol **9** was oxidized to aldehyde **10** by using pyridinium chlorochromate (PCC). Vinylmagnesium bromide addition to aldehyde **10** gave the allylic alcohol **11** in 70% yield. Reaction of **11** with triethyl orthoacetate in the presence of propionic acid proceeded through an orthoester Claisen rearrangement[9] to afford γ,δ-unsaturated ester **12** in 99% yield. Sharpless AD reaction[10] of **12** using AD-mix-β produced lactone **13** in 65% yield. The *ee* of lactone **13** was determined to be 99% based on ^{1}H NMR spectroscopy using [Eu(fod)$_3$] as the shift reagent. Finally, the iodination of **13** was carried out by treatment of **13** with NIS and a catalytic amount of silver nitrate in DMF[11] to give the iodoacetylene **4** in 99% yield.

The preparation of terminal acetylene **5** is shown in Scheme 3. Treatment of lactone **6** with LDA followed by allyl iodide in refluxing THF gave the allylation product **14** in 75% yield. Lactone **14** was then converted into epoxide **15** in 55% yield by the Sharpless AD reaction and the conversion of the diol into the epoxide in one-pot.[12] The sulfide of epoxide **15** was oxidized to a sulfoxide using MCPBA and thermal elimination of the sulfoxide produced α,β-unsaturated lactone **16**[13] in 95% yield. At this stage, the *ee* of the chiral center C-4 was identified as 76:24 by chiral GC/MS analysis. Epoxide ring-opening was accomplished by treatment of **16** with lithium acetylide, generated by reaction of trimethylacetylene with *n*-butyllithium and boron trifluoride, to give **17** in 80% yield. Lactone **17** was found to exist as a 3:1 mixture of diastereoisomers by ^{13}C NMR spectroscopy. Finally, desilylation of **17** using TBAF gave terminal acetylene **5** in 75% yield. In order to confirm the absolute configuration of the chiral center C-4, the major stereoisomer of lactone **17** was converted into



Scheme 3. Reagents and conditions: (a) **6**, LDA, THF, HMPA, 0 °C, 30 min, then allyl iodide, THF, reflux, 2 h, 75%; (b) i. AD-MiX-α, $CH_3SO_2NH_2$, *t*BuOH/H_2O, 0 °C, 24 h; ii. $CH_3C(OEt)_3$, CH_2Cl_2, PPTs, 15 min; iii. TMSCl, 40 min; iv. MeOH, K_2CO_3, 2 h, 55%; (c) i. MCPBA, CH_2Cl_2, 15 min; ii. toluene reflux, 2 h, 95%; (d) *n*BuLi, THF, trimethylsilylacetylene, $BF_3{\cdot}Et_2O$, –78 °C, 30 min, then **16**, THF, –78 °C, 2 h, 80%; (e) THF, TBAF, 0 °C, 2 h, 75%.

compound **18** in three steps and in 25% overall yield. This transformation included the acylation of the alcohol with 3,5-dinitrobenzoyl chloride, desilylation and coupling of the terminal acetylene with iodobenzene; see Equation (1). From the X-ray structure of the lactone **18**,[14] the absolute configuration at C-4 was assigned as *R* (Figure 1).



