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Convergent total synthesis of squamostolide

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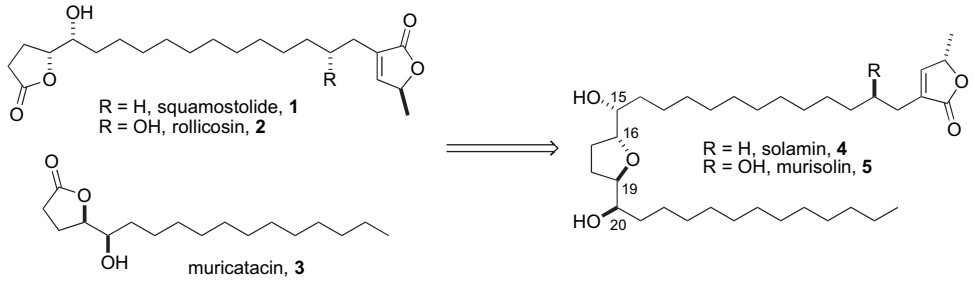
Abstract—A convergent total synthesis of the Annonaceous acetogenin squamostolide, in a longest linear sequence of nine steps from D-mannitol, is reported. Central to the efficiency of the synthesis is a highly selective tandem ring-closing/cross metathesis step in which lactone formation and fragment coupling are accomplished.

1. Introduction

Squamostolide[1] (**1**), rollicosin[2] (**2**), and muricatacin[3] (**3**) are three structurally related members of the Annonaceous acetogenin family of natural products (Scheme 1). Annonaceous acetogenins display a range of noteworthy biological properties including antitumor, antimalarial, insecticidal, and antibiotic activities. More than 400 acetogenins have been isolated from tropical and subtropical Annonaceae plants, with most possessing a terminal lactone and a terminal aliphatic side chain connected by a linker containing one or two tetrahydrofuran (THF) rings.[4] Solamin (**4**) and murisolin (**5**) are representative examples of mono(THF) acetogenins. It is likely that truncated analogs **1**–**3** are formed by oxidation of more common THF-containing acetogenins. For example, squamostolide or muricatacin may be generated by oxidative cleavage of either the C15–C16 bond or C19–C20 bond of solamin, respectively. As a result of their interesting structural and biological properties as well as their potential as structure–activity probes and intermediates in the preparation of more complex natural products, mono- and bis(lactone) acetogenins **1**–**3** have received considerable interest from the synthetic community.[5–7]

Previously, we reported total syntheses of muricatacin and rollicosin using a tandem ring-closing metathesis (RCM)[8]/cross metathesis (CM)[9] strategy for the construction of the 5-hydroxybutan-4-olide nucleus.[6a,7b] In this paper, we demonstrate the viability of this approach in a more complex setting than earlier reported and present a more complete examination of the RCM/CM transformation in the context of a highly convergent total synthesis of squamostolide.

Our synthetic strategy is based upon the observation that acrylate esters of 1,5-hexadiene-3,4-diol (e.g., **6**) undergo size selective RCM to produce butenolides **7** in preference to dihydropyranones **8** (Scheme 2). We have found that *tert*-butyldimethylsilyl (R=TBS) and benzyl (R=Bn) analogs of **6** give butenolides exclusively when treated with the second-generation Grubbs' catalyst (**9**).[10] In a related study, Blechert and Michaelis found that RCM of unprotected (R=H) and methoxymethyl (R=MOM) analogs of **6**



Scheme 1. Representative truncated and mono(THF) Annonaceous acetogenins.

Keywords: Squamostolide; Annonaceous acetogenin; Total synthesis; Olefin metathesis.
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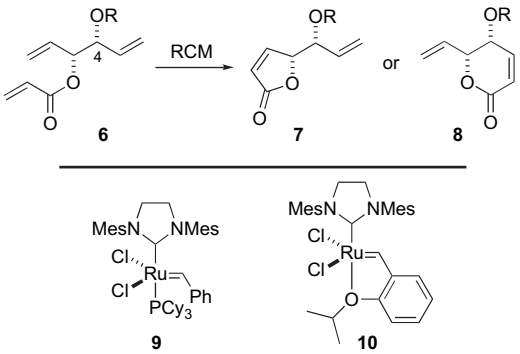
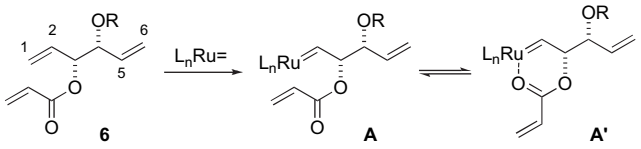


Scheme 2. Size selective RCM of trienes **6**.

