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Synthetic Efforts toward the Macrolactone Core of Leucascandrolide A

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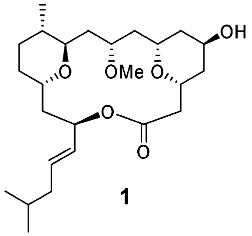

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A chemoselective synthesis of **1**, the macrocyclic core of leucascandrolide A, has been achieved by utilizing highly enantioselective allylmetalations, an enantioselective Noyori reduction of a propargylic ketone, and olefin metatheses as the key steps.

Leucascandrolide A was isolated in 1996 from the calcareous sponge *Leucascandra caveolata*,[1] which was collected along the east coast of New Caledonia. Although leucascandrolide A was isolated in a significant amount (70 mg from 240 g of sponge, 0.03%), further attempts to isolate leucascandrolide A from the sponge have proven unsuccessful since. In fact, this compound is not a metabolite of *Leucascandra* itself but rather that of an opportunistic bacteria that colonized the sponge.[2] The gross structure and relative configuration of leucascandrolide A were assigned on the basis of HRMS, MS−MS, ^{1}H NMR, ^{13}C NMR, and DEPT experiments, as well as elaborate 2D NMR studies. The absolute configurations were determined from degradation and Mosher ester analysis.[1] As shown in Figure 1, leucascandrolide A displays several distinctive architectural features. This compound is constituted by a 2,4-disubstituted oxazole on the lateral chain and an 18-membered macrolactone that encompasses two trisubstituted tetrahydropyrans (THP), one of which is a trans-2,6-disubstituted THP, and the second is a 2,6-cis-disubstituted THP. In all, eight stereogenic centers are present in the macrocyclic core of leucascandrolide A (Figure 1).

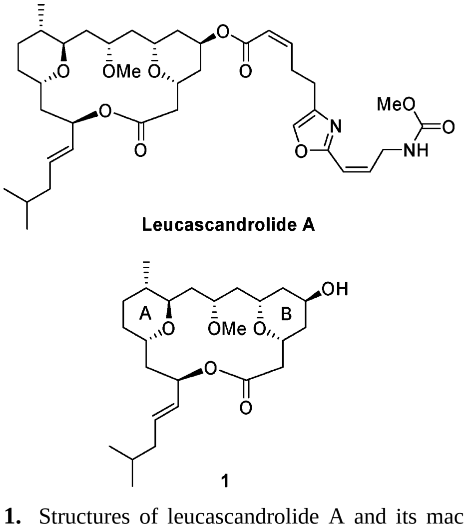

FIGURE 1. Structures of leucascandrolide A and its macrolactone core.

Leucascandrolide A displays a significant in vitro cytotoxicity (IC_{50} = 0.05 and 0.25 μg/mL with KB and P388 cells, respectively), as well as significant antifungal properties. Due to its structural complexity, its interesting biological properties and the lack of availability from natural sources, leucascandrolide A has sollicited considerable interest among organic chemists.[3−5] Recently, we reported the formal synthesis of leucascandrolide A,[6] and we would like to report here a full account of our synthetic studies toward the macrocyclic core of leucascandrolide A **1** by utilizing enantioselective reactions and olefin metatheses with chiral titanium complexes and ruthenium catalysts (Figure 2).

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[1] D'Ambrosio, M.; Guerriero, M.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51.

[2] D'Ambrosio, M.; Tato, M.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.

10.1021/jo701315h CCC: $40.75

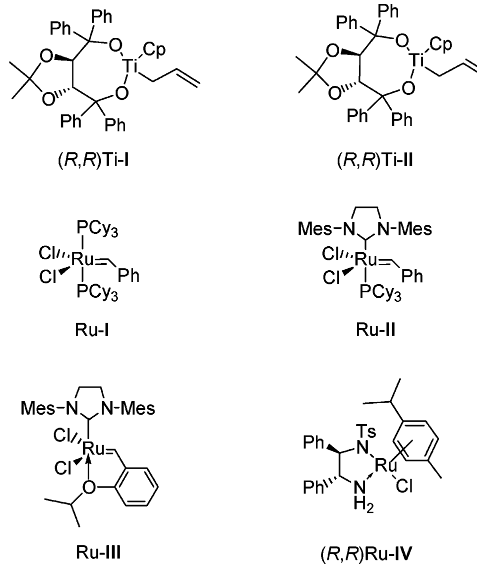
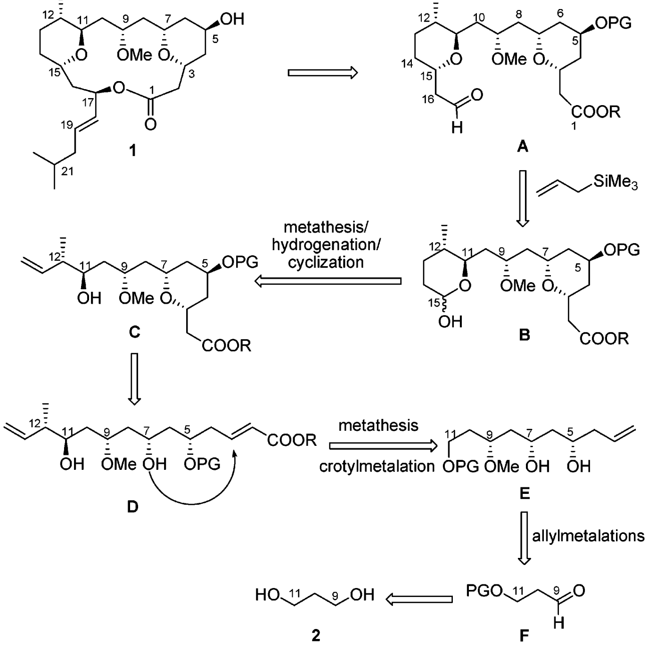


FIGURE 2. Chiral titanium complexes and ruthenium catalysts used in this study.

First Strategy

Our first retrosynthetic analysis for the synthesis of the macrocyclic core of leucascandrolide A, compound **1**, is illustrated in Scheme 1. Compound **1** would be obtained from aldehyde **A**, the C15 stereogenic center of which would be controlled by the addition of trimethylallylsilane on an oxonium species generated from lactol **B**. Lactol **B** would be prepared from **C** by using a one-pot sequence cross-metathesis (CM)/hydrogenation/cyclization utilizing acrolein as the CM partner.[7] The *cis*-THP present in **C** could be easily obtained from **D** through an intramolecular 1,4-addition of the hydroxyl group present at C7 on the unsaturated ester. This α,β-unsaturated ester would be built by using a cross-metathesis applied to compound **E** followed by a stereoselective crotylmetalation to control the stereogenic centers at C11 and C12. In order to control the C5, C7, and C9 stereogenic centers in **E**, iterative enantioselective allylmetalations applied to aldehyde **F** could be utilized. The starting aldehyde **F** would be easily prepared from 1,3-propanediol **2** (Scheme 1).

SCHEME 1



The synthesis of the C1−C12 fragment of leucascandrolide A started with the preparation of aldehyde **3**, easily accessible in two steps from 1,3-propanediol **2**.[8] Treatment of aldehyde **3** with allyltitanium complex (*R,R*)Ti-**I** (1.1 equiv, Et_2O, −78 °C)[9] led to the corresponding homoallylic alcohol which was directly transformed to the methyl ether **4**[10] (MeI, NaH, THF) with an overall yield of 76% for the two steps. In order to control the C7 stereogenic center, the required aldehyde for the enantioselective allylmetalation was easily obtained after ozonolysis of the terminal double bond present in **4**. Due to the instability of this aldehyde, the latter compound was directly treated with the highly face-selective allyltitanium complex (*R,R*)Ti-**I**. The resulting homoallylic alcohol was not fully purified but treated with TBSOTf (2.2 equiv) [2,6-lutidine (4.4 equiv), CH_2Cl_2, −78 °C] to produce the desired protected triol **5** in 68% yield for the three-step sequence (from **4**) and with a diastereomeric ratio superior to 95:5.[11]

In order to obtain the C5−C11 fragment and to control the C5 stereogenic center, olefin **5** was subjected to ozonolysis (O_3, PPh_3, CH_2Cl_2), leading to the corresponding aldehyde, which was engaged in a third enantioselective allyltitanation using the (*R,R*)Ti-**I** complex.[9] The obtained homoallylic alcohol was directly protected as a MOM ether (MOMCl, *i*-Pr_2NEt) to afford olefin **6** (67% overall yield from **5**) with an excellent diastereomeric ratio of 95/5.[10] In order to build up the *cis*-THP, by using an intramolecular 1,4-addition of an alcoholate on an unsaturated ester, a CM reaction between **6** and ethyl acrylate was achieved with Ru-**III** (2.5 mol %) to afford the α,β-unsaturated ester **7** in 85% yield. After selective deprotection of the primary alcohol (NH_4F, MeOH, reflux, 65% yield),[12]

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(3) a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. (b) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (c) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098. (d) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274. (e) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343. (f) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (g) Wang, Y.; Jelena, J.; Kozmin, S. A. *Pure Appl. Chem.* **2005**, *77*, 1161. (h) Su, Q.; Paneck, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223. (g) Su, Q.; Dakin, L. A.; Paneck, J. S. *J. Org. Chem.* **2005**, *72*, 2.

(4) For syntheses of the macrolide core of leucascandrolide A, see: (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (b) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (c) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934. (d) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 4641. (e) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641.

(5) For syntheses of other fragments of leucascandrolide A, see: (a) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 579. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (c) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242. (h) Dakin, L. A.; Langille, N. F.; Paneck, J. S. *J. Org. Chem.* **2002**, *67*, 6812. (g) Dakin, L. A.; Paneck, J. S. *Org. Lett.* **2003**, *5*, 3995.

(6) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461.

(7) Bargiggia, F. C.; Bouzbouz, S.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 6715.

(8) (a) Nacro, K.; Balats, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013−14030. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman *J. Am. Chem. Soc.* **1990**, 112, 6339.

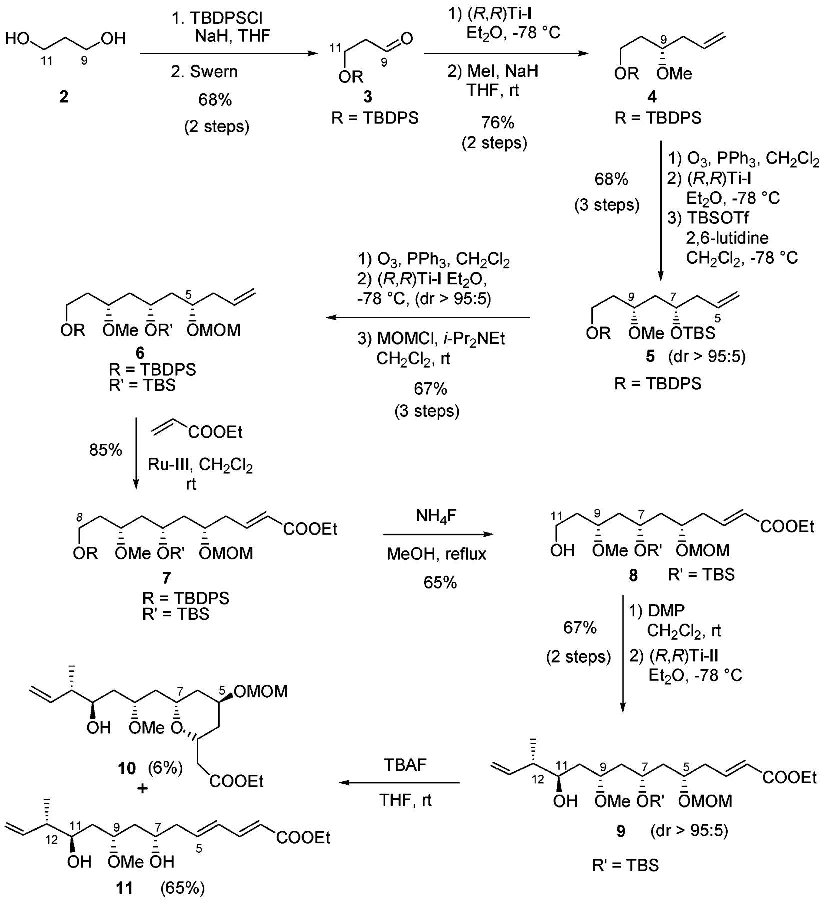
(9) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rhote-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(10) Paterson, I.; Ashton, K.; Britton, R.; Knust, H. *Org. Lett.* **2003**, *5*, 1963.

(11) dr based on the ^1H NMR spectra of the crude reaction mixture.

(12) Crich, D.; Herman, F. *Tetrahedron Lett.* **1993**, *34*, 3385.

SCHEME 2



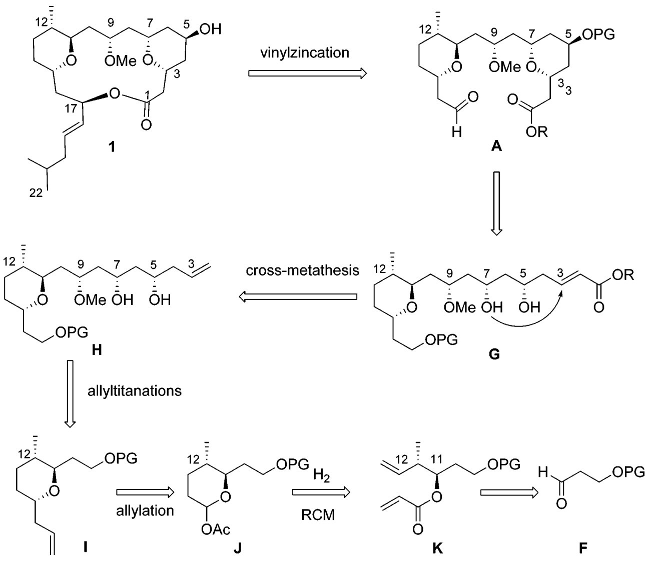
alcohol **8** was oxidized to the corresponding aldehyde (DMP, CH_2Cl_2, rt), which was directly treated with the highly face-selective crotyltitanium complex (*R*,*R*)Ti-**II**.[9] The homoallylic alcohol **9** was isolated in 65% yield with good diastereoselectivity (dr > 95:5).[10] Unfortunately, when compound **9** was treated with TBAF (5 equiv, THF, rt), a poor yield in the expected intramolecular 1,4-addition product **10** (6% yield) was obtained, accompanied by the (*E*,*E*)-dienoate **11** as the major product (65% yield), which is the result of the elimination of the methoxymethyl ether at C5 (Scheme 2).

At this point, a second strategy was considered, based again on a ring-closing metathesis to construct the *trans*-tetrahydropyran.