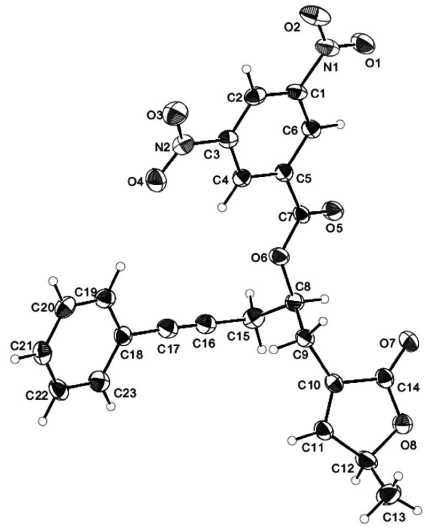
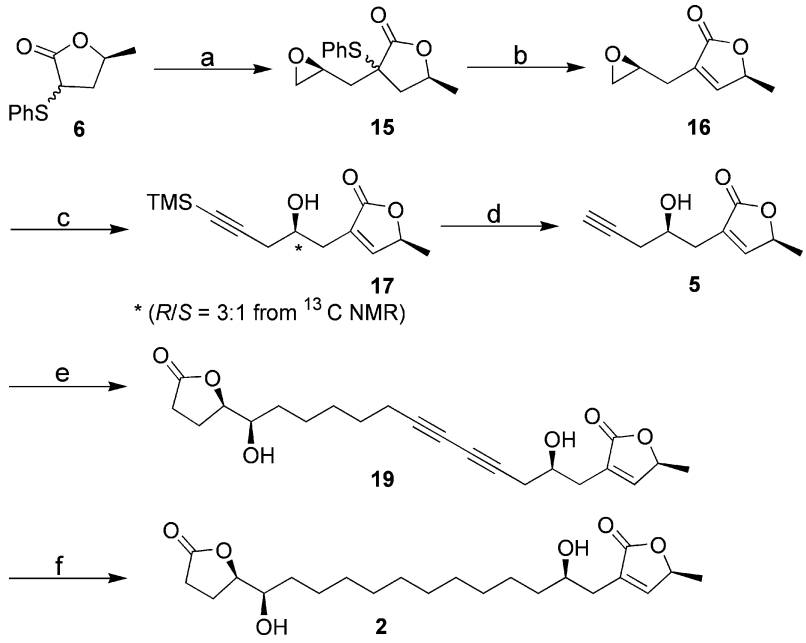
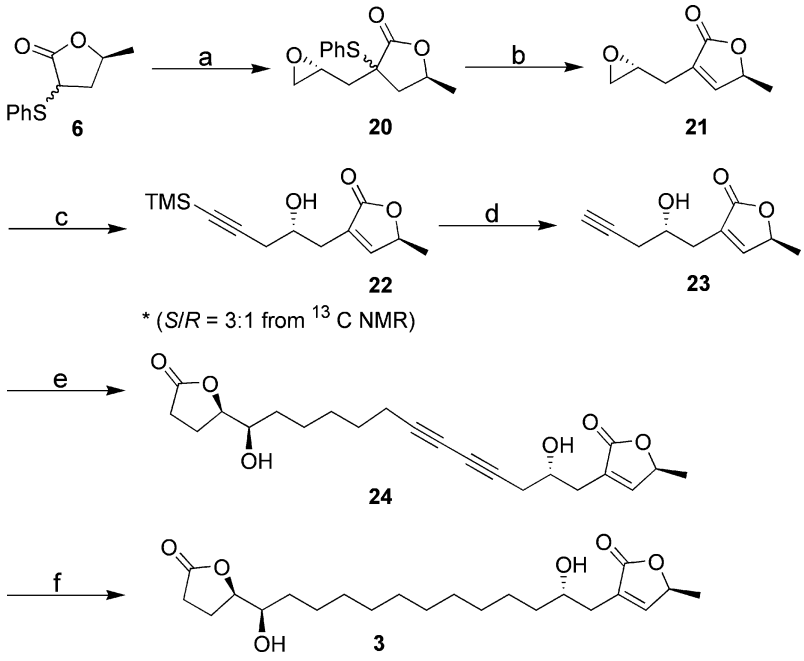


Figure 1. X-ray structure of compound **18**.

The epoxide **15** can also be prepared in 50% yield by alkylation of lactone **6** with (*S*)-epichlorohydrin using LHMDS as base (Scheme 4). Compound **15** was then converted into **17** by following the reaction procedures described above. The ^{13}C NMR spectrum indicated that this alcohol exists as a 3:1 mixture of diastereomers and the major isomer of C-4 was assigned to *R* configuration. Finally, coupling of iodoalkyne **4** with terminal acetylene **5** using $[Pd(PPh_3)_2Cl_2]$ as catalyst gave diyne **19** in 53% yield. Hydrogenation[15] of compound **19** using rhodium as a catalyst in benzene/methanol (1:1) under 1 atm of hydrogen pressure afforded rollicosin **2** in 80% yield. The crude product exists as a 6:1 mixture of diastereomers (by ^{13}C NMR spectroscopy). The pure stereoisomer of compound **2** was obtained as a white powder after recrystallization from ethyl acetate/hexane. The melting point (107–108 °C) and optical rotation $\{[\alpha]_D^{24} = +1.9$ (c = 1.0, $CHCl_3$)$\}$ of the synthetic rollicosin are similar to those reported by Makabe et al.[5d] {m.p. 104–106 °C, $[\alpha]_D^{24} = +2.5$ (c = 0.29, $CHCl_3$)}, but the optical rotation is markedly different to that of the natural product reported by Wu and co-workers[4] $\{[\alpha]_D^{24} = -26.0$ (c = 0.05, $CHCl_3$)$\}$.



Scheme 4. Reagents and conditions: (a) i. LHMDS, THF, HMPA, 0 °C, 30 min, ii. (*S*)-epichlorohydrin, NaI, 80 °C, 2 h, 50%; (b) i. MCPBA, CH_2Cl_2, 15 min; ii. toluene, reflux, 2 h, 95%; (c) *n*BuLi, THF, –78 °C, $BF_3{\cdot}Et_2O$, trimethylsilylacetylene, 30 min, then **16**, 4 h, 80%; (d) TBAF, THF, 0 °C, 2 h, 75%; (e) **4**, $[PdCl_2(PPh_3)_2]$, CuI, THF, *i*Pr_2NH, 2 h, 53%; (f) $[RhCl(PPh_3)_3]$, H_2, MeOH/benzene (1:1), 24 h, 80%.



Scheme 5. Reagents and conditions: (a) i. LHMDS, THF, HMPA, 0 °C, 30 min, ii. (*R*)-epichlorohydrin, NaI, 80 °C, 2 h, 55%; (b) i. MCPBA, CH_2Cl_2, 15 min; ii. toluene, reflux, 2 h, 90%; (c) *n*BuLi, THF, –78 °C, $BF_3{\cdot}Et_2O$, trimethylsilylacetylene, 30 min, then **21**, 4 h, 80%; (d) TBAF, THF, 0 °C, 2 h, 80%; (e) **4**, $[PdCl_2(PPh_3)_2]$, CuI, THF, *i*Pr_2NH, 2 h, 50%; (f) $[RhCl(PPh_3)_3]$, H_2, MeOH/benzene (1:1), 24 h, 80%.

