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Studies on Ring-Closing Metathesis for the Formation of the 11-Membered Ring System of Daphnezomine C

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For the purpose of synthesizing daphnezomine C, model systems were examined to see if the ring-closing metathesis (RCM) reaction could be applied to prepare an 11-membered ring system bearing a tri-substituted alkene. As a result, it was found that the connectivity pattern of the tethers bearing the reacting alkene moieties was crucial. Thus, whereas a system involving a single 1,3- or 1,4-disubstituted cyclohexane derivative did not give RCM products, a flexible system without any rings between the two terminal alkenes gave the cyclic product with a yield of up to 65% using the second generation Grubbs catalyst.

Daphniphyllum alkaloids are a group of natural products that have long been known and have attracted interest especially for there unique polycyclic structure and from a biogenetic point of view.[1] Heathcock and Wallace have devised an elegant biomimetic synthetic pathway, which involves cascade reactions to construct the polycyclic nitrogen-containing core, en route to the total synthesis of a variety of these compounds, such as secodaphniphylline (**1**) (Chart 1).[2] Rather recently, several new members to this group of compounds have been isolated, including daphnezomine C (**2**), which bears an anti-Bredt imine double bond.[3] Contrary to their unstable appearance, compounds with this double bond can be obtained in varying yields from their corresponding saturated precursors by using appropriate oxidizing reagents. We felt, however, that it would be versatile if there was a synthetic method that would give the double bond directly with concomitant formation of the complex multicyclic core. To this end, we designed the route shown in Scheme 1 for compound **3**, a model for the complete core. This plan called for the use of ring-closing metathesis (RCM)[4] and the hetero-Diels–Alder (HDA)[5] reactions in tandem as the key steps for full core construction (Scheme 1). Precursor **5** for the two reactions could be envisioned to be obtainable from **6** by amination, and **6** from fragments **7** and **8**, which in turn could both be prepared from malonate **9**. The RCM reaction has emerged as an extremely efficient method for the preparation of rings of various sizes, enabling in many cases ring formation, where conventional strategies failed. For the key RCM reaction to proceed as desired, there are two obstacles to be overcome. One is that a

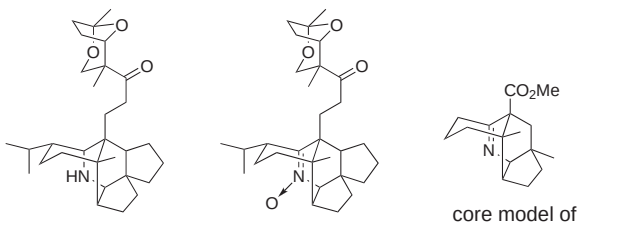
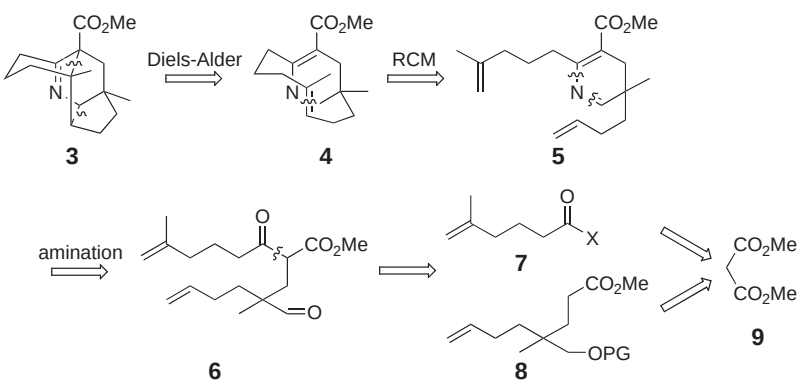


Chart 1.



Scheme 1. Retrosynthesis of the model compound.

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medium-sized eleven-membered ring has to be formed, which is usually considered difficult due to ring strain[6] and unfavorable entropy factors involving the ring-closing process.[7] The other is that in addition to the difficult task given above, the olefin to be formed is tri-substituted meaning ring formation would be difficult from a steric point of view. Possibly due to the entropic difficulties to prepare 11-membered rings, reports dealing with its formation using the RCM reaction are still rather limited.[8] Furthermore, for those that also have a tri-substituted alkene as in our case, there were, to our knowledge, no reports when we began our project. Only recently have there been successful examples put forward by Vassilikogiannakis, Nicolaou, and co-workers involving the synthesis of coleophomones, of which coleophomone C (**12**) is shown (Scheme 2).[8g,k] Here, the formation of an 11-membered ring to give **11** is somewhat facilitated entropy-wise by the inclusion of a 1,2-disubstituted benzene ring and a 1,3-disubstituted cyclohexadione ring in RCM precursor **10**. In order to see if the two difficult obstacles could be overcome in our synthetic plan, we decided to examine model systems using three representative RCM catalysts (**13**–**15**) (Chart 2). From these studies, we found that our original synthetic plan was unfortunately not suitable for total synthesis, because the RCM reaction would not go. However, we also found that adding flexibility to the system allowed the RCM reaction to proceed, despite the two obstacles, to give the 11-membered ring system using the Grubbs second generation catalyst that bears the Arduengo ligand.[9] Herein, we present our results.

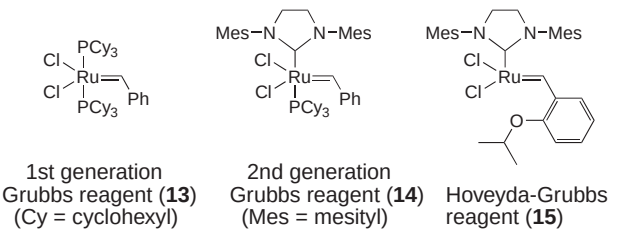
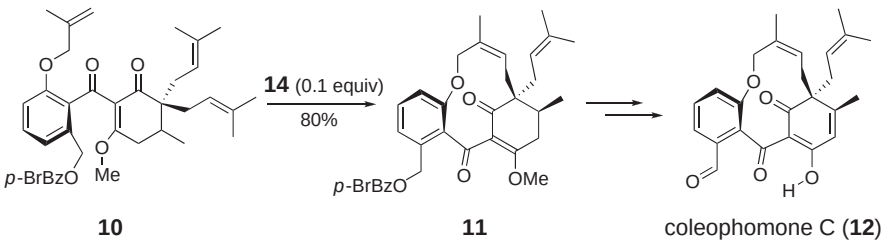


Chart 2.