Second Strategy

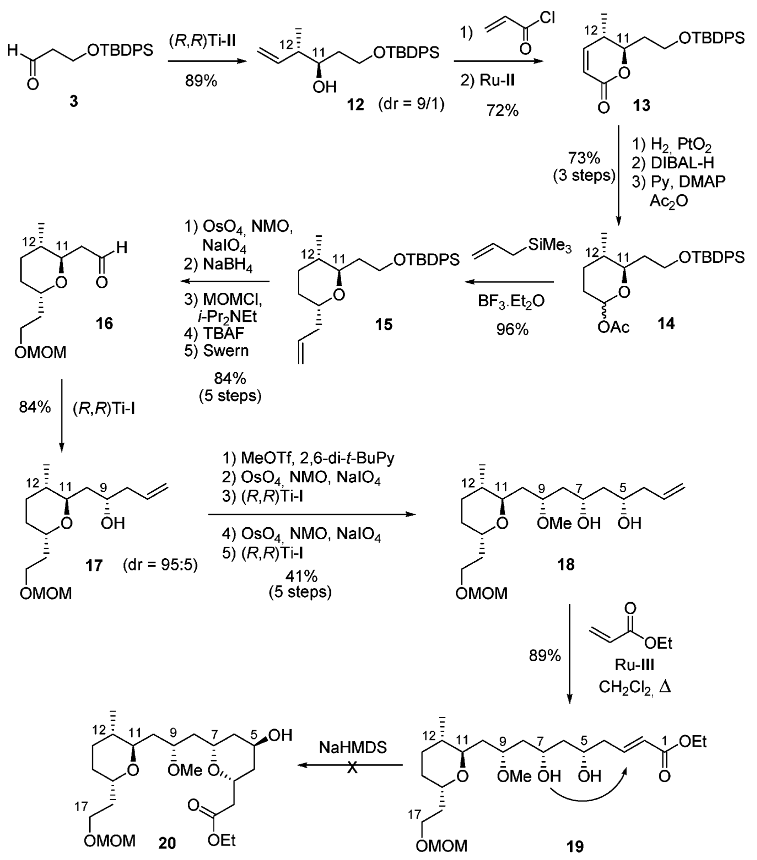
In this strategy, we envisioned to install at first the *trans*-THP instead of the *cis*-THP as in the previous strategy. The synthesis of the C1−C22 fragment of leucascandrolide A was envisaged from aldehyde ester **A**, and a vinylzincation of the aldehyde moiety would be used to control the C17 stereogenic center. As in our first strategy, an intramolecular 1,4-addition of the alkoxide at C7 on the unsaturated ester present in **G** would establish the *cis*-THP, and the unsaturated ester present in **G** would be assembled by using a cross-metathesis between **H** and ethyl acrylate. In compound **H**, the control of the stereogenic centers at C9, C7, and C5 would be achieved by using enantioselective allyltitanations applied to aldehydes. Tetrahydropyran **I**, precursor of **H**, would be obtained by allylation of an oxonium species obtained from lactol acetate **J**. This latter compound will be generated from a lactone, which will be the result of a ring-closing metathesis applied to dienic ester **K** (Scheme 3).

SCHEME 3

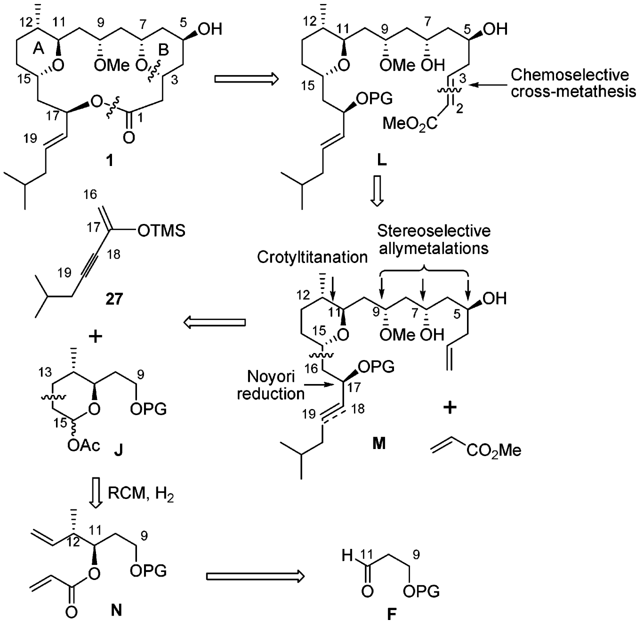


This new synthesis of the macrocyclic lactone of leucascandrolide A started with protected hydroxyaldehyde **3**.[8] To control the stereogenic centers at C11 and C12, aldehyde **3** was treated with the highly face-selective crotyltitanium complex (*R*,*R*)Ti-**II**.[9] The homoallylic alcohol **12** was isolated in 89% yield with

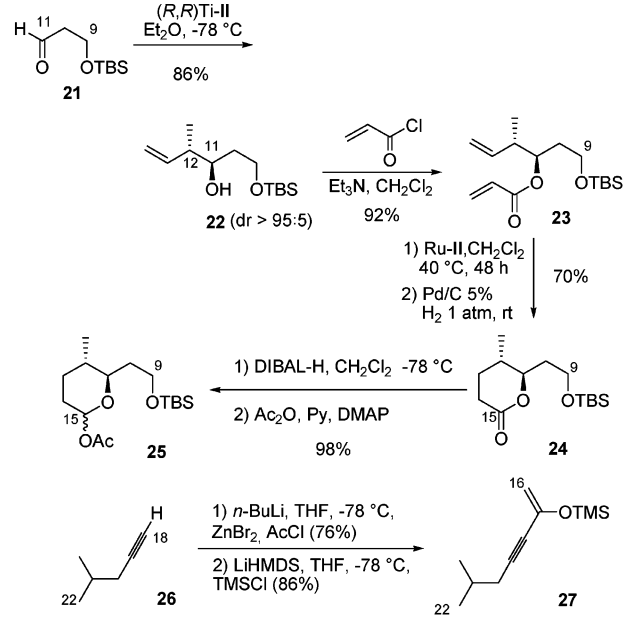
SCHEME 4



SCHEME 5



SCHEME 6



a 9:1 diastereomeric ratio.[13] The precursor of the *trans*-THP was achieved in six steps. After treatment of **12** with acryloyl chloride, the obtained dienic ester was submitted to a ring-closing metathesis (Ru-**II**),[14] and the unsaturated lactone **13** was obtained in 72% yield.[4b] After hydrogenation (H_2, PtO_2), reduction (DIBAL-H), and acetylation,[15] the acetoxylactol **14** was isolated (73% yield) and treated with trimethylallylsilane in the presence of $BF_3{\cdot}OEt_2$ to afford the *trans*-THP **15** in 96%

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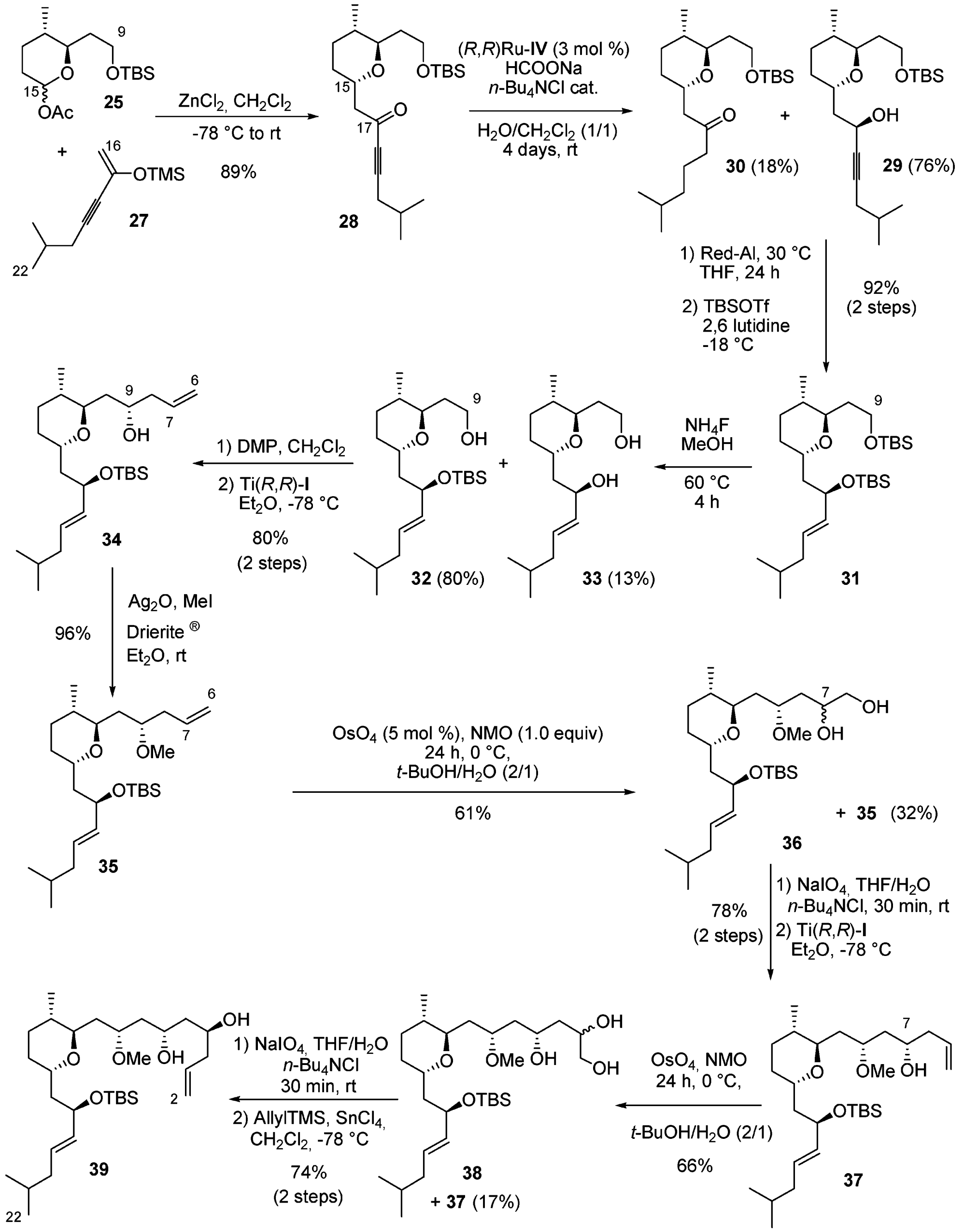
[13] Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001**; *66*; 2382.

[14] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[15] Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.

SCHEME 7



yield (dr = 9:1).[16] After an oxidative cleavage of the double bond in **15** (OsO$_4$/NaIO$_4$), reduction of the aldehyde (NaBH$_4$), protection of the alcohol (MOMCl, *i*-Pr$_2$NEt), selective deprotection (TBAF), and Swern oxidation (84% yield over five steps from **15**), the obtained aldehyde **16** was submitted to the (*R*,*R*)Ti-**I** allyltitanium complex[9] to afford the homoallylic alcohol **17** (84%, dr = 95/5).[10] After transformation of the newly created hydroxyl group at C8 into a methyl ether (MeOTf, 2,6-*tert*-butylpyridine),[17] the obtained compound was transformed to **18** by using two successive oxidative cleavage/allyltitanation sequences using the (*R*,*R*)Ti-**I** complex to control the stereogenic centers at C5 and C7. We have to point out that no protection of the hydroxyl group at C7 is required to run the second allyltitanation.[18] Compound **18** was transformed to the unsaturated ester **19** by using a CM reaction in the presence of ethyl acrylate in the aim of building up *cis*-THP by an intramolecular 1,4-addition. Unfortunately, treatment of **19** under basic conditions (NaHMDS, THF, −78 → 0 °C → rt) did not lead to the desired product **20** (Scheme 4). Due to this failure, a third strategy was then envisaged, utilizing chemoselective reactions in order to minimize the number of protecting groups.

Third Strategy[6]

In the third strategy, the formation of the *cis*-THP would be synthesized as previously by using an intramolecular 1,4-

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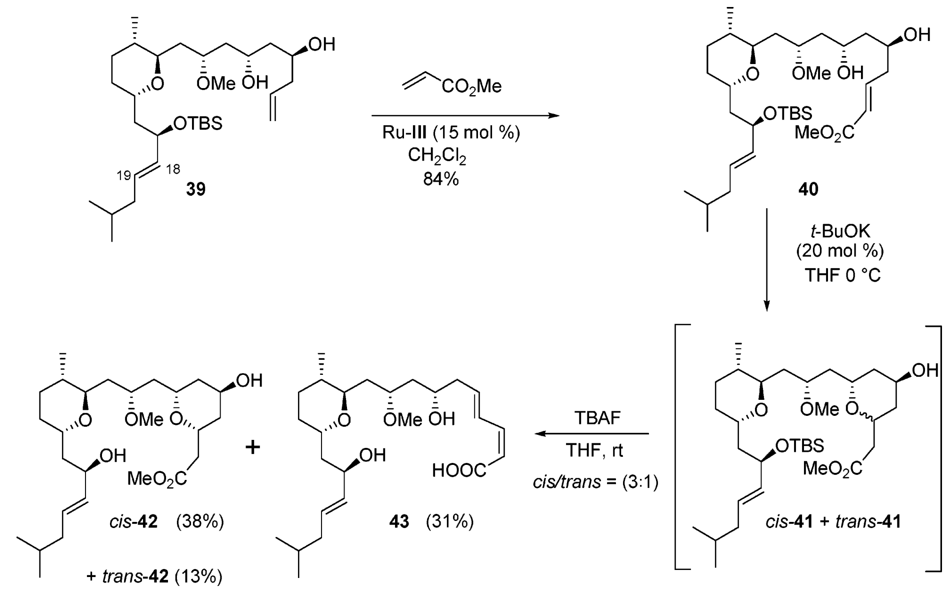
[16] (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803. (c) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1983**, *24*, 1563. (d) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (e) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.

[17] Walba, D. M.; Thurmes, W. H.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.

[18] BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501.

SCHEME 8



addition of the alkoxide at C7 on the unsaturated ester **L** which would be obtained from the homoallylic alcohol **M** by using a cross-metathesis reaction with methyl acrylate. As in our previous strategies, all the stereogenic centers at C5, C7, and C9 would be controlled by applying stereoselective allylmetalations to aldehydes, and the C11 and C12 stereogenic centers would be introduced by using an enantioselective crotylmetalation. However, contrary to the two previous approaches, the stereogenic center at C17 would be controlled at the beginning of the synthesis by applying a ruthenium-catalyzed Noyori reduction of a propargylic ketone. The addition of enol ether **27** to an oxonium species derived from **J** would allow us to control the stereogenic center at C15. In order to access the *trans*-THP, a RCM applied to diene **N**, which would be synthesized from the protected aldehyde **F**, was envisaged (Scheme 5).

By using this strategy, the synthesis of leucascandrolide A started with the preparation of the homoallylic alcohol **22**[8b] by adding (*R*,*R*)Ti-**II**[9] to aldehyde **21**, in order to control the stereogenic centers at C11 and C12. The desired homoallylic alcohol **22** was produced in 86% yield and with a dr superior to 95:5.[10]

After transformation of **22** to the unsaturated ester **23** (acryloyl chloride, Et$_3$N, CH$_2$Cl$_2$), two one-pot sequences were successfully applied to produce the desired acetoxy acetal **25**. The first one-pot reaction involved a tandem RCM/hydrogenation[7] [Ru-**II**[11] (3 mol %), 40 °C, then H$_2$, Pd/C] forming compound **24** in 70% yield.[4b] The second one-pot reaction was the transformation of **24** to **25** in 98% yield by reduction of lactone **24** with DIBAL-H followed by acylation of the alkoxy aluminum intermediate (Ac$_2$O, Py, DMAP).[13]

On the other hand, the known silyl enol ether **27**[3b] was prepared in two steps from the commercially available 4-methyl pent-1-yne **26**. The starting alkyne was acylated via an organozinc intermediate (*n*-BuLi, then ZnCl$_2$ and AcCl) providing the propargylic ketone (76% yield). This ketone was then treated with LiHMDS, and the lithium enolate was trapped with TMSCl to give the silyl enol ether **27** (86% yield) (Scheme 6).