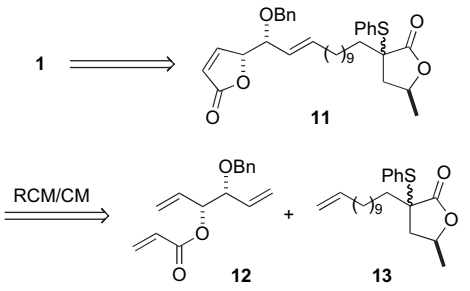
with **9** or the second-generation Hoveyda–Grubbs' catalyst (**10**)[11] resulted in less selective butenolide formation than the TBS and Bn analogs with ratios of **8**:**7** as high as 1:2.7 being observed.[12] Additionally, Virolleaud and Piva have reported that an analog of **6** lacking substitution at C4 undergoes RCM with catalyst **9** to produce a 2:1 ratio of butenolide to dihydropyranone.[13]

In these cases, we believe that the size selectivity is most likely governed by whether initiation by the catalyst occurs at the C1–C2 olefin or the C5–C6 olefin (Scheme 3). Initiation at the acrylate is unlikely due to its reduced reactivity. Our results can then be rationalized by a steric preference of initiation at the less hindered C1–C2 alkene. This rationale is less convincing in explaining the results of Blechert and Piva, in which one may reasonably expect a reversal of selectivity due to initiation at the C5–C6 olefin due to steric effects or directing effects of a chelating protecting group R. The inherent selectivity for five-membered ring formation in these examples seems to indicate that a factor other than these may also be influencing the site of initiation. We hypothesize that coordination of the acrylate carbonyl may be directing initiation to the proximal C1–C2 olefin to produce intermediate **A** as well stabilizing the resulting carbene intermediate by producing the six-membered chelate **A′**.



Scheme 3. Proposed rationale for size selectivity.

We have taken advantage of the size selectivity observed for the RCM of trienes **6** by using this reaction in tandem with a subsequent CM step to append a coupling partner to the unmetathesized, exocyclic alkene. We have shown that simple terminal olefins may be used as coupling partners in the CM.[6a,7b] More recently, Hoye and co-workers reported application of strategically similar RCM/CM approach in the total synthesis of the bis(THF) acetogenin gigantecin.[14] In order to maximize efficiency in the synthesis of **1**, we chose to pursue a convergent approach in which triene **12** was subjected to RCM/CM in the presence of coupling partner **13** as outlined retrosynthetically in Scheme 4. Practically, **12** and **13** were viewed as ideal substrates for the key metathesis step due

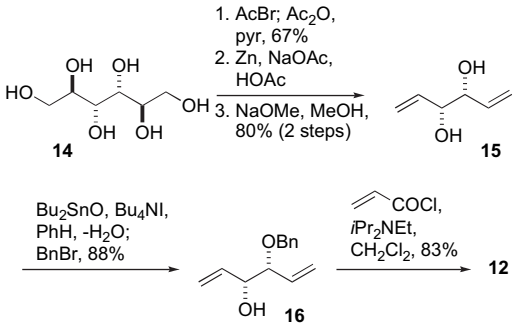


Scheme 4. Retrosynthetic analysis of **1**.

to their similar structural complexity and anticipated availability from simple starting materials.