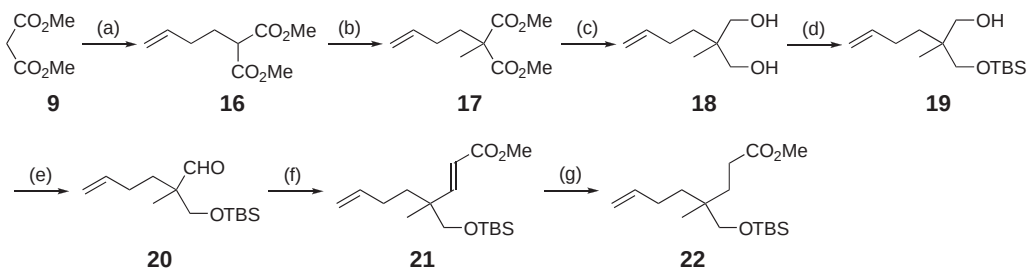
Results and Discussion

According to our retrosynthetic analysis, RCM reaction precursor **5** was prepared as described in Schemes 3 and 4. Methyl malonate (**9**) was alkylated successively with 4-bromo-1-butene and MeI to give **17**. Compound **17** was reduced with $LiAlH_4$ to give diol **18**, followed by monoprotection with TBSCl (TBS: *t*-$BuMe_2Si$) to furnish **19** in 90% yield. The use of TBSOTf with 2,6-lutidine or TBSCl with Et_3N lead to the formation of significant amounts of the double-protected species as a by-product, even when only 1 equivalent of the silylating agent was used. The free hydroxy group was oxidized to a formyl group under Swern conditions to give **20** in 97% yield. Aldehyde **20** was then subjected to the Horner–Wadsworth–Emmons reaction to give exclusively the *E*-olefin **21**. Conjugated reduction of the unsaturated olefin with Mg–MeOH yielded **22** in high yield. The use of the ethyl ester of **21** (in the place of the methyl ester) led to the formation of a mixture of **22** and the ethyl ester due to partial transesterification under the reaction conditions.

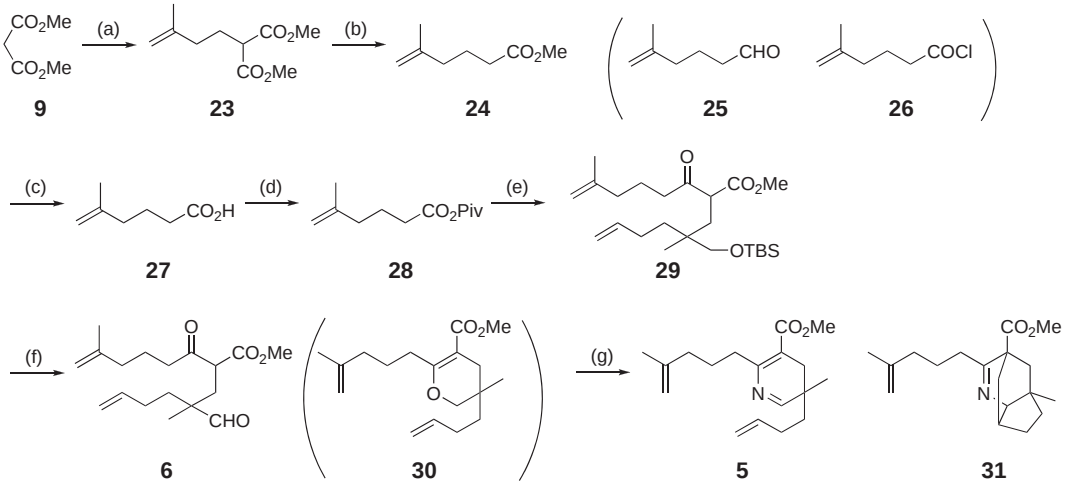
The reaction partner was also prepared from methyl malonate (Scheme 4). Malonate **9** was alkylated with 4-methyl-4-pentyl tosylate to give **23**, which was decarboxylated with NaCl in a DMF–H_2O mixture to give monoester **24**. This ester was converted to aldehyde **25** and acid chloride **26**. To our disappointment, neither **25** nor **26** reacted with the Li^+-enolate of ester **22**, generated with LDA. However, the mixed acid anhydride **28** prepared in situ from carboxylic acid **27** and pivaloyl chloride reacted to give keto ester **29**. The TBS protecting group was then removed with TBAF and immediately after workup, it was oxidized to aldehyde **6** with dipyridine–chromium(VI) oxide. Attempts to purify the intermediate alcohol



Scheme 2. The use of RCM for an 11-membered ring synthesis.

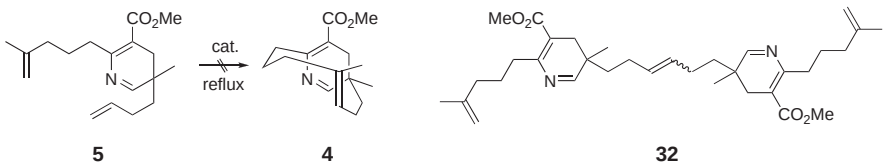


Scheme 3. Reagents and conditions: (a) NaH, THF, 0 °C; then 4-bromo-1-butene, TBAI, reflux (94%). (b) Cs_2CO_3, MeI, THF, rt (92%). (c) $LiAlH_4$, THF, rt (96%). (d) NaH, DMF, 0 °C; then TBSCl, rt (90%). (e) DMSO, $(COCl)_2$, Et_3N, −78 °C to rt (97%). (f) NaH, THF, 0 °C; then $(MeO)_2P(O)CH_2CO_2Me$, rt (96%). (g) Mg, MeOH, reflux (91%).



Scheme 4. Reagents and conditions: (a) NaH, THF, 0 °C; then $TsOCH_2CH_2CH(CH_3)=CH_2$, TBAI, reflux (94%). (b) NaCl, H_2O, DMF, reflux (83%). (c) 5% NaOH, EtOH, reflux (96%). (d) Et_3N, THF, 0 °C; then PivCl. (e) LDA, THF, −78 °C; then **22**, −78 °C to rt (63% in two steps). (f) TBAF, THF; then 2Py-CrO_3, CH_2Cl_2, rt (43% in two steps). (g) NH_4OAc, PhH-AcOH, reflux (**5**, 32%; **31**, 38%).