Fragment C16−C22 was then coupled with the C9−C15 fragment by using a Mukaiyama-type reaction.[3b,4d] An oxonium intermediate was generated from **25** by treatment with ZnBr$_2$ at −78 °C and quenched with the enol ether **27** to afford compound **28** (trans/cis = 13/1, 89% yield).[19] In order to install the stereogenic center at C17, a Noyori reduction of propargylic ketone **28** was planned. However, when classical reaction conditions were used [(*R*,*R*)Ru-**IV** (1−5 mol %), HCOOH, Et$_3$N], the reduction also resulted in the removal of the TBS protecting group. When the reduction of **28** was achieved under non-classical phase-transfer conditions, using (*R*,*R*)Ru-**IV** (HCO$_2$-Na, *n*-Bu$_4$NCl, H$_2$O/CH$_2$Cl$_2$),[20] the desired propargylic alcohol **29** was isolated in 76% yield accompanied by ketone **30** (18% yield).[21] It is worth noting that the use of the 16-electron Noyori catalyst in *i*-PrOH was also tested, but in this case, alcohol **29** was also accompanied by the saturated ketone **30** and the amount of catalyst needed was higher (10 mol %). Propargyl alcohol **29** was reduced to the (*E*)-allylic alcohol utilizing Red-Al (8 equiv), but a partial deprotection of the primary TBS ether at C9 was observed. Due to the formation of this byproduct, the crude material was directly subjected to TBSOTf (2,6-lutidine, 92% yield over the two steps) to give compound **31**. The primary alcohol was chemoselectively deprotected (NH$_4$F, MeOH, 60 °C, 4 h)[12] to afford alcohol **32** (80% yield) along with diol **33** (13%). Despite the formation of byproduct **33**, this latter compound could be easily recycled to **31**. Once primary alcohol **32** was obtained, it was oxidized (Dess−Martin periodinane) to an unstable aldehyde which was directly treated with the highly face selective titanium complex (*R*,*R*)Ti-**I**[9] to produce homoallylic alcohol **34** (80% yield from **32**, dr > 95:5).[10] The hydroxyl group at C9 in compound **34** was then transformed to a methyl ether (Ag$_2$O, MeI, 96% yield), leading to compound **35**. In order to introduce the stereogenic center at C7 by allylation, compound **35** had to be converted to an aldehyde by oxidative cleavage of the terminal double bond. However, it was necessary to perform a selective cleavage of the terminal double bond over the internal C18−C19 double bond. To realize this chemoselective transformation, the internal double bond was

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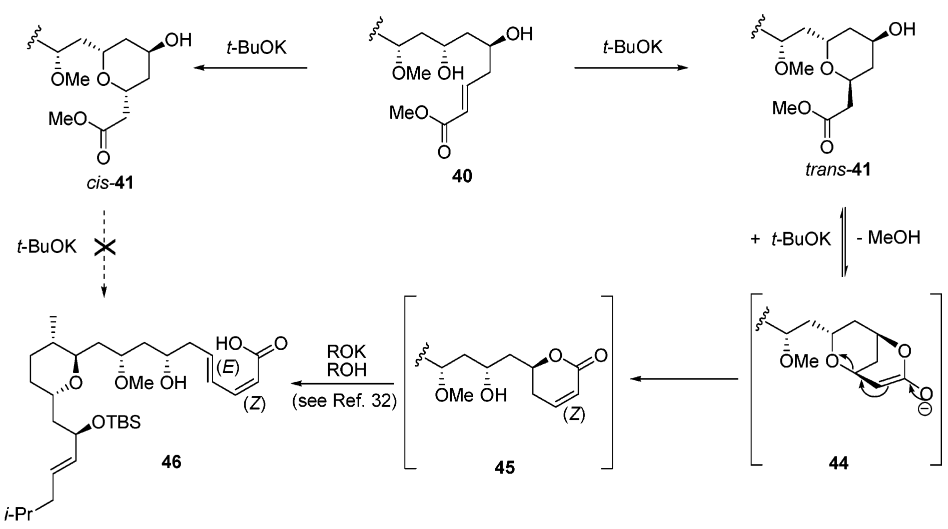
(19) Trans/cis ratio determined by GC/MS and GC analysis.

(20) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(21) A single diastereoisomer was observed by GC and NMR.

SCHEME 9



protected by the use of the sterically hindered TBS group at C17.[22] A dihydroxylation of **35** (OsO_4, NMO) led chemoselectively to diol **36** (61% yield, 32% unreacted starting material, dr = 1:1), which was then treated with $NaIO_4$ to furnish the desired aldehyde. This aldehyde was directly subjected to an enantioselective allylation using (*R*,*R*)Ti-**II**[9] to produce homoallylic alcohol **37** (78% from diol **36**). In order to control the stereogenic center at C5, alcohol **37** was transformed to an aldehyde using again the same chemoselective two-step oxidative cleavage. At first, triol **38** was obtained by dihydroxylation (OsO_4, 66% yield, 17% starting material recovered, dr = 1:1), and subsequent oxidative cleavage by $NaIO_4$ led to the corresponding aldehyde. At this stage, the stereodirected introduction of the C5 stereocenter was envisaged by using a stereoselective allylstannylation.[23] The unstable β-hydroxy aldehyde was directly treated with a solution of $allylSnCl_3$ in CH_2Cl_2 at −78 °C (prepared from allyltrimethylsilane and $SnCl_4$ at rt)[24] and was transformed to the *syn*-1,3-diol **39** (74% yield, two steps from **38**) (Scheme 7). The origin of the chiral induction giving the *syn*-diol in this reaction is not clear. Some stereodirected allylmetalations involving a chelation between the allylmetal and β-hydroxyaldehyde have been reported in the literature, but these reactions give the *anti*-diol.[25] This syn diastereoselectivity could be obtained via an internal delivery of the allyl moiety as it is obtained when β-allylsilyloxyaldehydes are treated with $TiCl_4$[26] (Scheme 7).

At this point of the synthesis, seven of the eight stereogenic centers of leucascandrolide A were installed. To complete the synthesis of macrolactone **1** and to introduce the last stereogenic center at C3, an intramolecular 1,4-addition of the hydroxyl group at C7 to an α,β-unsaturated ester was still envisaged. Compound **39** was treated with methyl acrylate in the presence of Hoveyda−Grubbs catalyst Ru-**III**[27] (15 mol %) to provide chemoselectively the unsaturated ester **40** (84% yield).[28] The elaboration of the *cis*-THP was realized under basic conditions using a catalytic amount of *t*-BuOK[29] (20 mol %), which afforded two diastereoisomers, *cis*-**41** and *trans*-**41**, in a modest ratio of 3:1. The two epimers *cis*-**41** and *trans*-**41** were difficult to separate at this stage, but fortunately, they were separable by column chromatography on silica gel in the next step. After treatment with TBAF in THF, diol **42** was isolated as a single cis diastereoisomer (38% over the two steps)[30] accompanied by the (*Z*,*E*)-dienoic acid **43** in 31% yield (Scheme 8).

The formation of **43** can be rationalized by the fact that during the reaction with *t*-BuOK, unsaturated ester **40** was transformed to a mixture of *cis*-**41** and *trans*-**41**.[31] When *cis*-**41** was treated with *t*-BuOK, no epimerization to *trans*-**41** was observed. On the other hand, when *trans*-**41** was treated with an excess of *t*-BuOK (5 equiv), (*Z*,*E*)-dienoic acid **43** was obtained, and no trace of *cis*-**41** was observed. It means that under these basic conditions, lactonization of *trans*-**41** to a bicyclic compound proceeds, followed by the formation of enolate **44**. This latter leads to the opening of the strained bicyclic system to give an intermediate α,β-unsaturated lactone **45** which, under basic conditions, produces (*Z*,*E*)-dienoic acid **46**.[32] After treatment of **46** with TBAF, it is transformed to (*Z*,*E*)-dienoic acid **43**. It is worth noting that *cis*-**41** cannot lactonize under these conditions due to the disfavored stereochemistry and does not lead to the formation of (*Z*,*E*)-dienoic acid **46** (Scheme 9).

In order to proceed to the macrocyclization, the *seco*-acid **47** was obtained from *cis*-**42** under mild saponification conditions utilizing TMSOK in Et_2O.[33] With the *seco*-acid **47** in hand, two attempts were achieved for the cyclization to the macrocyclic lactone **1**. The first protocol involved the addition of trichlorobenzoyl chloride to a solution of DMAP, Et_3N, and **47**

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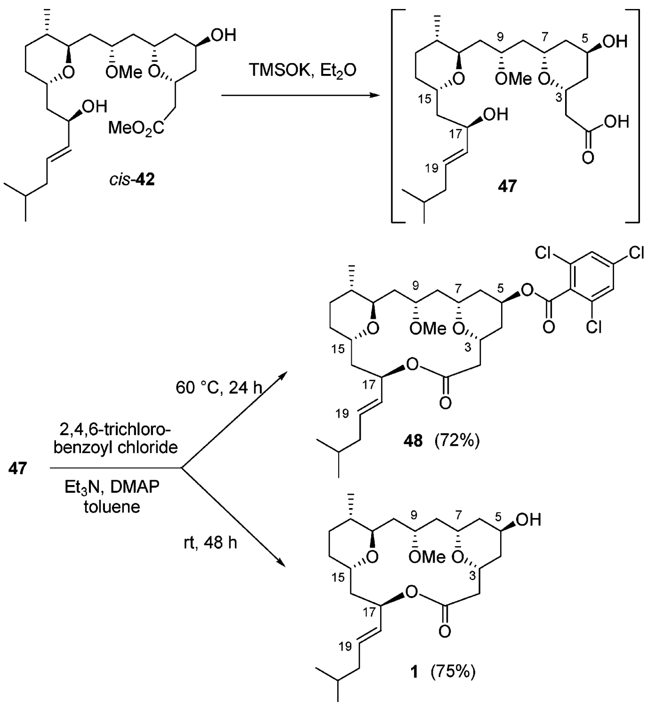
SCHEME 10



in toluene at 60 °C over 24 h.[34] Under these conditions, the macrocyclic lactone was formed but the hydroxyl group at C5 was esterified affording **48** in 72% yield. On the contrary, when the reaction was performed under milder conditions,[35] in toluene at rt for 48 h, the desired macrocyclic lactone **1** was isolated in 75% yield (Scheme 10).

Macrolide **1** was identical in all respect with the spectral data and the specific rotation reported previously.[3,4]

Three approaches of the macrolactone core of the leucascandrolide A were examined. Two of them failed in the formation of the *cis*-THP moiety, utilizing an intramolecular 1,4-addition of an alkoxide on an α,β-unsaturated ester. On the contrary, the third approach allowed us to minimize the number of steps by using chemoselective sequences, which avoids the protection/deprotection steps. Although side reactions occurred during the construction of the *cis*-THP, we were able to circumvent these difficulties in synthesizing macrolide **1** in 25 steps and 1.2% yield from but-1-en-ol. Synthetic highlights include highly stereoselective allylations to control the stereogenic centers at C5, C7, C9, C11, and C12, and an enantioselective Noyori reduction of an acetylenic ketone to control the stereogenic center at C5, a cross-metathesis reaction followed by an intramolecular 1,4-addition to build up the *cis*-tetrahydropyran and a ring-closing metathesis−Mukaiyama reaction to establish the *trans*-tetrahydropyran. Furthermore, by using chemoselective reactions such as selective deprotection of TBS, dihydroxylation, and cross-metatheses, this synthesis of the macrolide core of leucascandrolide A appears to be one of the shortest, considering the total number of steps.

Experimental Section

3-(*tert*-Butyldiphenylsilanyloxy)propionaldehyde (3).[8] To a solution of sodium hydride (788 mg, 19.71 mmol, 1 equiv) in THF (30 mL) at 0 °C was added dropwise 1,3-propanediol **2** (1.5 g, 19.71 mmol, 1 equiv). After 5 min of stirring, *tert*-butyldiphenylsilyl chloride (5.55 mL, 21.68 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for 3 h at rt. Water (50 mL) was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material is directly engaged in the next step without further purification.

To a solution of oxalyl chloride (4.82 mL, 55.23 mmol, 2.1 equiv) in CH_2Cl_2 (120 mL) at −78 °C was added dropwise a solution of DMSO (8.21 mL, 115.72 mmol, 4.4 equiv) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 20 min at −78 °C, and a solution of the above 3-[(*tert*-butyldiphenylsilyl)oxy]propan-1-ol (8.7 g, 26.3 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 90 min at −78 °C, and then Et_3N (30.6 mL, 8.2 equiv) was added dropwise. After 30 min at 0 °C, the temperature was raised to rt, and the reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. A purification of the residue by silica gel chromatography (petroleum ether/EtOAc 90/10) afforded aldehyde **3** (5.58 g, 68% over two steps) as a colorless oil: IR (neat) 3010, 2940, 1715, 1470, 1425, 1390, 1360, 1280, 1130, 1010, 940, 820, 745, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.85 (t, J = 2, 2 Hz, 1H), 7.70−7.62 (m, 4H), 7.50−7.34 (m, 6H), 4.05 (t, J = 5.9 Hz, 2H), 2.63 (td, J = 5.9, 2.2 Hz, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.7 (d), 135.4 (4d), 134.7 (s), 133.1 (s), 129.7 (2d), 127.6 (4d), 58.2 (t), 46.2 (t), 26.6 (3q), 19.0 (s); MS (EI) 256 (2), 199 (100), 181 (4), 152 (2), 137 (2), 121 (2), 105 (1), 77 (6), 51 (1).

***tert*-Butyl-(3-methoxyhex-5-enyloxy)diphenylsilane (4).** To a suspension of (R,R)-TaddolCpTiCl complex (4.55 g, 7.44 mmol, 1.3 equiv) in Et_2O (120 mL) at 0 °C was added allylmagnesium chloride (3.15 mL, 2.0 M in THF, 6.29 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of aldehyde **3** (2.02 g, 5.72 mmol, 1 equiv) in Et_2O was added at −78 °C. After 16 h at −78 °C, deionized water (50 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on Celite (washing with Et_2O). The resulting solution was dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by silica gel chromatography (petroleum ether/EtOAc 90/10) afforded impure alcohol (2.61 g) as a light yellow oil along with (R,R)-TADDOL which could not be separated from the product.

To a solution of the above impure alcohol in CH_2Cl_2 (50 mL) was added methyl iodide (12.48 g, 5.47 mmol, 15 equiv) and then sodium hydride (2.36 g, 48 mmol, 10 equiv, 60% in mineral oil) by portion. After 5 h of stirring, the reaction mixture was quenched by dropwise addition of a solution of NH_4Cl and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a residue which was purified by silica gel chromatography (petroleum ether/EtOAc 90:10) to afford methyl ether **4** (1.78 g, 76% over two steps) as a light yellow oil: $[\alpha]_D^{20}$ +2.1 (c 1.04, $CHCl_3$); IR (neat) 2930, 1427, 1086, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75−7.65 (m, 4H), 7.50−7.43 (m, 6H), 5.82 (m, 1H), 5.15−5.02 (m, 2H), 3.89−3.71 (m, 2H), 3.52 (m, 1H), 3.35 (s, 3H), 2.30 (t_{app}, J = 7.5 Hz, 2H) 1.80−1.70 (m, 2H) 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.6 (4d), 134.8 (d), 134.0 (2s), 129.6 (2d), 127.6 (4d), 117.0 (t), 77.2 (d), 60.5 (t), 56.7 (q), 37.8 (t), 36.6 (t), 27.0 (3q), 19.2 (s); MS (EI) 311 (M − ^{t}Bu$^+$, 9), 279 (M, 10), 243 (27), 225 (15), 213 (M − H − 2Ph$^+$, 100), 183 (46), 153 (17), 135 (22), 81 (38).

8-[(*tert*-Butyldiphenylsilyl)oxy]-4-[(*tert*-butyldimethylsilyl)-oxy]-6-methoxyoct-1-ene (5). To a solution of olefin **4** in CH_2Cl_2 (40 mL) at −78 °C was bubbled ozone until the solution turned

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blue, and then argon was bubbled through until the blue color vanished and triphenylphosphine (3.17 g, 12.07 mmol, 2.5 equiv) was added. After being stirred for 2 h at rt, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 90:10 to 95:5) to afford the corresponding aldehyde (1.77 g, 98%): $[\alpha]^{20}_{D}$ +3.4 (*c* 1.04, $CHCl_3$); IR (neat) 2930, 1709, 1427, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.81 (t, $J = 2.3$ Hz, 1H), 7.78−7.62 (m, 4H), 7.50−7.33 (m, 6H), 3.98 (quint$_{app}$, $J = 6.0$ Hz, 1H), 3.89−3.70 (m, 2H), 3.35 (s, 3H), 2.64−2.55 (m, 2H), 1.95−1.70 (m, 2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.5 (d), 135.6 (4d), 133.6 (2s), 129.8 (2d), 127.7 (4d), 73.6 (d), 60.1 (t), 57.0 (q), 48.2 (t), 36.7 (t), 27.0 (3q), 19.2 (s); MS (EI) 313 (M − ^{t}Bu$^+$, 2), 281 (M, 14), 251 (17), 225 (20), 213 (36), 199 (100), 183 (28), 78 (43), 53 (29).