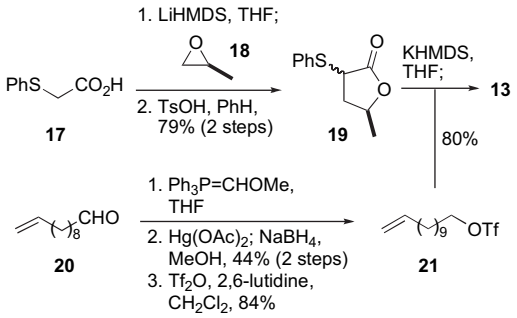
2. Results and discussion

The synthesis of triene **12** began with D-mannitol (**14**) and is outlined in Scheme 5. Conversion of **14** to C_2-symmetric (*R*,*R*)-hexa-1,5-diene-3,4-diol (**15**) was achieved by bromoacetylation followed by reductive elimination and acetate removal according to known protocol.[15] Monobenzylation of the stannylene acetal of **15** proved to be an efficient method for desymmetrization,[16] and acryloylation of the remaining hydroxyl gave metathesis substrate **12** in excellent overall yield. The benzyl protecting group was chosen for its compatibility and ease of removal by hydrogenolysis (vide infra); however, it should be noted that attempts to monoprotect the stannylene acetal of **15** with electrophiles other than BnBr (acryloyl chloride, TBSCl, TESCl, and MOMCl) met with failure.



Scheme 5. Synthesis of triene **12**.

Synthesis of the terminal alkene CM coupling partner is illustrated in Scheme 6. (5*S*)-Methyl-3-phenylsulfanyl-dihydrofuran-2-one (**19**) was prepared by alkylation of the enolate of (phenylthio)acetic acid (**17**) with (*S*)-propylene oxide (**18**) followed by acid-catalyzed lactonization.[17] The 12-carbon alkyl chain linker was prepared by Wittig homologation of commercially available 10-undecenal (**20**) followed by hydrolysis/reduction following the procedure of Crouch.[18] Conversion to the corresponding triflate **21** and addition to the potassium enolate of **19** produced the coupling partner **13** as a separable 3:1 mixture of diastereomers. Enolate alkylations such as this one, first reported by Hoye and co-workers, have proven to be widely effective for construction of acetogenin side chains.[19] Use of the potassium enolate of **19** rather than the lithium or sodium enolate

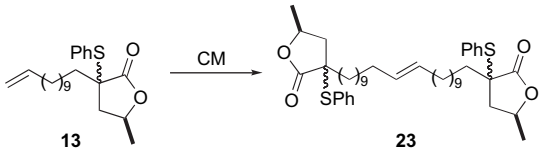


Scheme 6. Synthesis of terminal alkene **13**.

in the alkylation was necessary to avoid the requirement of elevated temperature and/or the use of HMPA as an additive.

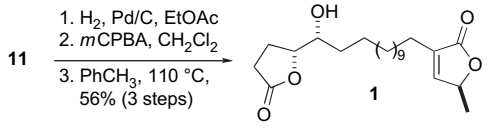
With substrates **12** and **13** in hand, the stage was set for evaluation of the key RCM/CM step. In previous RCM/CM studies, we employed only catalyst **9**, and aside from completion of a synthesis of squamostolide, one motivating factor for the research presented in this article was to carry out a more thorough evaluation of metathesis initiators for this transformation. A typical procedure involved refluxing a 0.02 M methylene chloride or benzene solution of triene **12** in the presence of 3 equiv of coupling partner **13** followed by dropwise addition of 10 mol % of a metathesis catalyst as a 0.01 M solution over 6 h via syringe pump. For consistency in catalyst evaluation, all reactions were heated under reflux for an additional 14 h. Our results are shown in Table 1. The first-generation Grubbs' catalyst[20] proved incapable of effecting the tandem RCM/CM affording **22**, the product of RCM only, in poor yield (entry 1). While the second-generation Grubbs' catalyst (**9**) and the first-generation Hoveyda–Grubbs' catalyst[21] gave workable yields of **11**, significant amounts of **22** were also observed (entries 2–4). Although **11** and **22** could be separated by column chromatography without difficulty, we felt that use of the more active second-generation Hoveyda–Grubbs' catalyst (**10**) may promote complete CM and increase our isolated yields of **11**. We were pleased to find this to be the case with yields of **11** as high as 77% being obtained (entries 5 and 6). We believe that the observed temperature dependence when catalyst **10** is employed is simply the result of an increased rate of catalyst decomposition at elevated temperature. The results detailed in Table 1 represent our most comprehensive study on the effect of Ru catalyst on reaction yield and clearly indicate that the second-generation Hoveyda–Grubbs' catalyst (**10**) is optimal for promoting the RCM and CM steps in tandem. Somewhat surprisingly, we found that the first-generation Hoveyda–Grubbs' catalyst resulted in slightly higher isolated yields of **22** (RCM only) than **10** in reactions of **12** run in the absence of coupling partner **13**.