Table 1. RCM Reaction of **5**

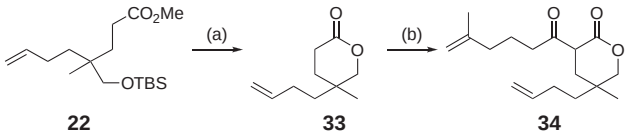


Entry	Catalyst	Solvent	Time	Yield
1	**13** (0.10 equiv)	Toluene (0.05 M)	8 h	Decomp.
2	**13** (0.15 equiv)	CH_2Cl_2 (0.01 M)	2 d	39% (**32**)
3	**14** (0.10 equiv)	Toluene (0.01 M)	18 h	Decomp.
4	**14** (0.10 equiv)	CH_2Cl_2 (0.01 M)	1 d	35% (**32**)
5	**15** (0.10 equiv)	Toluene (0.01 M)	15 h	14% (**32**)
6	**15** (0.13 equiv)	Toluene (0.0005 M)	3 d	18% (**32**)

by silica-gel chromatography lead to the formation of cyclized product **30**. Likewise, deprotection or oxidation using acidic conditions either gave rise to decomposition products or cyclized product **30**. Attempts to transform **30** back to usable material failed. Furthermore, the use of the Swern, the Dess-Martin, MnO_2, and PCC (pyridinium chlorochromate) reagents for the oxidation reaction resulted in essentially no reaction. Treatment of aldehyde **6** with ammonium acetate gave dihydropyridine derivative **5** (32%) along with a moderate amount of **31** (38%), which is the inverse demand hetero-Diels–Alder product of **5**. Although **31** was an undesired product, the fact that this formed suggested that the Diels–Alder reaction should be facile, once the RCM reaction proceeded. Attempts to optimize yields by minimizing the production of **31** were not carried out, due to the following discouraging results.

Attempts at RCM with **5** were carried out using Grubb's first and second generation catalysts along with the Hoveyda–Grubbs reagent at different temperatures (Table 1). However, the reactions turned out to be quite messy, giving dimer **32**, formed by the intermolecular metathesis reaction between two mono-substituted terminal alkene moieties, as the only identifiable product. The use of elevated temperatures with toluene as the solvent was detrimental, giving a gummy mess with the two Grubbs catalysts. The Hoveyda–Grubbs catalyst was found to be more robust, and the dimer was afforded even in refluxing toluene (Entry 5). However, even the use of an extremely dilute solution did not give rise to the desired RCM product (Entry 6). In compound **5**, not only are the tethers to be attached positioned in a 1,4-array, the 4-methyl-4-pentenyl tether is bonded to an sp^2 carbon. This hybridization would disallow the possibility of any dihydropyridine ring conformation, in which the carbon of this tether directly attached to the ring is oriented towards the 3-butenyl tether, and for the reaction to occur, the reacting end of this tether must twist back 180° to come over the dihydropyridine ring while the other tether must occupy a pseudoaxial position. Thus, we reasoned that the negative results were due to unfavorable entropy circumstances and decided to next examine the validity of the 1,3-disubstituted ring system.

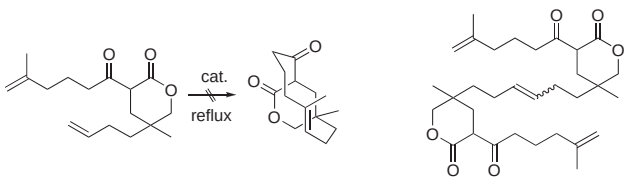
To this end, we prepared lactone **34** as a model compound for the RCM reaction as shown in Scheme 5. Acid hydrolysis of **22** gave lactone **33**, and ensuing condensation via the in situ anhydride method as subjected to **22** furnished **34**. The RCM reactions afforded only dimer **36** arising from metathesis be-



22 **33** **34**

Scheme 5. Reagents and conditions: (a) 1 M HCl, THF, reflux (81%). (b) LDA, THF, −78 °C; then **28**, −78 °C to rt (63% in two steps).

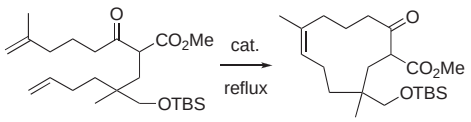
Table 2. RCM Reaction of **34**



34 **35** **36**

Entry	Catalyst	Solvent	Time/h	Yield/%
1	**13** (0.10 equiv)	CH_2Cl_2 (0.01 M)	4	34 (**36**)
2	**14** (0.15 equiv)	CH_2Cl_2 (0.01 M)	8	51 (**36**)

Table 3. RCM Reaction of **29**



29 **37**

Entry	Catalyst	Solvent	Time/h	Yield/%
1	**13** (0.10 equiv)	CH_2Cl_2 (1 mM)	48	Decomp.
2	**14** (0.15 equiv)	CH_2Cl_2 (0.5 mM)	48	36
3	**14** (0.10 equiv)	CH_2Cl_2 (1 mM)	36	38
4	**14** (0.10 equiv)	CH_2Cl_2 (2 mM)	36	65
5	**15** (0.13 equiv)	CH_2Cl_2 (1 mM)	48	23

tween two uncrowded terminal alkenes, instead of **35**, as in the case of **5** (Table 2).

We then decided to look into more flexible systems to see if the reaction would go at all. Thus, the first product obtained from our synthetic scheme that could potentially give rise to an 11-membered ring, i.e., **29**, was next examined (Table 3), and it was found to give the desired ring compound **37** in up to 65% yield as a diastereomeric mixture upon using the 2nd generation Grubbs catalyst **14** at high dilution. In our case, higher dilution was not necessarily better, as a comparison of Entries 3 and 4 show. The Hoveyda–Grubbs catalyst **15** gave a lower yield of the desired product, whereas the first generation catalyst only led to decomposition of the substrate. NOE experiments on **37** showed a signal enhancement between the methyl and hydrogen substituents upon the newly formed double bond for both diastereomers, thereby suggesting that the geometry of the double bond is *Z* for both isomers and that the diastereomers consist of those due to the two asymmetric centers, one of which easily epimerizes. In addition to the flexibility of the ring system for the RCM to occur, it could be that the success here is due to the presence of less ring strain in product **37** compared to that expected in **31** or **35**, which were not obtained.