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (3.8 g, 6.21 mmol, 1.3 equiv) in Et_2O (100 mL) at 0 °C was added allylmagnesium chloride (2.63 mL, 2.0 M in THF, 5.25 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of the above aldehyde (1.77 g, 4.78 mmol, 1 equiv) in Et_2O was added at −78 °C. After 4 h at 78 °C, deionized water (40 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on Celite (washing with Et_2O). The resulting solution was dried over $MgSO_4$, filtered, and concentrated to afford crude allylic alcohol which could not be purified from (*R*,*R*)-TADDOL by flash chromatography on silica gel. The crude material was used without further purification in the next step.

To a solution of above crude allylic alcohol in CH_2Cl_2 at −78 °C were added 2,6-lutidine (2.44 mL, 21.04 mmol, 4.4 equiv) and TBSOTf (2.42 mL, 10.52 mmol, 2.2 equiv). After 3.5 h at −78 °C, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/EtOAc: 98/2) to afford silyl ether **5** (2.03 g, 81% over two steps) as a light yellow oil: $[\alpha]^{20}_{D}$ +12.3 (*c* 1.06, $CHCl_3$); IR (neat) 2929, 1640, 1471, 1427, 1360, 1253, 1106, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68−7.60 (m, 4H), 7.42−7.28 (m, 6H), 5.78 (m, 1H), 5.05−4.95 (m, 2H), 3.83−3.63 (m, 3H), 3.45 (m, 1H), 3.22 (s, 3H), 2.32−2.10 (m, 2H), 1.80−1.60 (m, 2H), 1.56−1.42 (m, 2H), 1.03 (s, 9H), 086 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4 (4d), 135.0 (d), 133.8 (2s), 129.4 (2d), 127.5 (4d), 116.8 (t), 74.9 (d), 69.0 (d), 60.4 (t), 56.1 (q), 41.7 (t), 41.2 (t), 37.0 (t), 26.7 (3q), 25.8 (3q), 19.1 (s), 18.0 (s), −3.1(q), −4.4 (q); MS (EI) 469 (M − ^{t}Bu$^+$, 0.4), 453 (11), 213 (90), 185 (100), 159 (50), 135 (52), 107 (52), 89 (32), 75 (52), 73 (55).

10-[(*tert*-Butyldiphenylsilyl)oxy]-6-[(*tert*-butyldimethylsilyl)-oxy]-8-methoxy-4-methoxymethyldec-1-ene (6). To a solution of olefin **5** (1.31 g, 2.48 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at −78 °C was bubbled ozone until the solution turned blue, and then argon was bubbled until the blue color vanished and triphenylphosphine (2.6 g, 9.94 mmol, 4 equiv) was added. After being stirred for 80 min at rt, the reaction mixture was concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 95:5 to 90:10) to afford the corresponding aldehyde (1.29 g, 98%) as a colorless oil: $[\alpha]^{20}_{D}$ −6.5 (*c* 1.3, $CHCl_3$); IR (neat) 2929, 1725, 1472, 1428, 1361, 1253, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (t, $J = 2.2$ Hz, 1H), 7.65−7.55 (m, 4H), 7.40−7.26 (m, 6H), 4.30 (m, 1H), 3.78−3.60 (m, 2H), 3.42 (m, 1H), 3.20 (s, 3H), 2.60−2.40 (m, 2H), 1.80−1.52 (m, 4H), 1.00 (s, 9H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.1 (d), 135.4 (4d), 133.6 (2s), 129.5 (2d), 127.5 (4d), 74.5 (d), 65.5 (d), 60.2 (t), 56.1 (q), 50.5 (t), 42.0 (t), 36.5 (t), 26.7 (3q), 25.6 (3q), 19.0 (s), 17.8 (s), −4.5 (q), −4.9 (q); MS (EI) 433 (M − Ph − H_2O^+, 2), 339 (3), 307 (8), 229 (16), 213 (35), 199 (100), 183 (19), 135 (11), 108 (9), 77 (20).

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (3.02 g, 4.93 mmol, 1.4 equiv) in Et_2O (80 mL) at 0 °C was added allylmagnesium chloride (2.63 mL, 5.25 mmol, 1.1 equiv). The reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C, and a solution of the above aldehyde (1.85 g, 3.50 mmol, 1 equiv) in a small amount of Et_2O was added at −78 °C. After 4 h at −78 °C, deionized water (40 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on Celite (washing with Et_2O). The resulting solution was dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 98:2 to 90:10) to afford corresponding allylic alcohol (1.47 g, 74%) as a light yellow oil: $[\alpha]^{20}_{D}$ −25.3 (*c* 1.01, $CHCl_3$); IR (neat) 3448, 2929, 1640, 1472, 1428, 1361, 1253, 1106, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.50 (m, 4H), 7.35−7.18 (m, 6H), 5.71 (m, 1H), 5.04−4.93 (m, 2H), 3.96 (m, 1H), 3.71 (m, 1H), 3.68−3.52 (m, 2H), 3.36 (m, 1H), 3.15 (s, 3H), 3.10 (br s, 1H), 2.11 (t$_{app}$, $J = 6.6$ Hz, 2H), 1.71−1.35 (m, 6H), 0.94 (s, 9H), 0.78 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4 (4d), 134.8 (d), 133.6 (2s), 129.5 (2d), 127.5 (4d), 117.3 (t), 74.8 (d), 70.3 (d), 69.9 (d), 60.2 (t), 56.3 (q), 42.9 (t), 42.3 (t), 42.0 (t), 36.8 (t), 26.7 (3q), 25.7 (3q), 19.1 (s), 17.7 (s), −4.1 (q), −4.8 (q); MS (EI) 481 (2), 453 (3), 381 (13), 269 (15), 255 (33), 213 (100), 199 (53), 183 (48), 159 (35), 135 (64), 75 (72); HRMS (CI^+, CH_4) calcd for $C_{33}H_{54}O_4Si_2 + H^+$ 571.3639, found 571.3646.

To a solution of the above alcohol (1.42 g, 2.48 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at 0 °C were added *i*-Pr_2NEt (3.46 mL, 19.84 mmol, 8 equiv) and MOMCl (756 μL, 9.95 mmol, 4 equiv). After 24 h of stirring at rt, the reaction mixture was quenched by adding a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 90:10) to afford compound **6** (1.45 g, 95%) as a colorless oil: $[\alpha]^{20}_{D}$ +4.2 (*c* 1.02, $CHCl_3$); IR (neat) 2929, 2856, 1640, 1472, 1428, 1361, 1253, 1084, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63−7.55 (m, 4H), 7.40−7.25 (m, 6H), 5.78 (m, 1H), 5.09−4.97 (m, 2H), 4.58 (s, 2H), 3.82 (quint$_{app}$, $J = 6.0$ Hz, 1H), 3.77−3.60 (m, 3H), 3.41 (m, 1H), 3.30 (s, 3H), 3.20 (s, 3H), 2.37−2.13 (m, 2H), 1.76−1.42 (m, 6H), 1.00 (s, 9H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4 (4d), 134.5 (d), 133.8 (2s), 129.4 (2d), 127.5 (4d), 117.1 (t), 95.3 (t), 74.9 (d), 74.1 (d), 66.8 (d), 60.4 (t), 56.2 (q), 55.4 (q), 41.9 (t), 41.6 (t), 38.9 (t), 37.1 (t), 26.8 (3q), 25.8 (3q), 19.0 (s), 17.8 (s), −4.3 (q), −4.5 (q); MS (EI) 481 (M − ^{t}Bu − Ph^+, 0.4), 255 (4), 213 (15), 199 (63), 183 (7), 135 (8), 75 (100).

11-[(*tert*-Butyldiphenylsilyl)oxy]-7-[(*tert*-butyldimethylsilyl)-oxy]-9-methoxy-5-methoxyethylundec- 2-enoic Acid Ethyl Ester (7). To a solution of olefin **6** (1.37 g, 2.22 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at rt was added ethyl acrylate (720 μL, 6.66 mmol, 3 equiv) followed by Grubbs−Hoveyda catalyst Ru−**III** (35 mg, 2.5 mol %). After 24 h at rt, the brown reaction mixture was concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 95:5) to afford unsaturated ester **7** (1.30 g, 85%): $[\alpha]^{20}_{D}$ −2.2 (*c* 1.05, $CHCl_3$); IR (neat) 2930, 1720, 1472, 1428, 1257, 1087, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67−7.55 (m, 4H), 7.40−7.23 (m, 6H), 6.94 (dt, $J = 15.8$, 7.4 Hz, 1H), 5.81 (d, $J = 15.8$ Hz, 1H), 4.58 (d, $J = 6.6$ Hz, 1H), 4.54 (d, $J = 6.6$ Hz, 1H), 4.11 (q, $J = 7.4$ Hz, 2H), 3.90−3.75 (m, 2H), 3.75−3.60 (m, 2H), 3.41 (m, 1H), 3.30 (s, 3H), 3.20 (s, 3H), 2.52−2.26 (m, 2H), 1.77−1.43 (m, 6H), 1.22 (t, $J = 7.4$ Hz, 3H), 1.00 (s, 9H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0 (s), 145.0 (d), 135.4 (4d), 133.87 (2s), 129.5 (2d), 127.5 (4d), 123.6 (d), 95.4 (t), 74.8 (d), 73.4 (d), 66.7 (d), 60.4 (t), 60.0 (t), 56.1 (q), 55.5 (q), 41.8 (t), 41.6 (t), 37.4 (t), 36.9 (t), 26.8 (3q), 25.8 (3q), 19.0 (s), 17.8 (s), 14.1 (q), −4.3 (q), −4.5 (q); MS (EI) 507 (0.5), 491 (2), 433 (6), 309 (7), 283

(12), 213 (27), 199 (77), 183 (14), 135 (14), 75 (100), 56 (10); HRMS (CI$^+$, NH$_3$) calcd for $C_{38}H_{62}O_7Si_2 + NH_4^+$ 704.4378, found 704.4371.

7-[(*tert*-Butyldimethylsilyl)oxy]-11-hydroxy-9-methoxy-5-methoxymethylundec-2-enoic Acid Ethyl Ester (8). To a solution of compound **7** (1.12 g, 1.63 mmol) in refluxing methanol (25 mL) was added NH$_4$F (80 mg, 2.16 mmol, 13 equiv). After 12 h of stirring at methanol reflux, the reaction mixture was quenched by addition of brine and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 90/10 to 50/50 to afford **8** (500 mg, 65%) as an oil: $[\alpha]_D^{20}$ +25.4 (*c* 1.0, CHCl$_3$); IR (neat) 3463, 2929, 1719, 1256, 1094, 1033 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.90 (dt, *J* = 15.4, 7.4 Hz, 1H), 5.82 (dt, *J* = 15.8, 1.5 Hz, 1H), 4.58 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.89−3.65 (m, 4H), 3.49 (m, 1H), 3.32 (s, 3H), 3.29 (s, 3H), 2.52−2.30 (m, 2H), 1.86−1.49 (m, 6H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 166.2 (s), 144.8 (d), 123.9 (d), 95.6 (t), 77.8 (d), 73.6 (d), 66.7 (d), 60.7 (t), 60.3 (t), 56.3 (q), 55.8 (q), 41.1 (t), 40.5 (t), 37.4 (t), 35.5 (t), 25.8 (3q), 18.0 (s), 14.3 (q), −4.3 (q), −4.5 (q); MS (EI) 359 (0.2), 309 (3), 257 (2), 243 (11), 189 (10), 171 (8), 157 (7), 141 (8), 131 (8), 115 (23), 89 (43), 75 (100), 59 (22).

7-[(*tert*-Butyldimethylsilyl)oxy]-11-hydroxy-9-methoxy-5-methoxymethyl-12-methyltetradeca-2,13-dienoic Acid Ethyl Ester (9). To a solution of alcohol **8** (500 mg, 1.11 mmol, 1 equiv) in CH$_2$Cl$_2$ (15 mL) at rt was added Dess−Martin periodinane (865 mg, 2.11 mmol, 1.9 equiv). After 1.5 h of stirring, the reaction mixture was quenched by addition of a solution of Na$_2$S$_2$O$_3$ (15 mL), followed by the addition of a saturated solution of NaHCO$_3$ (15 mL) and then diluted with Et$_2$O (15 mL). The reaction mixture was stirred for 15 min and was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated. The residue was engaged in the next step without further purification (due to its presumably unstability).

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (883 mg, 1.44 mmol, 1.3 equiv) in Et$_2$O (20 mL) at 0 °C was added 2-butenylmagnesium chloride (3.49 mL, 0.5 M in THF, 1.22 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of the above aldehyde (1.85 g, 3.50 mmol, 1 equiv) in Et$_2$O was added at −78 °C. After 2 h at −78 °C, deionized water (30 mL) was added, and the reaction mixture was stirred at rt for 1 day. Celite was added, and the mixture was filtered on Celite (washing with EtOAc). The resulting solution was dried over MgSO$_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 80:20) to afford alcohol **9** (374 mg, 67% over two steps) as a light yellow oil: $[\alpha]_D^{20}$ +5.0 (*c* 1.0, CHCl$_3$); IR (neat) 3498, 2929, 1720, 1257, 1150, 1093, 1033 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.90 (dt, *J* = 14.7, 7.4 Hz, 1H), 5.83 (dt, *J* = 15.8, 1.5 Hz, 1H), 5.72 (m, 1H), 5.07−4.95 (m, 2H), 4.58 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.89−3.72 (m, 2H), 3.68 (m, 1H), 3.56 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.71 (br s, 1H), 2.51−2.29 (m, 2H), 2.15 (m, 1H), 1.89−1.36 (m, 6H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 9H), 0.00 (2s, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 166.0 (s), 144.7 (d), 140.3 (d), 123.6 (d), 115.3 (t), 95.5 (t), 76.1 (d), 73.5 (d), 71.4 (d), 66.6 (d), 60.0 (t), 56.5 (q), 55.6 (q), 44.1 (d), 41.8 (t), 40.6 (t), 37.5 (t), 36.8 (t), 25.7 (3q), 17.8 (s), 15.7 (q), 14.1 (q), −4.5 (2q); MS (EI) 381 (0.6), 329 (6), 283 (8), 243 (14), 213 (10), 99 (11), 89 (13), 75 (100), 59 (19); HRMS: (CI$^+$, CH$_4$) calcd for $C_{26}H_{50}O_7Si + H^+$ 503.3404, found 503.3397.

[6-(4-Hydroxy-2-methoxy-5-methylhept-6-enyl)-4-methoxymethyltetrahydropyran-2-yl]ethanoic Ethyl Ester (10). To a solution of unsaturated ester **9** (331 mg, 0.66 mmol) in THF (1 mL) at rt was added TBAF (3.3 mL, 1.0 M in THF, 5 equiv). After 18 h of stirring, the reaction mixture was quenched with brine and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and then concentrated. The residue was purified by silica gel chromatography (petroleum ether/EtOAc 60:40) to afford the expected THP **10** (15 mg, 6%) and (*E*,*E*)-dienoate **11** (140 mg, 65%): $[\alpha]_D^{20}$ +12.6 (*c* 1.0, CHCl$_3$); IR (neat) 3478, 2927, 1737, 1151, 1083, 1039 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.78 (m, 1H), 5.06−4.94 (m, 2H), 4.61 (s, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.00−3.52 (m, 5H), 3.30 (s, 3H), 3.28 (s, 3H), 2.40 (dd, *J* = 15.2, 8.6 Hz, 1H), 2.28 (dd, *J* = 15.2, 4.9 Hz, 1H), 2.15 (m, 1H), 1.90−1.30 (m, 8H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.2 (s), 140.7 (d), 115.31 (t), 95.0 (t), 76.0 (d), 71.6 (d), 69.7 (d), 69.4 (d), 69.2 (d), 60.4 (t), 56.7 (q), 55.4 (q), 44.2 (d), 41.3 (t), 38.9 (t), 36.8 (t), 36.7(t), 35.8 (t), 15.8 (q), 14.2 (q); MS (EI) 389 (M + H$^+$, 0.04), 355 (M − H − MeOH$^+$, 0.1), 315 (M − COOEt$^+$, 1), 301 (25), 269 (M, 3), 239 (29), 221 (30), 209 (10), 169 (100), 141 (20), 123 (22), 95 (18), 81 (44), 59 (16); HRMS (CI$^+$, CH$_4$) calcd for $C_{20}H_{36}O_7 + H^+$ 389.2539, found 389.2544.