(4*S*)-Rollicosin (**3**) was synthesized by using (*R*)-epichlorohydrin as the starting material. The synthesis of analogue **3** is outlined in Scheme 5. Epoxide **20** was obtained in 55% yield by alkylation of the enolate, prepared by mixing lactone **6** and LHMDS, with (*R*)-epichlorohydrin. Oxidation of **20** with MCPBA in CH_2Cl_2 afforded a sulfoxide and subsequent thermal elimination in heated toluene produced compound **21** in 90% yield. Epoxide **21** was then treated with the trimethylacetylenic lithium salt and boron trifluoride in THF, which led to the formation of the ring-opened adduct **22** in 80% yield. Desilylation of **22** by using TBAF gave terminal acetylene **23**. Palladium-catalyzed coupling of iodoalkyne **4** with acetylene **23** produced diyne **24** in 50% yield. Finally, hydrogenation of diyne **24** with $[Rh(PPh_3)_3Cl]$ in benzene/methanol (1:1) under 1 atm hydrogen pressure gave (4*S*)-rollicosin (**3**) in 82% yield. Pure (4*S*)-rollicosin (**3**) was obtained as a white powder after recrystallization from ethyl acetate/hexane {$[\alpha]_D^{24}$ = +7.5 (*c* = 1.0, $CHCl_3$), m.p. 86–87 °C}. Again, these data are in sharp contrast to those of the natural product.

Conclusions

In conclusion, we have established an efficient synthesis of (4*R*,15*R*,16*R*,21*S*)-rollicosin (**2**) and (4*S*,15*R*,16*R*,21*S*)-rollicosin (**3**). The ^1H and ^{13}C NMR spectral data of compound **2** match well those of the natural and synthetic rollicosin. Although the optical rotation of compound **2** is markedly different to that of the natural product, it matches well that of the synthetic product reported by Makabe et al.[5d] We can conclude that we have succeeded in preparing (4*R*,15*R*,16*R*,21*S*)-rollicosin. However, the stereochemistry of natural rollicosin is still undetermined.

Experimental Section

2-Octyn-1-ol (7): *n*BuLi (1.6 M, 62.5 mL, 100 mmol) was added dropwise to a solution of 1-heptyne (9.60 g, 100 mmol) in THF (100 mL) at –78 °C. After stirring for 1 h, paraformaldehyde (3.15 g, 105 mmol) was added to the reaction mixture and stirred for an additional 2 h at –78 °C. The reaction mixture was warmed to room temperature and stirred for 24 h at this temperature, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (5:1) as eluent] to give **7** (12.47 g, 99%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3373, 2932, 2856, 2147 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.22 (t, *J* = 2.2 Hz, 2 H), 2.23–2.13 (m, 2 H), 1.52–1.22 (m, 6 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 86.4, 78.2, 51.2, 31.0, 28.2, 22.1, 18.6, 13.8 ppm. MS (EI): *m*/*z* (%) = 126 (9) $[M]^+$, 95 (45), 41 (99). HRMS (EI): calcd. for $C_8H_{14}O$ 126.1045; found 126.1048.

7-Octyn-1-ol (8): Compound **7** (2.24 g, 17.8 mmol) was added to a solution of KH (8.0 g, 20 mmol) in 1,3-diaminopropane (40 mL) at 15 °C. After stirring for an additional 30 min, the reaction mixture was quenched with ice/water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (5:1) as eluent] to give **8** (2.59 g, 65%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3302, 2934, 2856, 2170 cm^{-1}. ^1H NMR ($CDCl_3$,

200 MHz): δ = 3.61 (t, J = 7.0 Hz, 2 H), 2.17 (td, J = 6.8, 2.8 Hz, 2 H), 1.92 (t, J = 2.8 Hz, 1 H), 1.62–1.29 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 84.5, 68.1, 62.7, 32.5, 28.4, 28.3, 25.2, 18.2 ppm. MS (EI): m/z (%) = 126 (9) $[M]^+$, 95 (30), 79 (99). HRMS (EI): calcd. for $C_8H_{14}O$ 126.1045; found 126.1037.

8-Trimethylsilyl-7-octyn-1-ol (9): *n*BuLi (1.6 M in THF, 38.2 mL, 61.1 mmol) was added to a solution of **8** (3.86 g, 30.6 mmol) in THF (50 mL) at 0 °C. After stirring for 40 min, TMSCl (11.6 mL, 91.7 mmol) was added. The resulting solution was warmed to room temperature, 10% aqueous H_2SO_4 solution (100 mL) was added, and the mixture stirred for another 30 min. The solution was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (5:1) as eluent] to give **9** (4.85 g, 80%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3350, 2172 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.61 (t, J = 6.6 Hz, 2 H), 2.20 (t, J = 6.8 Hz, 2 H), 1.62–1.29 (m, 8 H), 0.12 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 107.4, 84.4, 62.8, 32.5, 28.5 (2 C), 25.2, 19.7, 0.12 (3 C) ppm. MS(EI): m/z = 198 (39) $[M]^+$, 109 (55), 75 (99). HRMS (EI): calcd. for $C_{11}H_{22}OSi$ 198.1440; found 198.1447.