Conclusion

We found that the formation of tri-substituted 11-membered ring alkenes, which is generally thought to be difficult did not occur if a 1,4- or 1,3-disubstituted ring moiety was involved. However, if a flexible substrate was used in the presence of the second generation Grubbs catalyst, an 11-membered ring formed. Thus, it seems that our initial plan to carry out a tandem RCM-Diels–Alder process is difficult to realize. However, the fact that RCM occurred at all implies that if the substitution pattern is right, similar products can be obtained, even with difficult looking systems. Based upon these results, we are currently examining several other analogous systems bearing the fused 5-membered ring actually present in the natural product.

Experimental

General. Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a JEOL JNM-LA500 spectrometer. ^{1}H NMR chemical shifts are given in δ downfield from residual chloroform-*d* (δ 7.26). ^{13}C NMR chemical shifts are given in δ from chloroform-*d* (δ 77.0). For diastereomeric mixtures, NMR signals due to the minor component are given in ⟨ ⟩. High-resolution mass spectra were measured on a JEOL JMS-SX102A spectrometer under electron ionization conditions (70 eV) or fast atom bombardment conditions (glycerol as matrix). Elemental analyses (CHN) were carried out on a Perkin-Elmer 2400CHN elemental analyzer. IR spectra were measured on a HORIBA FT-720 infrared spectrometer.

All reactions were carried out under N_2, unless noted otherwise. THF and diethyl ether were freshly distilled from Na–benzophenone. Methanol was distilled from magnesium. All other solvents were distilled from CaH_2. Column chromatography was carried out on Merck silica gel 7734 (63–200 mesh). Preparative thin layer chromatography was carried out on plates of Merck silica gel 60 GF_{254}.

Dimethyl 2-But-3-enylmalonate (16). NaH (1.42 g, 35.4 mmol) was washed with hexane (2 times) and dried under vacuum. THF (150 mL) was added, and the suspension was cooled to 0 °C. Methyl malonate (**9**) (3.80 mL, 33.2 mmol) was added, and the mixture was stirred at the same temperature. After 25 min, 4-bromo-1-butene (3.0 mL, 29.5 mmol) and TBAI (3.27 g, 8.85 mmol) were added. The solution was allowed to warm to room temperature and was then refluxed for 19 h. The mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **16** (5.16 g, 27.7 mmol, 94%) as a colorless oil. $R_f = 0.34$ (silica gel, hexane/EtOAc = 6:1 v/v); IR (neat) 3077, 2954, 1735, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (tdd, $J = 6.7$, 10.4, 17.1 Hz, 1H), 5.04 (dd, $J = 1.5$, 17.1 Hz, 1H), 5.03–5.00 (m, 1H), 3.74 (s, 6H), 3.40 (t, $J = 7.3$ Hz, 1H), 2.10 (q, $J = 6.7$ Hz, 2H), 2.05–1.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 (×2), 136.7, 115.9, 52.3 (×2), 50.7, 31.2, 27.8. HRMS (EI): Calcd for $C_9H_{14}O_4$: 186.0892. Found: 186.0901.

Dimethyl 2-(But-3-enyl)-2-methylmalonate (17). To a suspension of cesium carbonate (7.76 g, 23.8 mmol) in DMF (80 mL) was added a solution of compound **16** (3.69 g, 19.8 mmol)

in DMF (20 mL) at room temperature, and the mixture was stirred for 15 min. Methyl iodide (5.00 mL, 80.3 mmol) was then added. After 21 h, the mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6:1 v/v) to afford **17** (3.64 g, 18.2 mmol, 92%) as a colorless oil. $R_f = 0.61$ (silica gel, hexane/EtOAc = 5:1 v/v); IR (neat) 3077, 2954, 1735, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.79 (tdd, J = 6.1, 10.4, 16.9 Hz, 1H), 5.04 (dd, J = 1.5, 16.9 Hz, 1H), 4.97 (dd, J = 1.5, 10.4 Hz, 1H), 3.74 (s, 6H), 2.05–1.94 (m, 4H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6 (×2), 137.4, 114.9, 53.3, 52.3 (×2), 34.8, 28.6, 19.9. HRMS (EI): Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1054.

2-(But-3-enyl)-2-methylpropane-1,3-diol (18). To a suspension of $LiAlH_4$ (1.49 g, 39.2 mmol) in THF (150 mL) was added a solution of compound **17** (3.93 g, 19.6 mmol) in THF (50 mL) at 0 °C and the mixture was stirred for 5 h at this temperature. Then, the mixture was quenched with 1 M HCl and filtered through celite. The aqueous layer was extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4:1 v/v) to afford **18** (2.71 g, 18.8 mmol, 96%) as a colorless oil. $R_f = 0.27$ (silica gel, hexane/EtOAc = 4:1 v/v); IR (neat) 3467, 3077, 2931, 2877, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.83 (tdd, J = 6.7, 10.4, 17.1 Hz, 1H), 5.03 (dd, J = 1.5, 17.1 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 3.53 (d, J = 10.7 Hz, 2H), 3.49 (d, J = 10.7 Hz, 2H), 2.07–2.01 (m, 2H), 1.42–1.37 (m, 2H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 114.2, 69.6 (×2), 38.7, 33.0, 28.0, 18.3. HRMS (EI): Calcd for $C_8H_{16}O_2$: 144.1150. Found: 144.1149.

2-(*t*-Butyldimethylsilanyloxymethyl)-2-methylhex-5-en-1-ol (19). NaH (660.0 mg, 16.5 mmol) was washed with hexane (2 times) and dried under vacuum. DMF (50 mL) was added, and the suspension was cooled to 0 °C. A solution of compound **18** (2.17 g, 15.0 mmol) in DMF (5.0 mL) was added, and the mixture was stirred at this temperature. After 45 min, *t*-butyldimethylsilyl chloride (2.49 g, 16.5 mmol) was added. The solution was allowed to warm to room temperature and was then stirred for 8 h. The mixture was quenched with water, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1 v/v) to afford **19** (3.51 g, 13.6 mmol, 90%) as a colorless oil. $R_f = 0.80$ (silica gel, hexane/EtOAc = 3:1 v/v); IR (neat) 3432, 3077, 2954, 2857, 1643, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.83 (tdd, J = 6.7, 10.4, 17.1 Hz, 1H), 5.02 (dd, J = 1.5, 17.1 Hz, 1H), 4.94 (d, J = 10.4, 1H), 3.52 (d, J = 9.8, 1H), 3.50 (s, 2H), 3.48 (d, J = 9.8, 1H), 2.12–1.96 (m, 2H), 1.47 (ddd, J = 5.5, 11.9, 13.4 Hz, 1H), 1.36 (ddd, J = 5.5, 11.9, 13.4 Hz, 1H), 0.90 (s, 9H), 0.81 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.3, 114.1, 71.4, 70.7, 38.7, 33.2, 27.8, 25.9 (×3), 18.5, 18.1, −5.70 (×2). HRMS (EI): Calcd for $C_{10}H_{21}O_2Si$ ($-^t$Bu): 201.1311. Found: 201.1308.