1-[(*tert*-Butyldiphenyl)silyloxy]-4-methylhex-5-ene-1,3-diol (12). To a suspension of (*R*,*R*)-TaddolCpTiCl complex (3.18 g, 5.2 mmol, 1.3 equiv) in Et$_2$O (30 mL) at 0 °C was added 2-butenylmagnesium chloride (14.7 mL, 0.5 M in THF, 4.4 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of aldehyde **3** (1.25 g, 5.72 mmol, 1 equiv) in Et$_2$O was added at −78 °C. After 16 h at −78 °C, deionized water (30 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on Celite (washing with Et$_2$O). The resulting solution was dried over MgSO$_4$, filtered, and concentrated. Purification of the residue by silica gel chromatography (petroleum ether/EtOAc 90:10) afforded alcohol **12** (1.32 g, 89%): $[\alpha]_D^{20}$ −4.6 (*c* 1.09, CHCl$_3$); IR (neat) 3460, 2900, 1960, 1820, 1640, 1590, 1470, 1425, 1390, 110, 910, 820, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.70 (m, 4H), 7.44 (m, 6H), 5.86 (m, 1H), 5.10 (m, 2H), 3.92 (m, 2H), 3.78 (m, 1H), 3.06 (d, *J* = 2.6 Hz, 1H, OH), 2.28 (m, 1H), 1.70 (m, 2H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 140.5 (d), 135.5 (4d), 133.1 (2s), 129.6 (2d), 127.6 (4d), 115.1 (t), 74.4 (d), 63.2 (t), 43.8 (d), 35.5 (t), 26.7 (3q), 18.9 (s), 15.7 (q); MS (EI) 311 (M-^{t}Bu$^+$, 3), 293 (3), 255 (18), 230 (4), 211 (8), 199 (100), 183 (15), 167 (3), 151 (3), 135 (16), 117 (6), 95 (7), 67 (10), 55 (7); HRMS (CI$^+$, CH$_4$) calcd for $C_{23}H_{32}O_2Si + H^+$ 369.2250, found 369.2249.

6-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-5-methyl-5,6-dihydropyran-2-one (13). To a solution of *i*-Pr$_2$NEt (4.2 mL, 24.3 mmol, 8 equiv) and alcohol **12** (1.12 g, 3.0 mmol, 1 equiv) in CH$_2$Cl$_2$ (20 mL) at − 78 °C was added dropwise acryloyl chloride (1.0 mL, 12.2 mmol, 4 equiv). After 20 min, the reaction mixture was quenched by addition of a saturated solution of NH$_4$Cl (20 mL), and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 95/5) to afford the corresponding ester (1.16 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ +14.5 (*c* 0.96, CHCl$_3$); IR (neat) 3060, 2960, 1725, 1640, 1470, 1425, 1400, 1270, 1190, 1110, 965, 820, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.70 (m, 4H), 7.43 (m, 6H), 6.40 (dd, *J* = 1.5, 17.3 Hz, 1H), 6.11 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.85−5.73 (m, 1H), 5.81 (dd, *J* = 10.3, 1.5 Hz), 55.20 (m, 1H), 5.05 (m, 2H), 3.73 (t, *J* = 6.6 Hz, 2H), 2.53 (m, 1H,), 1.86 (m, 2H), 1.09 (s, 9H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 165.6 (s), 139.2 (4d), 135.5 (2s), 133.5 (2d), 130.1 (t), 129.5 (d), 128.7 (d), 127.5 (4d), 155.5 (t), 73.9 (d), 60.2 (t), 41.3 (d), 33.9 (t), 26.8 (3q), 19.0 (s), 15.5 (q); MS (EI) 423 (M + 1, 80), 391 (5), 365 (14), 351 (68), 311 (3), 287 (8), 269 (26), 233 (30), 193 (11), 167 (9), 95 (100), 79 (17); HRMS (CI$^+$, CH$_4$) calcd for $C_{26}H_{35}O_3Si + H^+$ 423.2355, found 423.2346.

To a solution of the above ester (1.00 g, 2.37mmol, 1 equiv) in CH$_2$Cl$_2$ (40 mL) at reflux was added Grubbs catalyst second-generation Ru−**II** (0.100 g, 0.12 mmol, 0.05 equiv). After 3 h of stirring at reflux, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 9/1) to afford unsaturated lactone **13** (0.747 g, 80%): $[\alpha]_D^{20}$ +27.0 (*c* 1.00, $CHCl_3$); IR (neat) 1730, 1430, 1470, 1250, 1100, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (m, 4H), 7.42 (m, 6H), 6.65 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.97 (dd, *J* = 2.4, 9.6 Hz, 1H), 4.32 (m, 1H), 3.90 (m, 2H), 2.55 (m, 1H), 1.92 (m, 2H), 1.14 (d, *J* = 7.4 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8 (s), 151.3 (d), 135.4 (4d), 133.14 (2s), 129.6 (2d), 127.6 (4d), 120.0 (d), 80.3 (d), 59.2 (t), 35.6 (t), 33.1 (d), 26.7 (3q) 19.0 (s), 16.4 (q); MS (EI) 323 (M − ^{t}Bu − OAc^+, 52), 267 (100), 245 (16), 199 (83), 183 (28), 159 (10), 135 (11), 123 (8), 105 (10), 77 (6). Anal. Calcd for $C_{24}H_{30}O_3Si$ (394.60): C, 73.05; H, 7.66. Found: C, 73.15; H, 7.76.

Acetic Acid 6-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-5-methyltetrahydropyran-2-yl Ester (14). To a solution of unsaturated lactone **13** (1.09 g, 2.76 mmol, 1 equiv) in AcOEt (85 mL) was added PtO_2 (0.013 g, 55.2 μmol, 0.02 equiv), and the black suspension was stirred at rt under an atmosphere of H_2. After filtration of the suspension on Celite, the colorless solution was concentrated to afford the corresponding lactone (1.01 g, 93%) without further purification: $[\alpha]_D^{20}$ +45.1 (*c* 1.05, $CHCl_3$); IR (neat) 2900, 1730, 1110, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (m, 4H), 7.42 (m, 6H), 4.17 (td, *J* = 9.2, 2.2 Hz, 1H), 3.90 (m, 2H), 2.60 (ddd, *J* = 17.7, 7.0, 4.8 Hz, 1H), 2.46 (ddd, *J* = 17.7, 9.7, 7.0 Hz, 1H), 1.93 (m, 2H), 1.75 (m, 2H), 1.53 (m, 1H), 1.07 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4 (s), 135.4 (4d), 133.6 (2s), 129.6 (2d), 127.6 (4d), 82.4 (d), 59.3 (t), 36.4 (t), 32.3 (d), 29.3 (t), 27.7 (t), 26.7 (3q) 19.1 (s), 17.4 (q); MS (EI) 351 (M-45, 0.2), 339 (M − ^{t}Bu^+, 45), 309 (51), 261 (44), 199 (100), 183 (25), 139 (16), 77 (7). Anal. Calcd for $C_{24}H_{32}O_3Si$ (396.62): C, 72.68; H, 8.13. Found: C, 72.55; H, 8.31.

To a solution of the above lactone (1.75 mmol, 0.695 g, 1 equiv) in dry CH_2Cl_2 (11 mL) at −78 °C was added dropwise DIBAL-H (3.5 mL, 1.0 M in hexanes, 3.5 mmol, 2 equiv), and the solution was stirred for 1.5 h at −78 °C. Pyridine (0.425 g, 5.25 mmol, 3 equiv), DMAP (0.428 g, 3.5 mmol, 2 equiv), and finally Ac_2O (0.99 mL, 10.5 mmol, 6 equiv) were then added to the solution. The reaction mixture was stirred for 15 h at −78 °C and then warmed to 0 °C. The reaction was quenched by addition of a saturated aqueous solution of potassium sodium tartrate. After 10 min, a saturated aqueous $NaHCO_3$ solution was added. After being stirred for 20 min, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, with 1 M $KHSO_4$ solution, and finally with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/AcOEt 9:1) to afford the acetate **14** (606 mg, 79%): $[\alpha]_D^{20}$ +10.0 (*c* 1.00, $CHCl_3$); IR (neat) 2900, 1430, 1370, 1230, 1110, 820, 740, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (m, 4H), 7.42 (m, 6H), 5.62 (dd, *J* = 9.6, 2.2, 1H), 3.90−3.74 (m, 2H), 3.37 (td, *J* = 9.2, 2.2, 1H), 2.10(s, 3H), 1.96 (m, 1H), 1.85 (m, 2H), 1.66−1.31 (m, 4H), 1.05 (s, 9H), 0.84 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9 (s), 135.5 (4d), 134.0 (s), 133.8 (s), 129.4 (2d), 127.5 (4d), 94.9 (d), 79.1 (d), 59.9 (t), 35.8 (t), 34.0 (d), 31.0 (t), 30.4 (t), 26.7 (3q), 21.1 (q), 19.0 (s), 17.0 (q); MS (EI) 323 (M − tBu − OAc^+, 52), 267 (100), 245 (16), 199 (83), 183 (28), 159 (10), 135 (11), 123 (8), 105 (10), 77 (6).

[2-(6-Allyl-3-methyltetrahydropyran-2-yl)ethoxy]-*tert*-butyldiphenylsilane (15). To a solution of acetate **14** (0.600 g, 1.36 mmol, 1 equiv) in CH_2Cl_2 (9 mL) at −78 °C were added allyltrimethylsilane (0.43 mL, 2.72 mmol, 2 equiv) and $BF_3 \cdot Et_2O$ (0.26 mL, 2.04 mmol, 1.5 equiv) dropwise. After 1 h of stirring, a saturated solution of $NaHCO_3$ (10 mL) was added, and the solution was warmed to rt for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/AcOEt 95:5) to afford olefin **15** (0.550 g, 96%) as a light yellow oil: $[\alpha]_D^{20}$ +27.1 (*c* 1.00, $CHCl_3$); IR (neat) 2960, 1425, 1110, 820, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (m, 4H), 7.41 (m, 6H), 5.76 (m, 1H), 5.00 (m, 2H), 3.77 (m, 3H), 3.50 (ddd, *J* = 3.3, 6.6, 9.2 Hz, 1H), 2.43 (m, 1H), 2.16 (m, 1H), 1.82−1.38 (m, 7H), 1.06 (s, 9H), 0.94 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5 (d, 5C), 134.0 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 116.1 (t), 73.0 (d), 70.9 (d), 60.8 (t), 36.8 (t), 35.5 (t), 33.5 (d), 27.1 (t), 26.5 (t), 26.7 (q, 3C), 19.1 (s), 18.2 (q); MS (EI) 381 (5), 365 (48), 255 (9), 225 (13), 199 (100), 183 (31), 149 (35), 135 (20), 121 (13), 107 (32), 93 (27), 81 (24), 77 (7), 67 (18), 55 (6); HRMS (CI^+, CH_4) calcd for $C_{27}H_{38}O_2Si + H^+$ 423.2719, found 423.2721.

[6-(2-Methoxymethoxyethyl)-3-methyltetrahydropyran-2-yl]-acetaldehyde (16). To a solution of olefin **15** (0.550 g, 1.30 mmol, 1 equiv) in a mixture of acetone/water (3:1, 7 mL/2.3 mL) were added NMO (0.259 g, 2.21 mmol, 1.7 equiv) and OsO_4 (0.25 mL, 2.5 wt % in *t*-BuOH, 2.24 μmol, 0.018 equiv). The solution was stirred at rt until total disappearance of the starting material by TLC, and then $NaIO_4$ (0.554 g, 2.60 mmol, 2 equiv) and H_2O (5 mL) were added. After 1 h of stirring, the white suspension was filtered and washed with acetone, and the solution was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with a solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography column (petroleum ether/AcOEt 9/1) to furnish the corresponding aldehyde (0.446 g, 84%) as a pale yellow oil: $[\alpha]_D^{20}$ +30.8 (*c* 0.85, $CHCl_3$); IR (neat) 3060, 2920, 1725, 1585, 1430, 1390, 1110, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.70 (dd, *J* = 2.2, 2.6 Hz), 7.72 (m, 4H), 7.43 (m, 6H), 4.28 (m, 1H), 3.77 (m, 2H), 3.57 (m, 1H), 2.75 (ddd, *J* = 2.6, 8.5, 15.8 Hz, 1H), 2.42 (ddd, *J* = 2.2, 5.5, 15.8 Hz, 1H), 1.83−1.37 (m, 7H), 1.10 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3 (d), 135.4 (d, 4C), 133.8 (s, 2C), 129.4 (d, 2C), 127.5 (d, 4C), 73.6 (d), 69.4 (d), 60.5 (t), 46.6 (t), 35.1 (t), 32.9 (d), 27.5 (t), 26.1 (t), 26.8 (q, 3C), 19.0 (s), 18.1 (q); MS (EI) 367 (M-57, 31), 323 (8), 289 (5), 267 (25), 255 (10), 245 (13), 225 (44), 211 (11), 199 (100), 183 (67), 151 (21), 139 (15), 117 (16), 107 (22), 95 (15), 81 (15), 67 (6), 55 (14).

To a solution of the above aldehyde (0.460 g, 1.08 mmol, 1 equiv) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (0.061 g, 1.62 mmol, 1.5 equiv) in two portions. After 1 h of stirring, the reaction mixture was quenched with H_2O (10 mL) and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford the corresponding alcohol (0.460 g, quantitative): $[\alpha]_D^{20}$ +26.8 (*c* 1.00, $CHCl_3$); IR (neat) 3400, 2920, 1460, 1425, 1390, 1110, 820, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (m, 4H), 7.42 (m, 6H), 3.88−3.57 (m, 6H), 2.27 (br s, 1H, OH), 1.99−1.54 (m, 9H), 1.06 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5 (d, 4C), 133.8 (s, 2C), 129.5 (d, 2C), 127.5 (d, 4C), 73.3 (d), 69.9 (d), 60.7 (t), 60.2 (t), 35.1 (t), 35.0 (t), 32.8 (d), 26.7 (q), 27.6, 26.1 (2t), 19.1 (s), 18.2 (q); MS (EI) 427 (M + 1^+, 18), 425 (M − 1^+, 7), 349 (10), 291 (35), 271 (100), 241 (7), 199 (4), 171 (6), 153 (13), 135 (42), 109 (5); HRMS (CI^+, CH_4) calcd for $C_{26}H_{38}O_3Si + H^+$ 427.2668, found 427.2673.