8-Trimethylsilyl-7-octynal (10): A solution of **9** (1.98 g, 10 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirring solution of PCC (3.23 g, 15 mmol) in CH_2Cl_2 (20 mL) at room temperature. The resulting solution was stirred at room temperature for 4 h, then filtered through a short pad of silica gel, and washed with diethyl ether (3 × 20 mL). After removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (20:1) as eluent] to give **10** (1.18 g, 60%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 2933, 2856, 2750, 2174, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.75 (s, 1 H), 2.43 (t, J = 6.8 Hz, 2 H), 2.21 (t, J = 6.6 Hz, 2 H), 1.70–1.23 (m, 6 H), 0.12 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 178.7, 107.0, 84.7, 43.7, 28.2 (2 C), 21.6, 19.6, 0.12 (3 C) ppm. MS (EI): m/z (%) = 196 (11) $[M]^+$, 109 (45), 75 (99). HRMS (EI): calcd. for $C_{11}H_{20}OSi$ 196.1283; found 196.1280.

10-(Trimethylsilyl)dec-1-en-9-yn-3-ol (11): Vinylmagnesium bromide (1 M in THF, 20 mL, 20 mmol) was slowly added to a stirring solution of **10** (1.96 g, 10 mmol) in dry THF (15 mL) at –78 °C. After stirring for an additional 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (30:1) as eluent] to give **11** (1.57 g, 70%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3358, 3077, 2935, 2856, 2172 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.94–5.77 (m, 1 H), 5.25–5.06 (m, 2 H), 4.10 (q, J = 6.2 Hz, 2 H), 2.10 (t, J = 6.6 Hz, 2 H), 1.54–1.24 (m, 8 H), 0.12 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 141.2, 114.6, 107.5, 84.4, 73.1, 36.8, 28.6, 28.5, 24.7, 19.7, 0.12 (3 C) ppm. MS (EI): m/z (%) = 224 (8) $[M]^+$, 197 (45), 75 (99). HRMS (EI): calcd. for $C_{13}H_{24}OSi$ 224.1596; found 224.1599.

Ethyl (*trans*)-12-(Trimethylsilyl)dodec-4-en-11-ynoate (12): A mixture of **11** (2.24 g, 10 mmol), ethyl orthoacetate (3.19 g, 20 mmol), and a few drops of propanoic acid was heated at reflux and stirred at this temperature for 2 h. After cooling to room temperature, the liquid was removed under reduced pressure and the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (20:1) as eluent] to give **12** (2.91 g, 99%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.45–5.38 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 2.37–2.25 (m, 4 H), 2.20 (t, J = 7.2 Hz, 2 H), 2.05–1.93 (m, 2 H), 1.56–1.30 (m, 6 H), 1.25 (t, J = 7.0 Hz, 3 H), 0.12 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 173.2, 131.5, 128.1, 107.6, 60.2, 34.4, 32.3, 28.9, 28.5, 28.2, 27.9, 19.8, 14.2, 0.12 (3 C) ppm. MS (EI): m/z (%) = 224 (28) $[M]^+$, 249 (35), 117 (65). HRMS (EI): calcd. for $C_{17}H_{30}O_2Si$ 294.2015; found 294.2018.

(5*R*)-5-[(1*R*)-1-Hydroxy-8-trimethylsilyloct-7-ynyl]-4,5-dihydrofuran-2(3*H*)-one (13): Methanesulfonamide (0.475 g, 5 mmol) was added to a solution of AD-mix-β (7.0 g) in *tert*-butyl alcohol (10 mL) and water (10 mL) at 0 °C. The reaction mixture was stirred until homogeneous, compound **12** (1.47 g, 5 mmol) was then added, and the mixture stirred for 24 h. Sodium sulfite (7.5 g) was then added and the mixture stirred for an additional 30 min. The resulting solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with a 2 N KOH aqueous solution (100 mL) and dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (2:1) as eluent] to give **13** (0.92 g, 65%) as a colorless oil {99% *ee* based on ^{1}H NMR using [Eu(fod)$_3$] as the shift reagent}. IR (KBr): $\tilde{\nu}$ = 3438, 2934, 2174, 1726 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.40 (td, J = 7.4, 4.6 Hz, 1 H), 3.58–3.44 (m, 1 H), 2.66–2.50 (m, 2 H), 2.36 (br. s, 1 H), 2.31–2.03 (m, 4 H), 1.52–1.23 (m, 8 H), 0.11 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.3, 107.3, 84.4, 82.9, 73.4, 32.7, 28.6, 28.5, 28.3, 24.9, 24.0, 19.6, 0.1 (3 C) ppm. MS (EI): m/z (%) = 282 (5) $[M]^+$, 267 (35), 73 (99). HRMS (EI): calcd. for $C_{15}H_{26}O_3Si$ 282.1651; found 282.1649. $[\alpha]_D^{25}$ = –20.0 (c = 1.2, $CHCl_3$).