It is interesting to note that **13** undergoes dimerization by CM at a rate much faster than that of its CM with **22**, so, in fact, the CM step is likely occurring between **22** and dimer **23** (Scheme 7). This conclusion is supported by our observation of **23** by ^{1}H NMR and TLC analysis in which consumption of **13** is not observed concomitantly with that of **22**. Rather, fast formation of **22** (from **12**) and consumption of **13** (to produce **23**) are observed followed by relatively slow formation of **11**. Products of CM between two molecules of **12** and/or **22** were not observed. This is presumably due to their reduced reactivity as a result of allylic substitution.



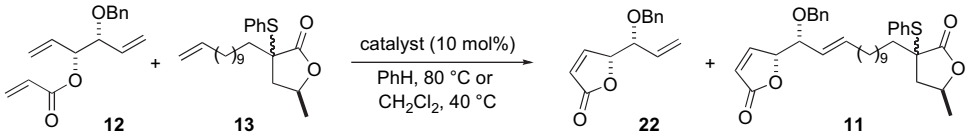
Scheme 7. Dimerization of **13** by CM.

The synthesis was completed by the three-step sequence outlined in Scheme 8. Catalytic hydrogenation/hydrogenolysis cleanly achieved alkene reduction and benzyl group deprotection, and subsequent sulfide oxidation with *m*-CPBA and thermolysis gave squamostolide (**1**) in 56% over three steps requiring purification after only at the last. Spectral data (IR, ^{1}H and ^{13}C NMR, and HRMS), optical rotation, and melting point of synthetic **1** were consistent with those reported in the literature.[1,5]



Scheme 8. Completion of the synthesis of **1**.

Table 1. RCM/CM of **12** and **13**



Entry	Catalyst[a]	Temperature (°C)	Yield of **22** (%)	Yield of **11** (%)
1	Grubbs' I	80	45	0
2	**9**	80	12	53
3	**9**	40	19	60
4	Hoveyda–Grubbs' I	80	16	66
5	**10**	80	0	68
6	**10**	40	0	77

[a] Grubbs' I catalyst: PhCH=$RuCl_2(PCy_3)_2$; Hoveyda–Grubbs' I catalyst: *o*-isopropoxyPhCH=$RuCl_2(PCy_3)$.

In conclusion, we have accomplished a convergent total synthesis of squamostolide that demonstrates the scope and power of our tandem RCM/CM strategy for preparation of hydroxylated butenolides. The efficiency and flexibility of this approach make it broadly useful, and we are currently in the process of generating analogs of truncated acetogenins as well as examining functionalization of RCM/CM products for the synthesis of more complex THF-containing acetogenins.

3. Experimental

3.1. General methods

Unless otherwise noted, all non-aqueous reactions were performed in flame-dried glassware under a stream of nitrogen. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at room temperature. Concentrations (*c*) are reported in g/100 mL. Infrared spectra (IR) were obtained on a Perkin–Elmer 1600 Series FTIR. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Inova-400 at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million relative to $CHCl_3$ (δ 7.27) for ^{1}H NMR and the central resonance of $CDCl_3$ (δ 77.0) for ^{13}C NMR. High resolution fast atom bombardment mass spectra (HRMS) were obtained on a JEOL MStation JMS-700 mass spectrometer at the University of Massachusetts-Amherst.

EM Science DriSolv® solvents (CH_2Cl_2, PhH, THF, pyridine, and MeOH) were used in moisture sensitive reactions. (*R*,*R*)-Hexa-1,5-diene-3,4-diol (**15**) was prepared from D-mannitol using the protocol reported by Burke and Sametz.[15] 11-Dodecen-1-ol was prepared from 10-undecanal according to the procedure of Crouch.[18] (5*S*)-Methyl-3-phenylsulfanyldihydrofuran-2-one (**19**) was prepared from (phenylthio)acetic acid (**17**) and (*S*)-propylene oxide (**18**) using the procedure of White.[17] Commercially available reagents and solvents were used as received without further purification.