To a solution of the above alcohol (72 mg, 0.17 mmol, 1 equiv) and *i*-Pr_2NEt (0.059 mL, 0.34 mmol, 2 equiv) in CH_2Cl_2 (2.3 mL) at 0 °C was added MOMCl (0.026 mL, 0.34 mmol, 2 equiv). After 15 h of stirring at rt, the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (3 mL) and was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/AcOEt 7:3) to afford the corresponding MOM ether (75 mg, 94%): $[\alpha]_D^{20}$ +31.7 (*c* 1.00, $CHCl_3$); IR (neat) 2940, 1460, 1425, 1390, 1100, 920, 820, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (m, 4H), 7.41 (m, 6H), 4.55 (s, 2H), 3.90 (m, 1H), 3.78 (m, 2H), 3.58−

3.47 (m, 3H), 3.32 (s, 3H), 2.03−1.28 (m, 9H), 1.06 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 127.5 (d, 4C), 96.3 (t), 72.6 (d), 67.9 (d), 64.5 (t), 60.7 (t), 54.9 (q), 35.5 (t), 33.6 (d), 32.1 (t), 26.7 (q, 3C), 27.9 (t), 26.6 (t), 19.0 (s), 18.2 (q); MS (EI) 439 (M − CH_3O^+, 0.3), 413 (5), 381 (9), 351 (10), 291 (19), 255 (28), 225 (27), 213 (36), 199 (100), 183 (59), 165 (23), 153 (17), 135 (46), 121 (19), 107 (22), 91 (33), 71 (23), 55 (12).

To a solution of the above MOM ether (0.460 g, 0.98 mmol, 1 equiv) in THF (5 mL) at rt was added dropwise TBAF (3.9 mL, 1 M in THF, 3.90 mmol, 4 equiv). After disappearance of the starting material by TLC, the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/AcOEt 5:5 to 3:7) to furnish the corresponding primary alcohol (0.220 g, 96%) as an oil: $[\alpha]_D^{20}$ +53.7 (c 1.15, $CHCl_3$); IR (neat) 3420, 2920, 1460, 1380, 1210, 1150, 1100, 1040, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.63 (s, 2H), 4.07 (m, 1H), 3.75 (m, 2H), 3.63 (m, 2H), 3.45 (td, J = 2.6, 8.8 Hz, 1H), 3.37 (s, 3H), 3.07 (m, 1H, OH), 2.17−1.32 (m, 9H), 0.87 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.3 (t), 75.4 (d), 69.2 (d), 64.6 (t), 60.9 (t), 55.1 (q), 34.7 (d), 34.6 (t), 30.5 (t), 28.4 (t), 26.8 (t), 17.9 (q); MS (EI) 200 (M-32, 30), 187 (25), 169 (26), 155 (34), 143 (100), 125 (63), 115 (43), 107 (79), 95 (71), 87 (91), 73 (29), 67 (45), 55 (87).

To a solution of oxalyl chloride (0.32 mL, 3.63 mmol, 2.5 equiv) in CH_2Cl_2 (8.5 mL) at −78 °C was added dropwise a solution of DMSO (0.41 mL, 7.25 mmol, 4 equiv) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 20 min at −78 °C, and a solution of the above alcohol (0.336 g, 1.45 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred for 90 min at −78 °C, and then Et_3N (1.0 mL, 7.25 mmol, 5 equiv) was added dropwise. After 30 min of stirring at 0 °C, the temperature was raised to rt, and the reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. A purification of the residue by silica gel chromatography (petroleum ether/EtOAc 8:2 to 7/3) afforded aldehyde **16** (0.330 g, 99%) as a colorless oil: $[\alpha]_D^{20}$ +43.8 (c 1.03, $CHCl_3$); IR (neat) 2920, 1720, 1450, 1150, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.70 (t, J = 2.6 Hz, 1H), 4.53 (s, 2H), 3.92 (m, 1H), 3.78 (m, 1H), 3.50 (dd, J = 5.5, 7.4 Hz, 2H), 3.27 (s, 3H), 2.50 (dd, J = 2.6, 6.3 Hz, 2H), 2.03 (m, 1H), 1.73−1.30 (m, 6H), 0.85 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.5 (d), 96.2 (t), 71.3 (d), 68.8 (d), 64.2 (t), 54.7 (q), 46.7 (t), 34.3 (d), 30.9 (t), 27.9 (t), 26.5 (t), 17.7 (q); MS (EI) 201 (M − CHO^+, 69), 183 (75), 165 (75), 141 (100), 123 (41), 109 (50), 100 (27), 95 (75), 87 (56), 81 (50), 71 (69), 55 (92).

1-[6-(2-Methoxymethoxyethyl)-3-methyltetrahydropyran-2-yl]pent-4-en-2-ol (17). To a suspension of (R,R)-TaddolCpTiCl complex (1.33 g, 2.17 mmol, 1.3 equiv) in Et_2O (14 mL) at 0 °C was added allylmagnesium chloride (0.92 mL, 2 M in THF, 1.84 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of aldehyde **16** (0.380 g, 1.650 mmol, 1 equiv) in a small amount of Et_2O was added at −78 °C. After 2 h at −78 °C, deionized water (15 mL) was added, and the reaction mixture was stirred at rt for 1 day. Celite was added, and the mixture was filtered on Celite (washing with AcOEt). The resulting solution was dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 8:2 to 7:3) to afford alcohol **17** (380 mg, 84%) as an oil: $[\alpha]_D^{20}$ +53.5 (c 1, $CHCl_3$); IR (neat) 3440, 2900, 1640, 1450, 1210, 1150, 1105, 1030, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.85 (m, 1H), 5.06 (m, 2H), 4.61 (s, 2H), 4.05 (m, 1H), 3.94 (m, 1H), 3.62 (m, 2H), 3.55 (m, 1H), 3.38 (s, 3H), 3.30 (br s, 1H, OH), 2.21 (m, 3H), 1.80 (m, 1H), 1.62−1.30 (m, 7H), 0.89 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1 (d), 117.0 (t), 96.2 (t), 72.6 (d), 69.2 (d), 67.1 (d), 64.9 (t), 55.0 (q), 41.9 (t), 38.5 (t), 34.4 (d), 30.5 (t), 28.6 (t), 27.1 (t), 17.9 (q); MS (EI) 241 (M−CH_3O^+, 2), 209 (2), 199 (100), 183 (10), 169 (11), 155 (17), 143 (19), 125 (17), 107 (22), 95 (50), 87 (25), 81 (33), 71 (29), 55 (38); HRMS (CI^+, CH_4) calcd for $C_{15}H_{28}O_4 + H^+$ 273.2066, found 273.2062.

8-Methoxy-9-[6-(2-methoxymethoxyethyl)-3-methyltetrahydropyran-2-yl]non-1-ene-4,6-diol (18). To a solution of 2,6-di-*tert*-butylpyridine (0.62 mL, 2.78 mmol, 2 equiv) and alcohol **17** (0.380 g, 1.39 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added MeOTf (0.21 mL, 1.81 mmol, 1.3 equiv) dropwise. After 2 h of stirring at 0 °C and 15 h of stirring at rt, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography to afford the corresponding methyl ether (0.360 g, 90%) as an oil: $[\alpha]_D^{20}$ +74.9 (c 1.04, $CHCl_3$); IR (neat) 2920, 1640, 1460, 1380, 1150, 1100, 1040, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.79 (m, 1H), 5.07 (m, 2H), 4.62 (s, 2H), 3.94 (m, 1H), 3.60 (m, 2H), 3.48 (m, 2H), 3.39, 3.35 (2s, 6H), 2.30 (m, 2H), 2.06 (dddd, J = 5.5, 9.6, 11.0, 14.7 Hz,), 1.80−1.35 (m, 8H), 0.79 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.3 (d), 116.9 (t), 96.3 (t), 76.0, 71.7 (2d), 68.0 (d), 64.4 (t), 56.5 (q), 54.9 (q), 37.8 (t), 37.7 (t), 34.3 (d), 31.8 (t), 28.1 (t), 26.7 (t), 18.1 (q); MS (EI) 245 (M − $allyl^+$, 13), 213 (19), 187 (38), 157 (61), 141 (11), 125 (27), 107 (24), 99 (100), 85 (85), 75 (6), 67 (22), 55 (31); HRMS (CI^+, CH_4) calcd for $C_{16}H_{30}O_4 + H^+$ 287.2222, found 287.2229.

To a solution of the above olefin (0.270 g, 0.96 mmol, 1 equiv) in a mixture of acetone/water (3:1, 6 mL/2 mL) were added NMO (0.190 g, 1.62 mmol, 1.7 equiv) and OsO_4 (0.19 mL, 2.5% in t-BuOH, 1.73 μmol, 0.018 equiv). The solution was stirred at rt until total disappearance of the starting material by TLC, and then $NaIO_4$ (0.41 g, 1.91 mmol, 2 equiv) and H_2O (5 mL) were added. After 1 h of stirring, the white suspension was filtered and washed with acetone, and the solution was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with a solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography column (petroleum ether/AcOEt 7:3) to furnish the corresponding aldehyde (0.240 g, 85%) as a pale yellow oil: $[\alpha]_D^{20}$ +56.8 (c 1.00, $CHCl_3$); IR (neat) 2920, 1720, 1460, 1380, 1210, 1150, 1100, 1030, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.78 (t, J = 2.2 Hz, 1H), 4.60 (s, 2H), 3.91 (m, 2H), 3.56 (m, 2H), 3.44 (m, 1H), 3.32 (s, 3H), 3.30 (s, 3H), 2.57 (dd, J = 2.2, 5.5 Hz, 2H), 2.00 (m, 1H), 1.79−1.33 (m, 8H), 0.88 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (d), 96.3 (t), 72.9 (d), 71.9 (d), 68.2 (d), 64.3 (t), 56.8 (q), 54.9 (q), 48.2 (t), 38.5 (t), 34.2 (d), 31.7 (t), 28.0 (t), 26.6 (t), 18.1 (q); MS (EI) 256 (2), 243 (37), 224 (6), 211 (26), 199 (8), 187 (18), 167 (53), 149 (26), 141 (25), 123 (35), 107 (38), 99 (100), 91 (12), 81 (62), 71 (46), 55 (64).

To a suspension of (R,R)-TaddolCpTiCl complex (0.643 g, 1.06 mmol, 1.3 equiv) in Et_2O (17 mL) at 0 °C was added allylmagnesium chloride (0.45 mL, 2 M in THF, 0.90 mmol, 1.1 equiv), and the reaction mixture was then stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of the above aldehyde (0.240 g, 0.83 mmol, 1 equiv) in a small amount of Et_2O was added at −78 °C. After 4 h at −78 °C, deionized water (15 mL) was added, and the reaction mixture was stirred at rt for 1 day. Celite was added, and the mixture was then filtered on Celite (washing with AcOEt). The resulting solution was dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 7:3) to afford the corresponding allylic alcohol (210 mg, 78%) as an oil: $[\alpha]_D^{20}$ +46.0 (c 1.00, $CHCl_3$); IR (neat) 3440, 1640, 1460, 1380, 1150, 1105, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.84 (m, 1H), 5.10 (m, 2H), 4.62 (s, 2H), 3.92 (m, 1H), 3.80 (m, 1H), 3.62 (m, 3H), 3.47 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 3.29 (br s, 1H, OH), 2.22 (dd, *J* = 1.1, 7.0 Hz, 2H), 2.00 (dddd, *J* = 5.9, 9.2, 11.0, 14.3 Hz, 1H), 1.72−1.37 (m, 10H), 0.96 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 134.9 (d), 117.2 (t), 96.3 (t), 77.5 (d), 73.1 (d), 69.2 (d), 68.0 (d), 64.5 (t), 56.4 (q), 55.0 (2q), 42.2 (t), 40.8 (t), 37.9 (t), 34.0 (d), 32.2 (t), 27.9 (t), 26.4 (t), 18.2 (q); MS (EI) 298 (M-32, 2), 257 (9), 239 (8), 225 (54), 209 (33), 195 (29), 187 (17), 177 (15), 165 (12), 155 (63), 143 (31), 123 (48), 107 (46), 99 (100), 85 (89), 71 (65), 59 (80); HRMS (CI$^+$, CH$_4$) calcd for $C_{18}H_{34}O_5 + H^+$ 331.2484, found 331.2487.

To a solution of the above olefin (0.140 g, 0.4 mmol, 1 equiv) in a mixture of acetone/water (3:1, 2.5 mL/0.85 mL) were added NMO (0.081 g, 0.70 mmol, 1.7 equiv) and OsO$_4$ (2.5 wt % in *t*-BuOH, 0.080 mL, 0.018 equiv). After 4 h, NaIO$_4$ (0.170 g, 0.82 mmol, 2 equiv) and H$_2$O (2 mL) were added. After 1 h, the resulting mixture was extracted with EtOAc, and the combined organic layers were washed with a solution of Na$_2$S$_2$O$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated. The obtained crude aldehyde (0.140 g, 0.42 mmol) was used in the next step without further purification.

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (0.310 g, 0.51 mmol, 1.3 equiv) in Et$_2$O (5 mL) at 0 °C was added allylmagnesium chloride (0.21 mL, 2 M in THF, 0.43 mmol, 1.1 equiv), and the reaction mixture was stirred at 0 °C for 90 min and then cooled to −78 °C. A solution of the above aldehyde (0.130 g, 0.39 mmol, 1 equiv) in a small amount of Et$_2$O was added at −78 °C. After 4 h at −78 °C, deionized water (10 mL) was added, and the reaction mixture was stirred at rt for 1 day. Celite was added, and the mixture was then filtered on Celite (washing with AcOEt). The resulting solution was dried over MgSO$_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 5:5 to 0:10) to afford diol **18** (105 mg, 69%) as an oil: $[\alpha]_D^{20}$ +40.0 (*c* 1.00, CHCl$_3$); IR (neat) 3400, 2920, 1640, 1440, 1380, 1210, 1150, 1100, 1030, 920 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.83 (m, 1H), 5.10 (m, 2H), 4.62 (s, 2H), 4.20 (br s, 1H, OH), 3.93 (m, 4H), 3.60 (m, 3H), 3.45 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.23 (m, 2H), 2.02−1.37 (m, 13H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 134.7 (d), 117.2 (t), 96.2 (t), 77.4 (d), 73.3 (d), 71.4 (d), 70.9 (d), 68.0 (d), 64.4 (t), 56.3 (q), 55.1 (q), 42.7 (t), 42.1 (t), 42.0 (t), 37.6 (t), 34.2 (d), 31.9 (t), 27.9 (t), 26.4 (t), 18.2 (q); MS (EI) 375 (M + 1$^+$, 52), 343 (100), 311 (19), 301 (16), 293 (15), 271 (9), 239 (9), 225 (4), 187 (7), 173 (1), 143 (11), 135 (20), 113 (3); HRMS (CI$^+$, CH$_4$) calcd for $C_{20}H_{38}O_6 + H^+$ 375.2747, found 375.2746.

5,7-Dihydroxy-9-methoxy-10-[6-(2-methoxymethoxyethyl)-3-methyltetrahydropyran-2-yl]dec-2-enoic Acid Ethyl Ester (19). To a solution of diol **18** (42 mg, 0.11 mmol, 1 equiv) in CH$_2$Cl$_2$ (1 mL) was added ethyl acrylate (72 μL, 0.68 mmol, 6 equiv) followed by Hoveyda−Grubbs catalyst Ru−**III** (3.5 mg, 5.6 μmol, 5 mol %). After 1.5 h at rt, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (petroleum ether/EtOAc 2:8 to 0:10) to afford diol **19** (44 mg, 89%) as a brown oil: $[\alpha]_D^{20}$ +31.4 (*c* 1.00, CHCl$_3$); IR (neat) 3420, 2920, 1720, 1650, 1440, 1370, 1270, 1150, 1100, 980, 920, 850 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.99 (td, *J* = 7.4, 15.4 Hz, 1H), 5.88 (dt, *J* = 1.5, 15.8 Hz, 1H), 4.61 (s, 2H), 4.25 (br s, 1H, OH), 4.22 (br s, 1H, OH), 4.18 (q, *J* = 7.0 Hz, 2H), 4.06−3.89 (m, 3H), 3.60 (m, 3H), 3.42 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.37 (m, 2H), 2.00−1.38 (m, 13H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 166.2 (s), 145.1 (d), 123.4 (d), 96.2 (t), 77.9 (d), 73.6 (d), 71.3 (d), 70.8 (d), 68.1(d), 64.3 (t), 60.1 (t), 56.3 (q), 55.1 (q), 42.8 (t), 42.1 (t), 40.3 (t), 37.5 (t), 34.2 (d), 31.9 (t), 27.9 (t), 26.4 (t), 18.2 (q), 14.1 (q); MS (EI) 447 (M + 1$^+$, 15), 415 (100), 383 (16), 365 (7), 353 (5), 301 (5), 271 (3), 239 (4), 225 (1), 187 (3), 143 (5), 135 (1); HRMS (CI$^+$, CH$_4$) calcd for $C_{23}H_{42}O_8 + H^+$ 447.2958, found 447.2947.