2-(*t*-Butyldimethylsilanyloxymethyl)-2-methylhex-5-enal (20). To a solution of DMSO (6.00 mL, 77.6 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added oxalyl chloride (5.00 mL, 57.3 mmol). After 20 min, a solution of compound **19** (4.90 g, 18.9 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred at that temperature for 30 min. Then, triethylamine (40.0 mL, 0.287 mol) was added, and the reaction mixture was allowed to gradually warm to room temperature. After 9 h, the mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1 v/v) to afford **20** (4.71 g, 18.3 mmol, 97%) as a colorless oil. $R_f = 0.80$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3081, 2954, 2857, 1731, 1643, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.56 (s, 1H), 5.78 (tdd, J = 6.7, 10.4, 17.1 Hz, 1H), 5.02 (dd, J = 1.5, 17.1 Hz, 1H), 4.99 (dd, J = 1.5, 10.4 Hz, 1H), 3.67 (d, J = 10.1 Hz, 1H), 3.58 (d, J = 10.1 Hz, 1H), 2.06–1.91 (m, 2H), 1.67 (ddd, J = 5.5, 11.6, 14.0 Hz, 1H), 1.53 (ddd, J = 5.5, 11.6, 14.0 Hz, 1H), 1.04 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.1, 138.3, 114.8, 66.8, 51.1, 31.5, 28.0, 25.7, 18.2, 16.0, −5.7. HRMS (EI): Calcd for $C_{10}H_{19}O_2Si$ ($-^t$Bu): 199.1154. Found: 199.1144.

Methyl 4-(*t*-Butyldimethylsilanyloxymethyl)-4-methylocta-2,7-dienoate (21). NaH (1.23 g, 30.8 mmol) was washed with hexane (2 times) and dried under vacuum. THF (300 mL) was added, and the mixture was cooled to 0 °C. Trimethyl phosphonatoacetate (4.50 mL, 30.9 mmol) was added, and the mixture was stirred at this temperature. After 30 min, a solution of compound **20** (5.25 g, 20.5 mmol) in THF (15 mL) was added, and the reaction mixture was allowed to warm to room temperature. After 10 h, the mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **21** (6.14 g, 19.66 mmol, 96%) as a colorless oil. $R_f = 0.60$ (silica gel, hexane/EtOAc = 20:1 v/v); IR (neat) 3077, 2954, 2857, 1727, 1654, 1643, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, J = 16.1 Hz, 1H), 5.78 (d, J = 16.1 Hz, 1H), 5.83–5.74 (m, 1H), 5.00 (dd, J = 1.8, 17.1 Hz, 1H), 4.98 (dd, J = 1.8, 10.1 Hz, 1H), 3.74 (s, 3H), 3.42 (d, J = 9.8 Hz, 1H), 3.40 (d, J = 9.8 Hz, 1H), 2.02–1.87 (m, 2H), 1.58–1.43 (m, 2H), 1.02 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 155.1, 138.8, 119.4, 114.3, 69.6, 51.4, 42.1, 36.0, 28.4, 25.8, 20.2, 18.2, −5.6. HRMS (EI): Calcd for $C_{13}H_{23}O_3Si$ ($-^t$Bu): 255.1416. Found: 255.1412.

Methyl 4-(*t*-Butyldimethylsilanyloxymethyl)-4-methyloct-7-enoate (22). A solution of compound **21** (1.89 g, 6.05 mmol) in dry MeOH (5 mL) was added to Mg (2.20 g, 90.5 mmol) in dry MeOH (65 mL) at room temperature. The mixture was stirred for 3 h and then refluxed for 3 h. The reaction mixture was then poured into 1 M HCl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1 v/v) to afford **22** (1.73 g, 5.49 mmol, 91%) as a colorless oil. $R_f = 0.47$ (silica gel, hexane/EtOAc = 15:1 v/v); IR (neat) 3077, 2954, 2857, 1743, 1643, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.79 (tdd, J = 6.7, 10.4, 17.1 Hz, 1H), 4.99 (dd, J = 1.8, 17.1 Hz, 1H), 4.91 (dd, J = 1.8, 10.4 Hz, 1H), 3.66 (s, 3H), 3.28 (d, J = 9.8 Hz, 1H), 3.26 (d, J = 9.8 Hz, 1H), 2.29–2.25 (m, 2H), 2.00–1.95 (m, 2H), 1.62–1.58 (m, 2H), 1.32–1.28 (m, 2H), 0.88 (s, 9H), 0.80 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 139.4, 114.0, 69.0, 51.9, 37.2, 35.7, 31.8, 29.0, 27.9, 25.8, 21.5, 18.2, −5.6. HRMS (EI): Calcd for $C_{13}H_{25}O_3Si$ ($-^t$Bu): 257.1573. Found: 257.1568.

Dimethyl 2-(3-Methylbut-3-enyl)malonate (23). NaH (4.06

g, 102 mmol) was washed with hexane (2 times) and dried under vacuum. THF (300 mL) was added, and the suspension was cooled to 0 °C. Dimethyl malonate (13.5 mL, 118 mmol) was added, and the mixture was stirred at this temperature. After 15 min, a solution of 3-methyl-3-butenyl tosylate (18.8 g, 78.2 mmol) in THF 10 mL was added. The solution was allowed to warm to room temperature and was then refluxed for 20 h. The mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **23** (14.73 g, 73.6 mmol, 94%) as a colorless oil. $R_f = 0.20$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3077, 2954, 2850, 1735, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.67 (s, 1H), 4.69 (s, 1H), 3.74 (s, 6H), 3.42–3.35 (m, 1H), 2.08–2.03 (m, 4H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8 (×2), 143.9, 111.1, 52.4, 51.0 (×2), 35.2, 26.6, 22.2. HRMS (EI): Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1051.