3.1.1. (4*R*)-Benzyloxyhexa-1,5-dien-(3*R*)-ol (16). To a solution of (*R*,*R*)-hexa-1,5-diene-3,4-diol **15** (861.0 mg, 7.55 mmol) in PhH (75 mL) at room temperature were added dibutyltin oxide (2.065 g, 8.30 mmol) and tetrabutylammonium iodide (696 mg, 1.89 mmol). The flask was equipped with a Dean–Stark trap (filled with 4 Å molecular sieves) and a reflux condenser. The trap was filled with PhH and the reaction mixture was heated under reflux until H_2O evolution appeared complete. The reaction mixture was cooled to room temperature and BnBr (1.08 mL, 9.04 mmol) was added. The resulting yellow solution was heated under reflux for 18 h. The mixture was diluted with Et_2O (50 mL) and washed with 10% $Na_2S_2O_3$ (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×40 mL). The combined organic layers were washed with H_2O (30 mL) and dried with $MgSO_4$. The drying agent was removed by filtration and solvents were removed in vacuo. Purification by silica gel chromatography (4:1 pentane/Et_2O) provided monobenzyl ether **16** (1.36 g, 88%) as a colorless oil. Data for **16**: $[\alpha]_D^{22}$ +42.7 (*c* 2.09, CH_2Cl_2); IR (thin film) 3449, 3085, 3030, 2868 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.29 (m, 5H), 5.84 (ddd, *J*=17.2, 10.6, 5.7 Hz, 1H), 5.76 (ddd, *J*=17.2, 10.5, 7.8 Hz, 1H), 5.39 (ddd, *J*=10.6, 1.8, 0.8 Hz, 1H), 5.37 (dt, *J*=17.2, 1.6 Hz, 1H), 5.34 (ddd, *J*=17.2, 1.8, 0.8 Hz, 1H), 5.22 (dt, *J*=10.5, 1.6 Hz, 1H), 4.67 (d, *J*=11.5 Hz, 1H), 4.39 (d, *J*=11.5 Hz, 1H), 4.09 (ddt, *J*=7.2, 5.7, 1.4 Hz, 1H), 3.68 (br t, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 136.0, 134.6, 128.5, 127.9, 127.8, 120.3, 117.0, 84.0, 74.7, 70.5; HRMS calcd for $C_{13}H_{17}O_2$ (MH^+) 205.1229, found 205.1295.

3.1.2. Acrylic acid (2*R*)-benzyloxy-(1*R*)-vinylbut-3-enyl ester (12). To a solution of **16** (586.2 mg, 2.90 mmol) in CH_2Cl_2 (29 mL) at room temperature was added *i*-Pr_2NEt (3.0 mL, 17.2 mmol) followed by acryloyl chloride (0.70 mL, 8.6 mmol). The reaction mixture was stirred at room temperature for 4 h, after which time it was quenched with 15 mL of water and diluted with Et_2O (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic phases were washed with satd NH_4Cl (20 mL) and brine (20 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and solvents were removed in vacuo. Purification by silica gel chromatography (6:1 pentane/Et_2O) gave triene **12** (625.2 mg, 83%) as a colorless oil. Data for **12**: $[\alpha]_D^{22}$ +61.1 (*c* 1.97, CH_2Cl_2); IR (thin film) 3088, 3029, 2867, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.25 (m, 5H), 6.44 (dd, *J*=17.4, 1.6 Hz, 1H), 6.17 (dd, *J*=17.4, 10.4 Hz, 1H), 5.88 (ddd, *J*=17.4, 10.7, 6.1 Hz, 1H), 5.84 (dd, *J*=10.4, 1.6 Hz, 1H), 5.77 (ddd, *J*=17.0, 10.6, 7.4 Hz, 1H), 5.50 (tt, *J*=6.1, 1.4 Hz, 1H), 5.37–5.30 (m, 3H), 5.25 (tt, *J*=10.7, 1.4 Hz, 1H), 4.67 (d, *J*=12.1 Hz, 1H), 4.43 (d, *J*=12.1 Hz, 1H), 3.93 (br t, *J*=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 137.9, 133.9, 132.6, 130.9, 128.3, 128.1, 127.5, 127.4, 119.7, 118.1, 80.5, 75.3, 70.2; HRMS calcd for $C_{16}H_{19}O_3$ (MH^+) 259.1334, found 259.1370.