(5*R*)-5-[(1*R*)-1-Hydroxy-8-iodooct-7-ynyl]-4,5-dihydrofuran-2(3*H*)-one (4): *N*-Iodosuccinimide (0.30 g, 1.1 mmol) followed by $AgNO_3$ (0.1 N standardized solution, 1.1 mL, 1.1 mmol) was added to a solution of **13** (0.28 g, 1 mmol) in DMF (10 mL). The resulting solution was stirred at room temperature for 15 min, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (1:1) as eluent] to give **4** (0.33 g, 99%) as a white solid, m.p. 89–90 °C. IR (KBr): $\tilde{\nu}$ = 3436, 2932, 2347, 1726 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.39 (td, J = 7.4, 4.4 Hz, 1 H), 3.58–3.49 (m, 1 H), 2.65–2.40 (m, 2 H), 2.37–2.24 (m, 2 H), 2.21–1.99 (m, 2 H), 1.52–1.38 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.5, 94.4, 83.0, 82.9, 73.3, 32.6, 28.6, 28.4, 28.1, 24.8, 24.0, 20.6, –7.1 ppm. MS (EI): m/z (%) = 336 (5) $[M]^+$, 131 (35), 85 (99). HRMS (EI): calcd. for $C_{12}H_{17}IO_3$ 336.0222; found 336.0224. $[\alpha]_D^{25}$ = –19.0 (c = 1.2, $CHCl_3$).

(5*S*)-3-Allyl-5-methyl-3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one (14): An LDA solution in THF (1.0 mL, 2.0 M, 2.0 mmol) was slowly added to a solution of lactone **6** (0.41 g, 2 mmol) in dry THF (3 mL) at 0 °C. After stirring for 10 min, HMPA (0.33 g, 2.0 mmol) was added and the mixture stirred for an additional 10 min. Allyl iodide (0.37 g, 2.2 mmol) was then added to the reaction mixture. The resulting solution was heated at 80 °C for 2 h whilst stirring. After cooling to room temperature, a saturated aqueous NH_4Cl solution (30 mL) was added and the mixture extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (10:1) as eluent] to give **14** (0.37 g, 75%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.59–7.46 (m, 2 H), 7.43–7.25 (m, 3 H), 5.89–5.66 (m, 1 H), 5.21–5.08 (m, 1 H), 4.45–4.35 (m, 1 H), 2.65–2.40 (m, 3 H), 1.98–1.79 (m, 1 H), 1.17 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 176.5, 136.8 (2 C), 132.1, 131.6, 129.7, 128.9 (2 C), 120.3, 73.2,

55.0, 40.7, 39.1, 21.4 ppm. MS (EI): *m*/*z* (%) = 264 (20) $[M]^+$, 135 (19), 110 (45). HRMS (EI): calcd. for $C_{14}H_{16}SO_2$ 248.0871; found 248.0865.

(5*S*)-5-Methyl-3-[(2*S*)-oxiran-2-ylmethyl]-3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one (15). Method A: Methanesulfonamide (0.475 g, 5 mmol) was added to a solution of AD-mix-β (7.0 g) in *tert*-butyl alcohol (10 mL) and water (10 mL) at 0 °C. The reaction mixture was stirred until homogeneous, compound **14** (1.24 g, 5 mmol) was added, and the mixture stirred for 24 h. Sodium sulfite (7.5 g) was then added and stirred for an additional 30 min. The resulting solution was extracted with EtOAc (30 × 5 mL). The combined organic extracts were washed with a 2 N KOH aqueous solution (100 mL) and dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was dissolved in CH_2Cl_2 (5 mL). PPTs (0.12 g, 0.5 mmol) and triethyl orthoacetate (1.01 g, 6.25 mmol) were added to the reaction mixture and stirred for 15 min. The solvent was then removed. The residue was dissolved in CH_2Cl_2 (5 mL) again and TMSCl (0.68 g, 6.25 mmol) was added. The resulting solution was stirred for an additional 40 min and the solvent was then removed. The residue was dissolved in methanol (5 mL) again and K_2CO_3 (1.20 g, 8.75 mmol) was added. The resulting solution was stirred for an additional 2 h, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (5:1) as eluent] to give **15** (0.72 g, 55%) as a pale yellow oil.

Method B: An LDA solution (1.0 mL, 2.0 M, 2.0 mmol) was slowly added to a solution of lactone **6** (0.41 g, 2 mmol) in dry THF (3 mL) at 0 °C. After stirring for 10 min, HMPA (0.33 g, 2.0 mmol) was added and the mixture stirred for an additional 10 min. (*S*)-Epichlorohydrin (0.37 g, 4.0 mmol) and NaI (0.03 g, 0.2 mmol) were then added to the reaction mixture. The resulting solution was heated at 80 °C for 2 h whilst stirring. After cooling to room temperature, saturated aqueous NH_4Cl solution (30 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (5:1) as eluent] to give **15** (0.26 g, 50%) as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3047, 2979, 1766 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58–7.54 (m, 2 H), 7.42–7.33 (m, 3 H), 4.66–4.61 (m, 1 H), 2.96–2.92 (m, 1 H), 2.85 (dd, *J* = 7.6, 6.4 Hz, 1 H), 2.76–2.74 (m, 1 H), 2.49–2.47 (m, 1 H), 2.23 (dd, *J* = 10.8, 3.6 Hz, 1 H), 2.01 (dd, *J* = 6.0, 4.0 Hz, 1 H), 1.76 (dd, *J* = 8.0, 6.4 Hz, 1 H), 1.26 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.4, 137.0 (2 C), 130.0, 129.7, 129.0 (2 C), 73.6, 54.3, 48.8, 46.0, 39.8, 39.6, 21.6 ppm. MS (EI) *m*/*z*: 264 (20) $[M]^+$, 135 (19), 110 (45). HRMS (EI): calcd. for $C_{14}H_{16}O_3Si$ 264.0820; found 264.0822.