Methyl 5-Methylhex-5-enoate (24). To a solution of compound **23** (4.37 g, 21.8 mmol) in distilled DMF (30 mL) were added water (0.80 mL, 44.4 mmol) and NaCl (1.28 g, 21.9 mmol). The mixture was refluxed for 28 h, and then cooled to room temperature. The reaction mixture was poured into water and extracted with ether. The organic extracts were combined, washed with water (2 times) and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **24** (2.59 g, 18.1 mmol, 83%) as a colorless oil. $R_f = 0.52$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3073, 2950, 2854, 1743, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.73 (s, 1H), 4.68 (s, 1H), 3.67 (s, 3H), 2.31 (t, $J = 7.6$ Hz, 2H), 2.04 (t, $J = 7.6$ Hz, 2H), 1.78 (quint, $J = 7.6$ Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 144.7, 110.6, 51.4, 37.0, 33.4, 22.7, 22.1. HRMS (EI): Calcd for $C_8H_{14}O_2$: 142.0994. Found: 142.0992.

5-Methylhex-5-enoic Acid (27). A solution consisting of compound **24** (245.0 mg, 1.72 mmol), 5% NaOH (1.8 mL), and 95% EtOH (2.5 mL) was refluxed for 3 h. After cooling, the reaction mixture was acidified with 6 M HCl and extracted with ether. The organic extracts were combined, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by bulb-to-bulb distillation (60 °C, ca. 1 mmHg) to afford **27** (212 mg, 1.65 mmol, 96%) as a colorless oil. $R_f = 0.66$ (silica gel, CH_2Cl_2/MeOH = 30:1 v/v); IR (neat) 3077, 2938, 1712, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.75 (s, 1H), 4.70 (s, 1H), 2.36 (t, $J = 7.6$ Hz, 2H), 2.07 (t, $J = 7.6$ Hz, 2H), 1.79 (quint, $J = 7.6$ Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.2, 144.5, 110.8, 36.9, 33.4, 22.4, 22.1. HRMS (FAB(+)): Calcd for $C_7H_{13}O_2$: 129.0915. Found: 129.0909.

Methyl 2-[2-(*t*-Butyldimethylsilanyloxymethyl)-2-methylhex-5-enyl]-7-methyl-3-oxooct-7-enoate (29). To a solution of the $(i\text{-Pr})_2NH$ (0.50 mL, 3.6 mmol) in THF (30 mL) at −78 °C was added dropwise a solution of *n*-BuLi (2.40 mL, 3.74 mmol; 1.56 M in hexane). The mixture was stirred at this temperature for 10 min and then at 0 °C for 5 min, and then cooled to −78 °C. A solution of compound **22** (330.8 mg, 1.05 mmol) in THF (5.0 mL) was added to the reaction mixture, and the solution was stirred at −78 °C for 30 min. On the other hand, to the solution of compound **27** (363.5 mg, 2.83 mmol) in THF (55.0 mL) were added triethylamine (0.60 mL, 4.30 mmol) and pivaloyl chloride (0.55 mL, 4.5 mmol) at 0 °C. The mixture was stirred for 40 min and cooled to −78 °C. The solution including compound **22** and LDA was transferred at −78 °C into the solution containing compound **28**, and the reaction mixture was allowed to warm to room temperature gradually. After 14 h, the mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50:1 v/v) to afford **29** (279 mg, 0.658 mmol, 63%) as a yellow oil. $R_f = 0.66$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3077, 2954, 2941, 2857, 1747, 1716, 1643, 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.77 (tdd, $J = 6.7$, 10.4, 17.1 Hz, 1H), 4.99 (dd, $J = 1.5$, 17.1 Hz, 1H), 4.92 (d, $J = 10.4$ Hz, 1H), 4.73 (s, 1H), 4.67 (s, 1H), 3.71 ⟨3.70⟩ (s, 3H), 3.67–3.62 (m, 1H), 3.28 (t, $J = 10.1$ Hz, 1H), 3.33–3.24 (m, 1H), 2.59–2.45 (m, 2H), 2.02–1.85 (m, 6H), 1.72 (quint, $J = 7.3$ Hz, 2H), 1.70 (s, 3H), 1.35–1.23 (m, 2H), 0.89 (s, 9H), 0.77 ⟨0.75⟩ (s, 3H), 0.03 ⟨0.03⟩ (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2 ⟨205.1⟩, 171.1, 144.9, 139.2, 114.1, 110.6, 69.4 ⟨69.1⟩, 55.1 ⟨55.0⟩, 52.4, 40.7 ⟨40.7⟩, 37.7 ⟨37.7⟩, 36.9, 36.5, 35.7, 34.7 ⟨34.6⟩, 27.9 ⟨27.9⟩, 25.9, 22.1, 21.7, 21.3 ⟨21.3⟩, 21.1 ⟨21.1⟩, 18.2, −5.5 ⟨−5.6⟩. HRMS (EI): Calcd for $C_{20}H_{35}O_4Si$ ($-{}^t$Bu): 367.2305. Found: 367.2296.

Methyl 2-(2-Formyl-2-methylhex-5-enyl)-7-enoate (6). To a solution of compound **29** (370.0 mg, 0.872 mmol) in THF (6 mL) was added TBAF (5.3 mL, 5.3 mmol; 1 M in THF), and the mixture was stirred for 20 min. The reaction mixture was poured into water and extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue containing the alcohol was used for the subsequent reaction without purification. To a solution of pyridine (1.80 mL, 22.2 mmol) in CH_2Cl_2 (15 mL) was added CrO_3 (1.09 g, 10.9 mmol), and the mixture was stirred for 25 min at 0 °C. A solution of the alcohol in CH_2Cl_2 (2 mL) was transferred at 0 °C into the solution containing $CrO_3 \cdot 2Py$ complex, and the reaction mixture was allowed to warm to room temperature gradually. After 4 h, the reaction mixture was added to ether (200 mL) and quenched with 5% NaOH, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with 5% NaOH, 1 M HCl, sat. $NaHCO_3$, and brine, dried over K_2CO_3, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **6** (116 mg, 0.377 mmol, 43% in 2 steps) as a yellow oil. $R_f = 0.19$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3073, 2938, 2854, 1739, 1712, 1623 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.35 ⟨9.34⟩ (s, 1H), 5.85–5.69 (m, 1H), 5.01 (dd, $J = 1.5$, 17.1 Hz, 1H), 4.96 (d, $J = 10.4$ Hz, 1H), 4.72 (s, 1H), 4.65 (s, 1H), 3.70 ⟨3.69⟩ (s, 3H), 3.44 (t, $J = 6.1$ Hz, 1H), 2.66–2.54 (m, 2H), 2.24–2.25 (m, 2H), 2.11–1.90 (m, 4H), 1.70–1.62 (m, 2H), 1.69 (s, 3H), 1.54–1.43 (m, 2H), 1.02 ⟨1.00⟩ (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0 ⟨205.0⟩, 204.3, 170.2, 144.8, 137.6, 115.2, 110.7, 54.5 ⟨54.5⟩, 52.6, 48.5 ⟨48.4⟩, 41.3, 36.7, 35.0, 32.6, 28.0, 22.3 ⟨22.1⟩, 21.1, 17.9. HRMS (EI): Calcd for $C_{18}H_{28}O_4$: 308.1988. Found: 308.1974.