1-(*tert*-Butyldimethylsilanyloxy)-4-methylhex-5-en-3-ol (22). To a suspension of (*R*,*R*)-TaddolCpTiCl complex (17.00 g, 27.8 mmol, 1.4 equiv) in Et$_2$O (200 mL) at 0 °C was added a solution of 2-butenylmagnesium chloride (45.7 mL, 0.5 M in THF, 22.8 mmol, 1.15 equiv). After 2.5 h at 0 °C, the solution was cooled to −78 °C, and a solution of aldehyde **21** (3.74 g, 19.9 mmol, 1.0 equiv) in dry Et$_2$O (30 mL) at −78 °C was added via canula. After 16 h at −78 °C, deionized water (50 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on a pad of Celite (washing with Et$_2$O). The resulting solution was dried over MgSO$_4$, filtered, and concentrated. The residue was diluted with pentane, and the white precipitate [(*R*,*R*)-TADDOL] was sonicated, filtered, and dried in vacuo (12.59 g, 97%). Pentane was evaporated and the residue was purified by silica gel chromatography (petroleum ether/Et$_2$O 9:1) to afford the homoallylic alcohol **22** (4.20 g, 86%): $[\alpha]_D^{20}$ −9.7 (*c* 1.10, CHCl$_3$); IR (neat) 3383, 3000−2800, 1639, 1463, 1255, 1086, 1003 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.83 (m, 1H), 5.06 (m, 2H), 3.88 (dt, *J* = 10.1, 5.0 Hz, 1H), 3.80 (m, 1H), 3.68 (dt, *J* = 7.2, 5.0 Hz, 1H), 3.20 (br s, 1H, OH), 2.23 (sext$_{app}$, *J* = 6.8 Hz, 1H), 1.70−1.56 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 140.7 (d), 115.1 (t), 75.1 (d), 62.8 (t), 43.9 (d), 35.5 (t), 25.9 (q, 3C), 18.2 (s), 15.7 (q), −5.5 (q, 2C); MS (EI), 189 ($M - CH_2{=}CHCHMe^+$, 37), 145 (11), 131 (46), 105 (52), 101 (35), 95 (100), 89 (38), 75 (93), 73 (41), 67 (23); HRMS (ESI) calcd for $C_{13}H_{28}O_2Si + Na^+$ 267.1751, found 267.1750.

Acrylic Acid 1-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-2-methylbut-3-enyl Ester (23). To a solution of alcohol **22** (4.99 g, 20.4 mmol, 1 equiv) and Et$_3$N (5.67 mL, 40.8 mmol, 2 equiv) in Et$_2$O (70 mL) at −18 °C was added dropwise acryloyl chloride (2.25 mL, 26.5 mmol, 1.3 equiv). The mixture was allowed to stir for 2 h, quenched by addition of a saturated solution of NaHCO$_3$, and then stirred at rt for 15 min. The aqueous layer was extracted with Et$_2$O, and the organic extracts were washed with aqueous 8% H$_3$PO$_4$ and brine, dried over MgSO$_4$, and filtered on a pad of silica gel. After concentration, the acrylic ester **23** (5.62 g, 92%) was obtained: $[\alpha]_D^{20}$ +21.0 (*c* 0.98 CHCl$_3$); IR (neat) 3000−2800, 1724, 1638, 1462, 1404, 1255, 1190, 1094 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.76 (m, 1H), 5.09−5.02 (m, 3H), 3.63 (ddd, *J* = 10.3, 6.7, 5.7 Hz, 1H), 3.60 (dt *J* = 10.2, 7.5 Hz, 1H), 2.23 (sext$_{app}$, *J* = 7.0 Hz, 1H), 1.78 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.02 (2s, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 165.8 (s), 139.3 (d), 130.3 (t), 128.8 (t), 115.6 (t), 74.2 (d), 59.7 (t), 41.6 (d), 34.3 (t), 25.9 (q), 18.2 (s), 15.6 (q), −5.5 (q); MS (EI) 243 ($M - CH_2{=}CH_2CO^+$, 12), 171 (10), 169 (15), 129 (96), 101 (18), 95 (100), 89 (13), 75 (31), 73 (17), 67 (15), 55 (34); HRMS (ESI) calcd for $C_{16}H_{30}O_3Si + Na^+$ 321.1856, found 321.1856.

6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-methyltetrahydropyran-2-one (24). To a solution of ester **23** (5.49 g, 18.4 mmol, 1 equiv) in CH$_2$Cl$_2$ at 40 °C was added Grubbs catalyst second-generation Ru−**II** (475 mg, 0.55 mmol, 0.03 equiv). After being refluxed for 48 h, the solution was allowed to cool to rt, and Pd/C 5% (790 mg, 0.37 mmol, 0.02 equiv) was added. The solution was stirred under a gentle bubbling of H$_2$ for 8 h and was left overnight under a H$_2$ atmosphere. The black suspension was filtered on Celite and then the solution was concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ Et$_2$O 7:3) to afford tetrahydropyran **24** (3.50 g, 70%): $[\alpha]_D^{20}$ +60.0 (*c* 0.58, CHCl$_3$); IR (neat) 3000−2800, 1733, 1462, 1250, 1208, 1087, 1035, 1001, 833 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.10 (td, *J* = 9.5, 2.4 Hz, 1H), 3.81 (ddd, *J* = 10.2, 8.4, 5.0 Hz, 1H), 3.78 (ddd, *J* = 10.2, 6.6, 4.5 Hz, 1H), 2.61 (ddd, *J* = 17.7, 6.8, 4.8 Hz, 1H), 2.46 (ddd, *J* = 17.7, 9.7, 7.0 Hz, 1H), 1.99−1.87 (m, 2H), 1.81−1.66 (m, 2H), 1.55 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.7 (s), 82.7 (d), 58.6

(t), 36.7 (t), 32.5 (d), 29.5 (t), 27.8 (t), 25.9 (q, 3C), 18.2 (s), 17.5 (q), −5.4 (q, 2C); MS (EI) 215 (M− *t*-Bu$^+$, 37), 197 (59), 185 (100), 171 (9), 129 (26), 123 (38), 95 (28), 75 (71); HRMS (ESI) calcd for $C_{14}H_{28}O_3Si + Na^+$ 295.1700, found 295.1700.

Acetic acid 6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-methyltetrahydropyran-2-yl Ester (25). To a solution of lactone **24** (11.96 mmol, 3.24 g, 1 equiv) in dry CH_2Cl_2 (75 mL) at −78 °C was added dropwise DIBAL-H (16.74 mL, 1.0 M in hexanes, 16.74 mmol, 1.4 equiv), and the solution was stirred for 1.5 h at −78 °C. Pyridine (4.74 g, 60 mmol, 5 equiv), DMAP (4.36 g, 36 mmol, 3 equiv), and finally Ac_2O (6.12 g, 60 mmol, 5 equiv) were then added. The reaction mixture was stirred for 30 min at −78 °C and then warmed to 0 °C. The reaction was quenched by addition of a saturated aqueous solution of potassium sodium tartrate. After 10 min, a saturated aqueous $NaHCO_3$ solution was added. After being stirred for 20 min, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, with a saturated aqueous $CuSO_4$ solution, and finally with brine. The organic layer was dried over $MgSO_4$, filtered on a plug of silica gel (4 cm, Et_2O/petroleum ether 50:50), and concentrated to afford the unstable acetate **25** (3.76 g, 98%) in a 12:1 ratio. This compound was directly engaged in the next step: ^{1}H NMR (C_6D_6, 400 MHz) δ 5.70 (dd, J = 9.3, 3.0 Hz, 1H), 3.90 (ddd, J = 9.8, 8.4, 5.7 Hz, 1H), 3.80 (ddd, J = 9.8, 6.7, 4.3 Hz, 1H), 3.21 (td, J = 9.5, 2.3 Hz, 1H), 1.90 (dddd, J = 13.9, 8.4, 6.8, 2.3 Hz, 1H), 1.65 (s, 3H), 1.60 (m, 1H), 1.54 (m, 1H), 1.48 (tdd, J = 12.5, 9.5, 4.2 Hz, 1H), 1.40 (m, 1H), 1.15 (m, 1H), 0.88 (dddd, J = 13.4, 12.5, 11.9, 5.2 Hz, 1H), 1.00 (s, 9H), 0.58 (d, J = 6.6 Hz, 3H), 0.13 (s, 3H) 0.09 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 168.6 (s), 94.8 (d), 79.2 (t), 59.6 (d), 36.7 (t), 34.4 (t), 31.4 (t), 30.8 (t), 26.2 (q, 3C), 20.73 (q), 18.5 (s), 17.1 (q), −5.2 (q, 2C).

Trimethyl(5-methyl-1-methylenehex-2-ynyloxy)silane (27). To a solution of 4-methylpentyne **26** (5.88 mL, 50 mmol, 1 equiv) in Et_2O (150 mL) at −78 °C was added dropwise *n*-BuLi (24.4 mL, 2.15 M in hexanes, 52.5 mmol, 1.05 equiv), and the solution was stirred at −78 °C for 1.5 h. A freshly prepared solution of $ZnBr_2$ (60 mL, 1.2 M in Et_2O, 1.45 equiv, 72 mmol) was then added, and the reaction mixture was raised to 0 °C for 30 min. The solution was transferred by cannula to a solution of AcCl (7.85 g, 2 equiv, 100 mmol) in Et_2O (60 mL) at −78 °C, and the solution was allowed to stir at rt for 1 h. The ethereal solution was carefully concentrated under vacuum and diluted with a mixture of pentane/Et_2O (8:2, 30 mL). This solution was filtered on a short silica gel column containing a Celite layer upside (pentane/Et_2O 8:2). After careful evaporation of the solvent, the methyl propargylic ketone (4.71 g, 76%) was obtained: IR (neat) 3000−2800, 2207, 1675, 1358, 1226, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 2.23 (d, J = 6.7 Hz, 2H), 1.88 (m, J = 6.7 Hz, 1H), 0.98 (d,J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.8 (s), 93.1 (s), 82.2 (s), 32.7 (q), 27.9 (t), 27.5 (d), 21.9 (q, 2C); MS (EI) 124 ($M^{\bullet+}$, 3), 109 (M − Me$^+$, 100), 82 (81), 79 (9), 67 (22).

To a solution of the above methyl propargylic ketone (3.54 g, 28.5 mmol, 1 equiv) in THF (100 mL) at −78 °C was added LiHMDS (7.55 g, 45.2 mmol, 1.6 equiv) in THF (20 mL). After 20 min, TMSCl (4.13 mL, 34.2 mmol, 1.2 equiv) was added dropwise, and the solution was stirred for 30 min at 0 °C. The solution was concentrated under vacuum until the precipitation of the salts and was diluted with pentane (150 mL). The resulting suspension was filtered on Celite (washing with pentane) and was concentrated under vacuum. Distillation of the residue (43−50 °C, 0.5 mbar) afforded the TMS enol ether **27** (4.81 g, 86%): IR (neat) 3000−2800, 1605, 1286, 1251, 911, 839, 760, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76 (d, J = 0.4 Hz, 1H), 4.75 (d, J = 0.4 Hz, 1H), 1.93 (d, J = 6.5 Hz, 2H), 1.61 (m, J = 6.7 Hz, 1H), 0.82 (d, J = 6.7 Hz, 6H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3 (s), 101.4 (t), 87.9 (s), 80.0 (s), 28.3 (t), 28.1 (d), 22.0 (q, 2C), 0.3 (q, 3C); MS (EI) 196 ($M^{\bullet+}$, 29), 181 (M − Me$^+$, 27), 153 (M − *i*-Pr$^+$, 58), 154 (79), 139 (M − CH_2-*i*-Pr$^+$, 100), 75 (63), 73 (36).

1-{6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-methyltetrahydropyran-2-yl}-6-methylhept-3-yn-2-one (28). To a solution of the freshly prepared silyl enol ether **27** (4.66 g, 23.8 mmol, 2 equiv) and freshly prepared acetate **25** (3.76 g, 11.9 mmol, 1.0 equiv) in CH_2Cl_2 (160 mL) at −78 °C was added a solution of $ZnCl_2$ (26.2 mL, 1.0 M in Et_2O, 26.18 mmol, 2.2 equiv). The reaction mixture was allowed to warm to rt, quenched by addition of a saturated solution of $NaHCO_3$, and diluted with Et_2O. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/Et_2O 95:5 to 90:10) to afford the *trans*-tetrahydropyran **28** (4.03 g, 89%)-(*trans/cis* THP 13:1 by GC): $[\alpha]_D^{20}$ +44.9 (*c* 0.92, $CHCl_3$); IR (neat) 3000−2800, 2210, 1673, 1462, 1251, 1165, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.60 (dddd, J = 7.7, 6.4, 5.0, 4.6 Hz, 1H), 3.70 (ddd, J = 10.0, 7.5, 5.1 Hz, 1H), 3.61 (m, 1H), 3.36 (ddd, J = 8.7, 7.3, 3.7 Hz, 1H), 2.90 (dd, J = 15.1, 7.7 Hz, 1H), 2.66 (dd, J = 15.1, 6.4 Hz, 1H), 2.26 (d, J = 6.6 Hz, 2H), 1.90 (m, J = 6.7 Hz, 1H), 1.82−1.64 (m, 4H), 1.54−1.28 (m, 3H), 1.01 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.7, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.8 (s), 93.6 (s), 81.8 (s), 73.8 (d), 67.7 (d), 60.1 (t), 48.6 (t), 35.8 (t), 33.6 (d), 28.0 (t), 27.6 (d), 27.5 (t), 26.6 (t), 26.0 (q, 3C), 22.0 (q, 2C), 18.3 (s), 18.2 (q), −5.3 (2q); MS (EI), 323 (M − *t*-Bu$^+$, 27), 293 (58), 199 (100), 175 (10), 143 (37), 139 (14), 131 (19), 109 (41), 107 (34), 99 (25), 81 (M − C_7H_9O, 15), 75 (48); HRMS (ESI) calcd for $C_{22}H_{40}O_3Si + Na^+$ 403.2639, found 403.2640.

1-{6-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-5-methyltetrahydropyran-2-yl}-6-methylhept-3-yn-2-ol (29). To a solution of the propargylic ketone **28** (732 mg, 1.93 mmol, 1 equiv) in a mixture of CH_2Cl_2 (4 mL) and H_2O (4 mL) were added HCOONa (1.31 g, 19.3 mmol, 10 equiv), *n*-Bu_4Cl (96 mg, 0.579 mmol, 0.3 equiv), and Noyori catalyst (*R,R*)Ru-**IV** (12.3 mg, 0.0193 mmol, 0.01 equiv). The solution was stirred for 24 h at rt, and two new portions of catalyst (2 × 0.01 equiv) were added after 24 h and after 48 h of stirring. After 72 h, the aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (AcOEt/petroleum ether 8:92) to afford the propargylic alcohol **29** (558 mg, 76%): $[\alpha]_D^{20}$ +134.7 (*c* 1.15, $CHCl_3$); IR (neat) 3431, 3000−2800, 1462, 1253, 1141, 1089, 1054, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.56 (m, 1H), 4.23 (m, 1H), 3.78−3.66 (m, 2H), 3.55 (m, 1H), 3.27 (d, J = 7.0, 1H, OH), 2.12 (m, 1H), 2.09 (dd, J = 6.6, 2.0 Hz, 2H), 1.92−1.66 (m, 4H), 1.64−1.43 (m, 4H), 1.37 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 7.0, 6H), 0.89 (s, 9H), 0.05 (2s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 84.2 (s), 82.0 (s), 73.9 (d), 68.3 (d), 60.7 (d), 59.8 (t), 40.1 (t), 35.3 (t), 32.8 (d), 28.0 (d), 27.9 (t), 27.6 (t), 26.0 (t), 25.9 (q, 3C), 22.0 (q, 2C), 18.3 (s), 18.2 (q), −5.3 (q), −5.4 (q); MS (EI), 364 (M − 18$^+$, 0.1), 325 (M−*t*Bu$^+$, 1), 217 (26), 199 (38), 143 (31), 125 (32), 107 (49), 105 (36), 101 (30), 99 (100), 95 (39), 81 (33), 75(75), 55 (23); HRMS (ESI) calcd for $C_{22}H_{42}O_3Si + Na^+$ 405.2795, found 405.2795.