(5*S*)-5-Methyl-3-[(2*S*)-oxiran-2-ylmethyl]furan-2(5*H*)-one (16): A mixture of MCPBA (0.16 g, 1.0 mmol) and **15** (0.26 g, 1.0 mmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 30 min. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was dissolved in toluene (2 mL). The solution was heated at reflux for 2 h whilst stirring. After cooling to room temperature, the solvent was removed and the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (1:1) as eluent] to give **16** (0.15 g, 95%) as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3062, 2986, 1748 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (d, *J* = 1.6 Hz, 1 H), 4.98 (qd, *J* = 6.8, 1.6 Hz, 1 H), 3.14–3.05 (m, 1 H), 2.77–2.73 (m, 1 H), 2.62–2.29 (m, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2, 151.5, 129.4, 77.7, 49.6, 46.5, 28.1, 18.8 ppm. MS (EI): *m*/*z* (%) = 154 (6) $[M]^+$, 112 (85), 67 (99). HRMS (EI): calcd. for $C_8H_{10}O_3$ 154.0630; found 154.0621. $[\alpha]_D^{25}$ = +14.3 (*c* = 1.0, $CHCl_3$).

(5*S*)-3-[(2*S*)-2-Hydroxy-5-(trimethylsilyl)pent-4-ynyl]-5-methylfuran-2(5*H*)-one (17): *n*BuLi (1.87 mL, 1.6 M, 3.0 mmol) was slowly added to a solution of trimethylsilylacetylene (0.29 g, 3.0 mmol) in dry THF (3 mL) at – 78 °C. After stirring this solution for 20 min, $BF_3{\cdot}OEt_2$ (0.43 g, 3.0 mmol) was added and the mixture stirred for another 10 min. A solution of **16** (0.31 g, 2.0 mmol) in dry THF (1 mL) was added to this reaction mixture which was stirred for an additional 4 h. The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (2:1) as eluent] to give **17** (0.40 g, 80%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.22 (d, *J* = 1.4 Hz, 1 H), 5.05 (qd, *J* = 6.8, 1.4 Hz, 1 H), 4.05–3.94 (m, 1 H), 2.66–2.47 (m, 2 H), 2.43 (d, *J* = 6.0 Hz, 2 H), 1.42 (d, *J* = 7.2 Hz, 3 H), 0.14 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.5, 152.3, 130.4, 102.4, 68.0, 31.9, 28.5, 19.0, 0.1 (3 C) ppm. MS (EI): *m*/*z* (%) = 252 (9) $[M]^+$, 141 (99), 73 (75). HRMS (EI): calcd. for $C_{13}H_{20}O_3Si$ 252.1182; found 252.1179. $[\alpha]_D^{25}$ = +26.5 (*c* = 1.0, $CHCl_3$).

(5*S*)-3-[(2*S*)-2-Hydroxypent-4-ynyl]-5-methylfuran-2(5*H*)-one (5): TBAF (1 M in THF, 3 mL, 3.0 mmol) was added to a solution of **17** (0.76 g, 3.0 mmol) in dry THF (10 mL) at 0 °C. After stirring for 5 h, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined ether extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (2:1) as eluent] to give **5** (0.41 g, 75%) as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3436, 3290, 2974, 2148, 1745 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.23 (d, *J* = 1.4 Hz, 1 H), 5.03 (qd, *J* = 6.6, 1.4 Hz, 1 H), 4.06–3.94 (m, 1 H), 2.66–2.47 (m, 2 H), 2.38 (dd, *J* = 6.0, 2.6 Hz, 2 H), 2.05 (t, *J* = 2.6 Hz, 1 H), 1.38 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 174.5, 152.5, 130.2, 80.1, 71.1, 67.8, 31.8, 26.9, 18.8 ppm. MS (EI): *m*/*z* (%) = 180 (9) $[M]^+$, 165 (20), 41 (99). HRMS (EI): calcd. for $C_{10}H_{12}O_3$ 180.0786; found 180.0784. $[\alpha]_D^{25}$ = +36.1 (*c* = 1.0, $CHCl_3$).