Methyl 5-But-3-enyl-5-methyl-2-(4-methylpent-4-enyl)-4,5-dihydropyridine-3-carboxylate (5) and Methyl 3-Methyl-9-(4-methylpent-4-enyl)-8-azatricyclo[4.3.1.0^{3,7}]dec-8-ene-1-carboxylate (31). To a solution of compound **6** (15.4 mg, 0.050 mmol) in a mixture of benzene and AcOH (1.5 mL, 5:1) was added NH_4OAc (38.5 mg, 0.499 mmol). The mixture was refluxed for 18 h with the Dean-Stark apparatus and then cooled to room temperature. The mixture was quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and

concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **5** (4.5 mg, 0.016 mmol, 32%) as a pale yellow oil and an intramolecular Diels–Alder product **31** (5.4 mg, 0.019 mmol, 38%) as a pale yellow oil. Compound **5**: $R_f = 0.56$ (silica gel, hexane/EtOAc = 3:1 v/v); IR (neat) 3463, 3316, 3077, 2946, 2850, 1735, 1662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.79 (tdd, $J = 6.7$, 10.4, 17.1 Hz, 1H), 5.75 (s, 1H), 4.99 (dd, $J = 1.5$, 17.1 Hz, 1H), 4.92 (d, $J = 10.4$ Hz, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 3.70 (s, 3H), 2.38 (d, $J = 15.2$ Hz, 1H), 2.31–2.26 (m, 2H), 2.23 (d, $J = 15.2$ Hz, 1H), 2.19–2.14 (m, 2H), 2.05–1.99 (m, 2H), 1.75 (s, 3H), 1.50–1.43 (m, 1H), 1.39–1.32 (m, 1H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 152.5, 144.7, 143.0, 139.3, 130.9, 114.0, 110.6, 50.5, 39.6, 36.8, 34.4, 33.4, 29.2, 28.9, 27.2, 25.2, 22.6. HRMS (EI): Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2030.

Compound **31**: $R_f = 0.31$ (silica gel, hexane/EtOAc = 3:1 v/v); IR (neat) 3471, 3073, 2950, 2869, 1731, 1627 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.70 (s, 1H), 4.66 (s, 1H), 3.88 (d, $J = 4.6$ Hz, 1H), 3.76 (s, 3H), 2.37 (dd, $J = 7.0$, 9.1 Hz, 2H), 2.11–2.06 (m, 1H), 2.03 (t, $J = 7.6$ Hz, 2H), 1.99–1.92 (m, 1H), 1.92–1.85 (m, 1H), 1.73–1.66 (m, 2H), 1.70 (s, 3H), 1.62–1.53 (m, 4H), 1.42–1.35 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 174.7, 145.2, 110.3, 69.2, 51.9, 48.9, 44.0, 40.9, 38.1, 38.0, 37.5, 34.4, 34.1, 29.4, 26.4, 23.7, 22.2. HRMS (EI): Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2029.

Attempted RCM Reaction of 5. To a solution of compound **5** (12.7 mg, 0.0439 mmol) in CH_2Cl_2 (5.0 mL) was added the 2nd generation Grubbs catalyst (5.1 mg, 0.0060 mmol), and the mixture was refluxed for 1 day. Then, the solvent was evaporated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford dimeric compound **32** (4.30 mg, 0.0078 mmol) as a pale yellow oil instead of the desired product **4**. $R_f = 0.16$ (silica gel, hexane/EtOAc = 5:1 v/v); ^1H NMR (500 MHz, $CDCl_3$): δ 5.77–5.73 (br, 2H), 5.35 (d, $J = 4.0$ Hz, 2H), 4.76 (s, 2H), 4.70 (s, 2H), 3.70 ⟨3.69⟩ (s, 6H), 2.40–2.34 (m, 2H), 2.31–2.26 (m, 4H), 2.25–2.19 (m, 2H), 2.19–2.14 (m, 4H), 2.00–1.90 (m, 4H), 1.74 (s, 6H), 1.45–1.38 (m, 2H), 1.34–1.27 (m, 2H), 0.97 ⟨0.96⟩ (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 152.5, 144.7, 143.2, 136.9, 131.2, 110.6, 50.5, 39.9, 36.8, 34.4, 33.7, 29.2, 28.8, 27.2, 25.2, 22.6. HRMS (EI): Calcd for $C_{34}H_{50}N_2O_4$: 550.3771. Found: 550.3745.

5-(But-3-enyl)-5-methyltetrahydropyran-2-one (33). A solution consisting of compound **22** (615.8 mg, 1.96 mmol), 1 M HCl (5.0 mL), water (15 mL), and THF (20 mL) was refluxed for 40 h. After cooling, the reaction mixture was quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with ether. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1 v/v) to afford **33** (265.6 mg, 1.58 mmol, 81%) as a colorless oil. $R_f = 0.32$ (silica gel, hexane/EtOAc = 3:1 v/v); IR (neat) 3077, 2962, 2931, 1739, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.80 (tdd, $J = 6.7$, 10.4, 17.1 Hz, 1H), 5.02 (dd, $J = 1.5$, 17.1 Hz, 1H), 4.98 (dd, $J = 1.5$, 10.4 Hz, 1H), 4.04 (d, $J = 11.3$ Hz, 1H), 3.96 (d, $J = 11.3$ Hz, 1H), 2.54 (t, $J = 7.3$ Hz, 2H), 2.11–2.02 (m, 2H), 1.80–1.72 (m, 1H), 1.71–1.64 (m, 1H), 1.44 (t, $J = 8.5$ Hz, 2H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 138.0, 114.9, 77.3, 36.8, 32.1, 31.1, 27.8, 27.1, 22.0. HRMS (EI): Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1148.