3.1.3. 3-Dodec-11-enyl-(5*S*)-methyl-3-phenylsulfanyldihydrofuran-2-one (13). To a solution of 11-dodecen-1-ol (471.0 mg, 2.53 mmol) and 2,6-lutidine (0.88 mL, 7.58 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added Tf_2O (0.64 mL, 3.80 mmol). After 10 min, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 30 min. The reaction was quenched by addition of satd NH_4Cl (15 mL) and diluted with Et_2O. The layers were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were washed with satd NH_4Cl (40 mL), H_2O (20 mL), and brine (20 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (6:1 hexanes/Et_2O) gave triflate **21** (676.7 mg, 84%) as a colorless oil, which was used immediately in the next step.

(5*S*)-Methyl-3-phenylsulfanyldihydrofuran-2-one **19** (554.0 mg, 2.66 mmol) in THF (2.6 mL) was cooled to 0 °C, and 5.32 mL of a 0.5 M solution of KHMDS in $PhCH_3$ (2.66 mmol) was added. The resulting pale yellow solution was stirred at 0 °C for 10 min after which time triflate **21** (676.7 mg, 2.13 mmol) in 2 mL of THF was added via syringe. The reaction mixture was warmed to room

temperature and stirred for 16 h. The reaction was quenched by addition of satd NH_4Cl (15 mL) and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with satd NH_4Cl (20 mL), H_2O (20 mL), and brine (20 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (6:1 hexanes/EtOAc) gave terminal alkene **13** (638.3 mg, 80%) as a colorless oil. Data for **13** (major diastereomer): IR (thin film) 3027, 2929, 2855, 1769 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.54 (m, 3H), 7.41–7.33 (m, 2H), 5.79 (ddt, J=16.9, 10.2, 6.6 Hz, 1H), 4.93 (dq, J=16.9, 1.0 Hz, 1H), 4.85 (ddt, J=10.2, 2.3, 1.0 Hz, 1H), 4.55 (m, 1H), 2.50 (m, 1H), 2.13–1.97 (m, 5H), 1.80–1.72 (m, 2H), 1.65–1.52 (m, 2H), 1.41–1.23 (m, 13H), 1.19 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 139.2, 136.7, 130.4, 129.6, 129.0, 114.1, 74.2, 56.6, 34.0, 32.7, 29.7, 29.6, 29.5, 29.4, 29.1, 25.9, 25.8, 25.2, 24.7, 21.5; HRMS calcd for $C_{23}H_{35}O_2S$ (MH^+) 375.2358, found 375.2389.

3.1.4. (5*R*)-[(1*R*)-Benzyloxyallyl]-5*H*-furan-2-one (22). To a solution of triene **12** (51.0 mg, 0.20 mmol) and terminal alkene **13** (218.1 mg, 0.58 mmol) in refluxing PhH (10 mL) was added first-generation Grubbs' catalyst (15.6 mg, 0.02 mmol) in 2 mL of PhH dropwise over 6 h by syringe pump. Heating was continued for an additional 14 h after addition was completed. After cooling to room temperature, the brown solution was filtered through a short pad of silica gel and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (4:1 pentane/Et_2O) gave butenolide **22** (19.7 mg, 45%) as a slightly yellow oil. Data for **3**: $[\alpha]_D^{22}$ −11.7 (c 1.11, CH_2Cl_2); IR (thin film) 3059, 2984, 2869, 1757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, J=5.8, 1.6 Hz, 1H), 7.39–7.29 (m, 5H), 6.19 (dd, J=5.8, 2.0 Hz, 1H), 5.65 (ddd, J=17.2, 10.5, 7.6 Hz, 1H), 5.43–5.36 (m, 2H), 5.13 (dt, J=5.6, 1.6 Hz, 1H), 4.68 (d, J=11.9 Hz, 1H), 4.46 (d, J=11.9 Hz, 1H), 4.11 (dd, J=7.6, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 153.4, 137.4, 132.4, 128.5, 127.9, 127.8, 123.0, 121.7, 83.8, 79.5, 70.8; HRMS calcd for $C_{14}H_{15}O_3$ (MH^+) 231.1021, found 231.0989.