(5*S*)-3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(5*R*)-2-oxo-4,5-dihydro-3*H*-furan-2-yl]trideca-4,6-diynyl}-5-methylfuran-2(5*H*)-one (19): A mixture of **4** (67.2 mg, 0.2 mmol) and $[Pd(PPh_3)_2Cl_2]$ (7 mg, 0.01 mmol) in dry THF (1 mL) was stirred for 5 min before addition of **5** (21 mg, 0.12 mmol), CuI (2.0 mg, 0.01 mmol), and iPr_2NH (0.055 mL, 0.4 mmol). The resulting solution was stirred at room temperature for 2 h, quenched with 10% aqueous HCl solution, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (2:1) as eluent] to give **19** (41 mg, 53%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (d, *J* = 1.2 Hz, 1 H), 5.12–5.01 (m, 1 H), 4.41 (td, *J* = 7.2, 4.4 Hz, 1 H), 4.06–3.96 (m, 1 H), 3.59–3.48 (m, 1 H), 2.66–2.49 (m, 6 H), 2.29–2.19 (m, 3 H), 2.16–2.06 (m, 1 H), 1.60–1.24 (m, 11 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 177.4, 174.6, 152.7, 130.2, 83.0, 78.3, 78.2, 77.3, 73.9, 73.4, 72.8, 68.2, 32.6, 32.2, 28.6, 28.5, 27.8, 24.8, 24.0, 19.0, 18.9 ppm. MS (EI): *m*/*z* (%) = 388 (6) $[M]^+$, 218 (20), 141 (99). HRMS (EI): calcd. for $C_{22}H_{28}O_6$ 388.1886; found 388.1876. $[\alpha]_D^{25}$ = –9.0 (*c* = 1.0, $CHCl_3$).

(4*R*)-Rollicosin (2): A mixture of **19** (78 mg, 0.2 mmol) and $[Rh(PPh_3)_3Cl]$ (0.2 g, 0.2 mmol) in benzene/methanol (1:1, 2 mL) was stirred under hydrogen (1 atm) at room temperature for 24 h. After removal of the solvent, the residue was purified by column chromatography [silica gel, *n*-hexane/EtOAc (2:1) as eluent] to give **2** (63 mg, 80%) as a white solid, m.p. 107–108 °C [ref.[5d] 104–106 °C]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (d, J = 1.6 Hz, 1 H), 5.12–5.02 (m, 1 H), 4.42 (td, J = 7.6, 4.4 Hz, 1 H), 3.87–3.78 (m, 1 H), 3.59–3.50 (m, 1 H), 2.66–2.42 (m, 3 H), 2.40–2.36 (m, 1 H), 2.29–2.20 (m, 1 H), 2.16–2.04 (m, 2 H), 1.60–1.46 (m, 8 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.39–1.20 (m, 13 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 177.1, 174.6, 151.8, 131.2, 82.9, 78.0, 73.6, 70.0, 37.4, 33.3, 33.0, 29.4 (2 C), 28.7, 25.5, 25.4, 24.1, 19.1 ppm. MS (EI): *m*/*z* (%) = 396 (5) $[M]^+$, 267 (25), 73 (99). HRMS (EI): calcd. for $C_{22}H_{36}O_6$ 396.2512; found 396.2517. $[\alpha]_D^{25}$ = +1.9 (c = 1.0, $CHCl_3$) {ref.[4] $[\alpha]_D^{24}$ = –26.0 (c = 0.05, $CHCl_3$); ref.[5d] $[\alpha]_D^{24}$ = +2.5 (c = 0.29, $CHCl_3$)].

(5*S*)-5-Methyl-3-[(2*R*)-oxiran-2-ylmethyl]-3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one (20): Prepared following the procedure used for compound **15** by Method B using (*R*)-epichlorohydrin as the starting material in 55% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.60–7.50 (m, 2 H), 7.46–7.30 (m, 3 H), 4.72–4.56 (m, 1 H), 2.99–2.92 (m, 1 H), 2.87–2.73 (m, 2 H), 2.50–2.46 (m, 1 H), 2.24 (dd, J = 11.0, 3.6 Hz, 1 H), 2.01 (dd, J = 7.6, 6.4 Hz, 1 H), 1.75 (dd, J = 8.0, 6.4 Hz, 1 H), 1.27 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 176.4, 137.0 (2 C), 130.0, 129.8, 129.0 (2 C), 73.6, 54.3, 48.8, 46.0, 39.9, 39.7, 21.6 ppm. MS (EI): *m*/*z* (%) = 264 (90) $[M]^+$, 135 (35), 110 (95). HRMS (EI): calcd. for $C_{14}H_{16}O_3Si$ 264.0820; found 264.0811.

(5*S*)-5-Methyl-3-[(2*R*)-oxiran-2-ylmethyl]furan-2(5*H*)-one (21): Prepared following the procedure used for compound **16** in 90% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.21 (d, J = 1.6 Hz, 1 H), 4.98 (qd, J = 6.8, 1.6 Hz, 1 H), 3.14–3.06 (m, 1 H), 2.77–2.72 (m, 1 H), 2.64–2.28 (m, 3 H), 1.37 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 173.3, 151.5, 129.4, 77.8, 49.6, 46.6, 28.2, 18.8 ppm. MS (EI): *m*/*z* (%) = 154 (6) $[M]^+$, 112 (45), 67 (99). HRMS (EI): calcd. for $C_8H_{10}O_3$ 154.0630; found 154.0627. $[\alpha]_D^{25}$ = +78.5 (c = 1.0, $CHCl_3$).