5-(But-3-enyl)-3-(5-methyl-1-oxo-5-hexenylidene)-5-methyltetrahydropyran-2-one (34). To a solution of the $(i\text{-Pr})_2NH$ (0.125 mL, 0.954 mmol) in THF (3.5 mL) at −78 °C was added dropwise *n*-BuLi (0.580 mL, 0.911 mmol; 1.56 M in hexane). The mixture was stirred at this temperature for 20 min and then cooled to −78 °C. A solution of compound **33** (73.0 mg, 0.434 mmol) in THF (1.0 mL) was added to the reaction mixture, and the solution was stirred at −78 °C for 30 min. On the other hand, to a solution of compound **27** (83.4 mg, 0.651 mmol) in THF (3.5 mL) were added triethylamine (0.12 mL, 0.86 mmol) and pivaloyl chloride (0.10 mL, 0.81 mmol) at 0 °C. The mixture was stirred for 40 min and cooled to −78 °C. The solution containing compound **33** was transferred at −78 °C into the solution containing compound **28**, and the reaction mixture was allowed to gradually warm to room temperature. After 7 h, the mixture was quenched with sat. NH_4Cl, and the aqueous layer was extracted with ether. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **34** (41.8 mg, 0.150 mmol, 35%) as a pale yellow oil. $R_f = 0.38$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 3074, 2965, 2933, 1719, 1641, 1607; ^1H NMR (500 MHz, $CDCl_3$): δ 13.88 (s, 1H), 5.80 (tdd, $J = 6.7$, 10.4, 17.1 Hz, 1H), 5.02 (dd, $J = 1.8$, 17.1 Hz, 1H), 4.98 (d, $J = 10.4$ Hz, 1H), 4.75 (s, 1H), 4.70 (s, 1H), 3.98 (dd, $J = 1.2$, 11.0 Hz, 1H), 3.92 (dd, $J = 1.2$, 11.0 Hz, 1H), 2.27 (t, $J = 7.6$ Hz, 2H), 2.24 (d, $J = 14.3$ Hz, 1H), 2.18 (d, $J = 14.3$ Hz, 1H), 2.11–2.03 (m, 4H), 1.79–1.74 (m, 2H), 1.73 (s, 3H), 1.48–1.36 (m, 2H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.7, 179.3, 172.7, 144.8, 138.1, 114.9, 110.6, 91.4, 76.1, 37.2, 36.0, 34.8, 32.0, 31.3, 27.8, 23.8, 22.2, 21.4. HRMS (EI): Calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1880.

Attempted RCM Reaction of 34. To a solution of compound **34** (28.37 mg, 0.102 mmol) in CH_2Cl_2 (10.0 mL) was added the 2nd generation Grubbs catalyst (8.65 mg, 0.0102 mmol), and the mixture was refluxed for 8 h. The reaction mixture was then evaporated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1 v/v) to afford dimeric compound **36** (4.30 mg, 0.0078 mmol) as a pale yellow oil instead of the desired product **35**. $R_f = 0.26$ (silica gel, hexane/EtOAc = 3:1 v/v); ^1H NMR (500 MHz, $CDCl_3$): δ 13.87 (s, 2H), 5.42–5.39 (br, 2H), 4.75 (s, 2H), 4.70 (s, 2H), 3.98 (dd, $J = 1.2$, 11.0 Hz, 2H), 3.91 (dd, $J = 1.2$, 11.0 Hz, 2H), 2.29–2.23 (m, 4H), 2.22–2.15 (m, 4H), 2.11–1.97 (m, 8H), 1.79–1.73 (m, 4H), 1.73 (s, 6H), 1.44–1.30 (m, 4H), 0.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.7, 179.6, 172.5, 148.2, 144.8, 110.6 ⟨110.6⟩, 91.4, 75.7, 37.2, 36.6, 34.8, 32.0, 31.3, 26.4, 23.8, 22.2, 21.4. HRMS (EI): Calcd for $C_{32}H_{48}O_6$: 528.3451. Found: 528.3454.

Methyl 10-(*t*-Butyldimethylsilanyloxymethyl)-6,10-dimethyl-2-oxocycloundec-6-ene-1-carboxylate (37). To a solution of compound **29** (47.4 mg, 0.111 mmol) in CH_2Cl_2 (200 mL) was added the 2nd generation Grubbs catalyst (14.1 mg, 0.0167 mmol) in CH_2Cl_2 (5.0 mL), and the mixture was refluxed for 2 days. The reaction mixture was then evaporated and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 v/v) to afford **37** (15.9 mg, 0.040 mmol, 36%) as a pale yellow oil. $R_f = 0.66$ (silica gel, hexane/EtOAc = 10:1 v/v); IR (neat) 2954, 2931, 2861, 1751, 1712, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.26 (t, $J = 9.2$ Hz, 1H), 3.68 ⟨3.65⟩ (s, 3H), 3.33–3.20 (m, 2H), 2.90–2.79 (m, 1H), 2.68–2.59 (m, 1H), 2.52 (td, $J = 3.4$, 13.1 Hz, 1H), 2.12–1.87 (m, 3H), 1.75–1.52 (m, 5H), 1.66 ⟨1.65⟩ (s, 3H), 1.29–1.18 (m, 2H), 0.90 ⟨0.89⟩ (s, 9H), 0.87 ⟨0.81⟩ (s, 3H), 0.03 ⟨0.01⟩ (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.3 ⟨208.8⟩, 170.4 ⟨170.3⟩, 132.7 ⟨132.5⟩, 127.2 ⟨127.1⟩, 73.1, 69.3, 53.4, 52.6 ⟨52.5⟩, 41.3 ⟨41.2⟩, 38.7, 37.7, 35.8, 35.4, 34.6, 28.3 ⟨28.3⟩, 25.8 ⟨25.8⟩, 24.5, 23.4 ⟨23.3⟩, 23.1, 22.3, 18.8 ⟨18.8⟩,

−5.7 ⟨−5.8⟩. HRMS (EI): Calcd for $C_{18}H_{31}O_4Si$ ($-^tBu$): 339.1992. Found: 339.1979.

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