3.1.5. (5*R*)-[(1*R*)-Benzyloxy-13-[(5*S*)-methyl-2-oxo-3-phenylsulfanyltetrahydrofuran-3-yl]-tridec-2-enyl]-5*H*-furan-2-one (11). To a solution of triene **12** (49.9 mg, 0.19 mmol) and terminal alkene **13** (215.5 mg, 0.58 mmol) in refluxing PhH (10 mL) was added second-generation Hoveyda–Grubbs' catalyst **10** (12.1 mg, 0.02 mmol) in 2 mL of PhH dropwise over 6 h by syringe pump. Heating was continued for an additional 14 h after addition was completed. After cooling to room temperature, the brown solution was filtered through a short pad of silica gel and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (4:1 pentane/Et_2O) gave RCM/CM product **11** (84.3 mg, 77%) as a yellow oil. Data for **11** (major diastereomer): IR (thin film) 3053, 2928, 2859, 1765, 1756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60–7.55 (m, 2H), 7.45 (dd, J=5.8, 1.8 Hz, 1H), 7.41–7.29 (m, 8H), 6.15 (dd, J=5.8, 1.9 Hz, 1H), 5.75 (dt, J=15.1, 7.0 Hz, 1H), 5.26 (ddt, J=15.1, 7.9, 1.4 Hz, 1H), 5.10 (dt, J=5.8, 1.8 Hz, 1H), 4.65 (d, J=11.9 Hz, 1H), 4.43 (d, J=11.9 Hz, 1H), 4.51 (m, 1H), 4.04 (dd, J=8.0, 5.8 Hz, 1H), 2.61–2.47 (m, 3H), 2.33–1.94 (m, 4H), 1.80–1.72 (m, 2H), 1.65–1.52 (m, 2H), 1.41–1.23 (m, 11H), 1.16 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3, 172.7, 153.6, 139.3, 137.7, 135.5, 130.4, 129.6, 129.0, 128.3, 127.6, 127.4, 126.6, 122.8, 84.5, 79.2, 73.1, 70.3, 56.3, 39.8, 36.1, 32.3, 30.3, 29.6, 29.4, 29.3, 29.2, 28.6, 25.2, 24.6, 19.9; HRMS calcd for $C_{35}H_{45}O_5S$ (MH^+) 577.2988, found 577.2972.

3.1.6. Squamostolide (1). To a solution of RCM/CM product **11** (62.1 mg, 0.11 mmol) in EtOAc (3 mL) at room temperature was added a spatula tip of 10 wt % Pd on activated carbon. The reaction mixture was stirred under 1 atm of H_2 for 24 h after which time it was filtered through a pad of silica gel and concentrated in vacuo to give the corresponding saturated, debenzylated analog (50.1 mg) as a pale yellow oil, which was carried on without purification.

To a solution of crude hydrogenation/hydrogenolysis product (50.1 mg, 0.10 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added *m*-CPBA (77% max, 25.2 mg, 0.11 mmol). After 30 min, the reaction was quenched by addition of satd $NaHCO_3$ (5 mL) and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic extracts were washed with satd $NaHCO_3$ (5 mL) and brine (5 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated in vacuo. The crude sulfoxide was dissolved in $PhCH_3$ (4 mL) and heated to 110 °C for 40 min. Solvent was removed in vacuo and purification by silica gel chromatography (5:1 $PhCH_3$/EtOAc) gave squamostolide **1** (22.8 mg, 56% over three steps) as a white solid. Data for **1**: $[\alpha]_D^{22}$ −3.6 (c 0.10, acetone); IR (thin film) 3401, 2925, 2857, 1768, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.99 (d, J=1.6 Hz, 1H), 5.00 (qd, J=6.7, 1.6 Hz, 1H), 4.41 (q, J=7.3 Hz, 1H), 3.55 (m, 1H), 2.64–2.53 (m, 2H), 2.30–2.21 (m, 3H), 2.09 (m, 1H), 1.87 (br s, 1H), 1.57–1.42 (m, 6H), 1.39 (d, J=6.7 Hz, 3H), 1.37–1.20 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 174.0, 148.9, 134.3, 82.9, 77.4, 73.6, 33.0, 29.5, 29.4, 29.2, 29.1, 28.7, 27.3, 25.4, 25.1, 24.1, 19.2; HRMS calcd for $C_{22}H_{37}O_5$ (MH^+) 381.2641, found 381.2635.

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