(5*S*)-3-[(2*R*)-2-Hydroxy-5-(trimethylsilyl)pent-4-ynyl)-5-methylfuran-2(5*H*)-one (22): Prepared following the procedure used for compound **17** in 80% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22 (d, J = 1.4 Hz, 1 H), 5.05 (qd, J = 6.8, 1.4 Hz, 1 H), 4.05–3.93 (m, 1 H), 2.66–2.47 (m, 2 H), 2.44 (d, J = 6.0 Hz, 2 H), 1.42 (d, J = 7.0 Hz, 3 H), 0.14 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.4, 152.3, 130.4, 102.4, 78.0, 68.0, 31.9, 28.5, 19.0, 0.1 (3 C) ppm. MS (EI): *m*/*z* (%) = 237 (10) $[M - 15]^+$, 141 (99), 73 (75). HRMS (EI): calcd. for $C_{12}H_{17}O_3Si$ 237.0947; found 237.0949. $[\alpha]_D^{25}$ = +47.0 (c = 1.0, $CHCl_3$).

(5*S*)-3-[(2*R*)-2-Hydroxypent-4-ynyl)-5-methylfuran-2(5*H*)-one (23): Prepared following the procedure used for compound **4** in 80% yield as a pale yellow oil. IR (neat): $\tilde{\nu}$ = 3432, 3288, 2974, 2148, 1745 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.24 (d, J = 1.6 Hz, 1 H), 5.04 (qd, J = 7.0, 1.6 Hz, 1 H), 4.08–3.96 (m, 1 H), 2.66–2.47 (m, 2 H), 2.39 (dd, J = 6.0, 2.6 Hz, 2 H), 2.07 (t, J = 2.6 Hz, 1 H), 1.42 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 174.5, 152.5, 130.3, 80.1, 71.2, 67.8, 31.9, 27.0, 18.9 ppm. MS (EI): *m*/*z* (%) = 180 (9) $[M]^+$, 141 (99), 67 (99). HRMS (EI): calcd. for $C_{10}H_{12}O_3$ 180.0786; found 180.0777. $[\alpha]_D^{25}$ = +45.0 (c = 1.0, $CHCl_3$).

(5*S*)-3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(5*R*)-2-oxo-4,5-dihydro-3*H*-furan-5-yl]trideca-4,6-diynyl}-5-methylfuran-2(5*H*)-one (24): Prepared following the procedure used for compound **19** in 50% yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (d, J = 1.2 Hz, 1 H), 5.09–5.04 (m, 1 H), 4.41 (td, J = 7.6, 4.4 Hz, 1 H), 4.06–3.97 (m, 1 H), 3.59–3.47 (m, 1 H), 2.65–2.48 (m, 6 H), 2.28–2.17 (m, 3 H), 2.16–2.06 (m, 1 H), 1.60–1.28 (m, 11 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 177.4, 174.6, 152.7, 130.2, 83.0, 78.3 (2 C), 78.2, 77.3, 73.9, 73.3, 72.8, 68.1, 32.6, 32.2, 28.7, 28.5, 27.9, 24.8, 24.0, 19.0, 18.9 ppm. MS (EI): *m*/*z* (%) = 388 (26) $[M]^+$, 218 (30), 141 (99). HRMS (EI): calcd. for $C_{22}H_{28}O_6$ 388.1886; found 388.1882. $[\alpha]_D^{25}$ = +17.2 (c = 1.0, $CHCl_3$).

(4*S*)-Rollicosin (3): Prepared following the procedure used for rollicosin (**2**) in 80% yield as a white solid, m.p. 86–87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (d, J = 1.2 Hz, 1 H), 5.10–5.02 (m, 1 H), 4.41 (td, J = 7.2, 4.4 Hz, 1 H), 3.87–3.79 (m, 1 H), 3.58–3.50 (m, 1 H), 2.67–2.42 (m, 3 H), 2.40–2.36 (m, 1 H), 2.29–2.21 (m, 1 H), 2.16–2.04 (m, 2 H), 1.60–1.46 (m, 8 H), 1.42 (d, J = 6.8 Hz, 3 H), 1.39–1.20 (m, 13 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 177.1, 174.6, 152.0, 131.1, 82.9, 78.0, 73.6, 69.8, 37.4, 33.4, 33.0, 29.4, 29.3, 28.7, 25.5, 25.3, 24.1, 19.1 ppm. MS (EI): *m*/*z* (%) = 396 (7) $[M]^+$, 267 (99), 112 (90). HRMS (EI): calcd. for $C_{22}H_{36}O_6$ 396.2512; found 396.2518. $[\alpha]_D^{25}$ = +7.5 (c = 1.0, $CHCl_3$).

Owing to the small quantities of the final products **2** and **3**, we were unable to obtain elemental analysis data. In order to prove the purity of the two final products **2** and **3** – within the limits of this method – the ^{1}H and ^{13}C NMR spectra of these products are given (see electronic supporting information).

Supporting Information (see also the footnote on the first page of this article): The ^{1}H and ^{13}C NMR spectra of the two final products **2** and **3**.

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