2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-[2-(*tert*-butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran (31). To a solution of propargyl alcohol **29** (522 mg, 1.367 mmol, 1 equiv) in THF (15 mL) was added dropwise a Red-Al solution (3.3 mL, 70% in toluene, 10.9 mmol, 8 equiv). After 18 h at 30 °C, the reaction mixture was quenched at 0 °C by a dropwise addition of a saturated solution of potassium sodium tartrate, and the reaction mixture was stirred 30 min at rt. The aqueous layer was extracted with AcOEt (4 × 40 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum.

To a solution of the above residue in CH_2Cl_2 (25 mL) was added 2,6-lutidine (650 μL, 5.47 mmol, 4 equiv). The solution was cooled to −18 °C, and TBSOTf (941 μL, 4.10 mmol, 3 equiv) was added dropwise. The solution was stirred for 2 h at 0 °C, and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was extracted with Et_2O, and the combined organic extracts were washed with H_3PO_4 8% and brine, dried over $MgSO_4$, filtered, and concentrated under vaccum. The residue was purified by silica gel chromatography to afford the allylic TBS ether **31** (624 mg, 92%): $[\alpha]_D^{20}$ +36.6 (*c* 1.02, $CHCl_3$); IR (neat) 3000−2800, 1463, 1254, 1089, 1053, 971, 938, 833, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.52 (dt, *J* = 15.1, 7.0 Hz, 1H), 5.41 (dd, *J* = 15.1, 6.5 Hz, 1H), 4.16 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 4.01 (m, 1H), 3.78 (ddd, *J* = 9.8, 7.8, 4.8 Hz, 1H), 3.69 (dt, *J* = 9.8, 7.3 Hz, 1H), 3.29 (td, *J* = 9.0, 3.0 Hz, 1H), 1.98−1.86 (m, 3H), 1.86−1.72 (m, 2H), 1.68−1.56 (m, 3H), 1.46−1.24 (m, 4H), 0.86−0.91 (m, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4 (d), 128.5 (d), 72.3 (d), 70.4 (d), 68.1 (d), 60.5 (t), 41.6 (t), 40.1 (t), 36.6 (t), 34.8 (d), 29.0 (t), 28.4 (d), 27.4 (t), 26.0 (q, 3C), 25.9 (q, 3C), 22.4 (q), 22.3 (q), 18.3 (q), 18.3 (s), 18.2 (s), −4.0 (q), −4.7 (q), −5.2 (q, 2C); MS (EI), 441 (M − *t*-Bu$^+$, 11), 331 (12), 309 (15), 239 (24), 227 (95), 217 (24), 199 (21), 187 (27), 171 (45), 131 (29), 107 (35), 99 (39), 89 (31), 75 (100), 73 (65); HRMS (ESI) calcd for $C_{28}H_{58}O_3Si_2$ + Na$^+$ 521.3817, found 521.3812.

2-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}ethanol (32). To a solution of compound **31** (3.04 g, 6.09 mmol, 1 equiv) in MeOH (183 mL) was added NH_4F (4.50 g, 122 mmol, 20 equiv), and the reaction was stirred for 4 h at 60 °C. The reaction was quenched by addition of an aqueous solution saturated $NaHCO_3$ (50 mL) and brine (50 mL) and diluted with Et_2O (150 mL). The aqueous layer was extracted with Et_2O (4 × 50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography (Petroleum Ether/AcOEt : 92/8 to 50/50) to afford the unreacted starting material **32** (103 mg, 4%), the monoprotected alcohol **32** (1.88 g, 80%), and the diol **33** (211 mg, 13%): $[\alpha]_D^{20}$ +34.3 (*c* 0.81, $CHCl_3$); IR (neat) 3442, 3000−2800, 1461, 1250, 1070, 1006, 970, 938, 833, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.41 (ddt, *J* = 15.1, 6.5, 1.3 Hz, 1H), 4.19−4.08 (m, 2H), 3.79 (ddd, *J* = 10.8, 6.5, 3.7 Hz, 1H), 3.75 (ddd, *J* = 10.8, 7.5, 3.5 Hz, 1H), 3.40 (td, *J* = 9.0, 3.0 Hz, 1H), 1.99 (ddd, *J* = 14.3, 9.5, 3.3 Hz, 1H), 1.94−1.80 (m, 4H), 1.54−1.72 (m, 3H), 1.51−1.37 (m, 3H), 1.36−1.20 (m, 2H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (d), 129.1 (d), 76.2 (d), 70.8 (d), 69.0 (d), 61.6 (t), 41.5 (t), 39.4 (t), 35.2 (d), 34.8 (t), 29.1 (t), 28.4 (d), 27.3 (t), 25.9 (q, 3C), 22.4 (q), 22.3 (q), 18.2 (s), 18.1 (q), −3.9 (q), −4.9 (q); MS (EI), 327 (M − *t*-Bu$^+$, 0.4), 227 (4), 217 (3), 199 (3), 187 (2), 171 (2), 143 (2), 131 (6), 125 (5), 99 (10), 75 (100); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si$ + Na$^+$ 407.2952, found 405.2952.

1-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}pent-4-en-2-ol (34). To a solution of the primary alcohol **32** (2.12 g, 5.52 mmol, 1 equiv) in CH_2Cl_2 (110 mL) was added dropwise the Dess−Martin periodinane reagent (24.0 mL, 15 wt % in CH_2Cl_2, 11.04 mmol, 2 equiv) at 0 °C. The solution was stirred for 2 h at rt, and the reaction was quenched by the addition of a saturated aqueous solution of K_2CO_3 (20 mL), an aqueous solution of 10% $Na_2S_2O_3$ (20 mL), and water (20 mL). The reaction mixture was stirred for 30 min and then diluted with pentane (100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered over a small pad of silica gel (3 cm, washing with Et_2O), and concentrated under vacuum to obtain the crude aldehyde, which was used in the next step without further purification.

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (4.73 g, 7.73 mmol, 1.4 equiv) in Et_2O (60 mL) at 0 °C was added a solution of allylmagnesium chloride (3.3 mL, 0.5 M in THF, 6.62 mmol, 1.2 equiv). After 2.5 h at 0 °C, the solution was cooled to −78 °C and a solution of the above crude aldehyde in dry Et_2O (10 mL) was added via syringe. After 16 h at −78 °C, deionized water (20 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added, and the mixture was filtered on Celite (washing with Et_2O). The resulting solution was dried over $MgSO_4$, filtered, and concentrated. The residue was diluted with pentane, and the white precipitate [(*R*,*R*)-TADDOL] was sonicated, filtered, and dried in vacuo (2.5 g). Pentane was evaporated and the residue was purified by silica gel chromatography (petroleum ether/Et_2O 95:5 to 7:3) to afford the homoallylic alcohol **34** (1.87 g 80%) and (*R*,*R*)-TADDOL (0.95 g, 95% in total): $[\alpha]_D^{20}$ +31.4 (*c* 0.51, $CHCl_3$); IR (neat) 3446, 3000−2800, 1641, 1462, 1383, 1251, 1141, 1070, 1053, 972, 912, 835, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, *J* = 17.1, 10.3, 7.1 Hz, 1H), 5.53 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.41 (ddt, *J* = 15.1, 7.0, 1.2 Hz, 1H), 5.13−5.06 (m, 2H), 4.19 (ddd, *J* = 9.5, 7.0, 3.1 Hz, 1H), 4.12 (m, 1H), 3.97 (m, 1H), 3.49 (dt, *J* = 9.4, 5.3 Hz, 1H), 3.16 (d, *J* = 3.5 Hz, 1H, OH), 2.29 (dtt, *J* = 13.9, 7.0, 1.3 Hz, 1H), 2.22 (m, 1H), 2.00 (ddd, *J* = 14.2, 9.8, 3.3 Hz, 1H), 1.92−1.81 (m, 3H), 1.67 (dd, *J* = 5.8, 5.1, 2H), 1.66−1.56 (m, 2H), 1.55−1.42 (m, 2H), 1.38 (ddd, *J* = 14.2, 9.5, 4.0 Hz, 1H), 1.35−1.20 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.2 (d), 135.1 (d), 128.9 (d), 117.3 (t), 73.2 (d), 70.7 (d), 69.0 (d), 67.8 (t), 42.1 (t), 41.5 (t), 39.1 (t), 38.1 (t), 34.5 (d), 29.2 (t), 28.3 (d), 27.5 (t), 25.9 (q, 3C), 22.4 (q), 22.3 (q), 18.2 (s), 18.1 (q), −4.0 (q), −4.8 (q); MS (EI), 367 (M − *t*-Bu$^+$, 3), 257 (36), 239 (12), 227 (33), 187 (18), 165 (20), 145 (42), 131 (35), 99 (39), 95 (58), 75 (100); HRMS (ESI) calcd for $C_{25}H_{48}O_3Si$ + Na$^+$ 447.3263, found 447.3265.

***tert*-Butyl-{1-[6-(2-methoxypent-4-enyl)-5-methyltetrahydropyran-2-ylmethyl]-5-methylhex-2-enyloxy}dimethylsilane (35).** To a solution of the homoallylic alcohol **34** (1.80 g, 4.37 mmol, 1 equiv) in Et_2O (8 mL) were added MeI (12.4 g, 87.40 mmol, 20 equiv), Drierite (2 g), and freshly prepared Ag_2O (3.04 g, 13.11 mmol, 3 equiv). After 20 h of vigorous stirring at 20 °C, the brown reaction mixture was filtered on a pad of Celite and concentrated, and the residue was purified by silica gel chromatography (petroleum ether/Et_2O 96/4) to afford the methyl ether **35** (1.79 g, 96%): $[\alpha]_D^{20}$ +48.0 (*c* 0.55, $CHCl_3$); IR (neat) 3000−2800, 1642, 1462, 1252, 1096, 1074, 971, 911, 835, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.54 (dt, *J* = 15.3, 7.1 Hz, 1H), 5.42 (ddt, *J* = 15.3, 6.7, 1.2 Hz, 1H), 5.03−5.12 (m, 2H), 4.20 (ddd, *J* = 9.2, 6.9, 3.0 Hz, 1H), 4.05 (m, 1H), 3.57 (m, 1H), 3.38 (m, 1H), 3.38 (s, 3H), 2.29 (m, 2H), 1.99 (ddd, *J* = 14.1, 9.5, 3.3 Hz, 1H), 1.91 (m, 2H), 1.80 (m, 1H), 1.70 (ddd, *J* = 14.4, 10.1, 2.1 Hz, 1H), 1.66−1.53 (m, 2H), 1.48−1.25 (m, 5H), 0.89 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.3 (d), 134.5 (d), 128.5 (d), 117.2 (t), 76.4 (d), 71.4 (d), 70.4 (d), 68.4 (d), 56.5 (q), 41.5 (t), 40.0 (t), 38.5 (t), 37.8 (t), 35.4 (d), 29.2 (t), 28.3 (d), 27.5 (t), 25.9 (q, 3C), 22.4 (q), 22.2 (q), 18.3 (q), 18.2 (s), −3.9 (q), −4.6 (q); MS (EI), 438 (M$^{\bullet+}$, 0.1), 381 (M − *t*-Bu$^+$, 7), 349 (9), 257 (9), 239 (10), 230 (11), 229 (60), 227 (75), 187 (50), 171 (31), 147 (37), 131 (40), 95 (40), 85 (100), 75 (73), 73 (44); HRMS (ESI) calcd for $C_{26}H_{50}O_3Si$ + Na$^+$ 461.3421, found 461.3419.

5-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}-4-methoxypentane-1,2-diol (36). To a solution of olefin **35** (1.78 g, 4.06 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide (4.26 mmol, 435 mg, 1.05 equiv) in a mixture of *t*-BuOH (40 mL) and H_2O (20 mL) at 0 °C was added a solution of OsO_4 (2.57 mL, 2.5 wt % in *t*-BuOH, 0.203 mmol, 0.05 equiv), and the solution was stirred at 0 °C for 18 h. After 30 min at rt, the reaction mixture was quenched by addition of $Na_2S_2O_3$, and the solution was stirred for 30 min. The solution was diluted with EtOAc and the aqueous layer was extracted with EtOAc. The organic layer was finally washed with brine, dried over

Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ EtOAc 50:50) to afford diol **36** (1.169 g, 61%) in a 1:1 ratio of diastereoisomers and the unreacted starting material **35** (561 mg, 32%): IR (neat) 3398, 3000−2800, 1461, 1380, 1251, 1075, 971, 938, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.52 (dt, $J = 15.3$, 6.9 Hz, 1H), 5.42 (dd, $J = 15.3$, 6.8, Hz 1H), 4.18 (m, 1H), 4.03 (m, 1.5H), 3.89 (m, 0.5H), 3.78 (m, 0.5H), 3.71 (m, 0.5H), 3.61 (m, 1H), 3.46 (m, 1H), 3.41 (s, 1.5H), 3.38 (s, 1.5H), 3.42−3.30 (m, 1H), 2.32 (m, 0.5H), 2.08−1.16 (m, 15.5H), 0.92−0.84 (m, 18H), 0.06 (s, 1.5H), 0.07 (s, 1.5H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (2d), 129.0 (d), 128.9 (d), 77.5 (d), 76.6 (d), 72.6 (d), 72.2 (d), 70.8 (d), 70.7 (d), 70.6 (d), 69.5 (d), 68.8 (d), 68.7 (d), 67.0 (2t), 57.1 (q), 56.2 (q), 41.5 (2t), 40.1 (t), 40.0 (t), 38.6 (t), 38.3 (t), 37.4 (d), 35.5 (d), 35.4 (d), 35.0 (d), 29.1 (t), 29.0 (t), 28.4 (2d), 27.3 (2t), 25.9 (2q, 3C), 22.4 (2q), 22.3 (2q), 18.3 (2s), 18.2 (2q), −3.9 (2q), −4.6 (2q); HRMS (ESI) calcd for $C_{26}H_{52}O_5Si + Na^+$ 495.34762, found 495.34727.

7-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}-6-methoxyhept-1-en-4-ol (37). To a solution of diol **36** (1.15 g, 2.44 mmol, 1 equiv) and *n*-Bu_4NCl (121 mg, 0.732 mmol, 0.3 equiv) in THF (20 mL) was added a saturated aqueous solution of $NaIO_4$ (20 mL, 0.6 M in H_2O, 12.2 mmol, 5 equiv), and the reaction mixture was stirred for 30 min at rt. Celite was added, and the reaction mixture was filtered on a pad of Celite and washed with Et_2O. The ethereal solution was dried over $MgSO_4$, filtered on a pad of silica gel eluting with Et_2O, and concentrated. The crude aldehyde was used in the next step without further purification.

To a suspension of (*R*,*R*)-TaddolCpTiCl complex (3.9 mmol, 2.39 g, 1.6 equiv) in Et_2O (28 mL) at 0 °C was added a solution of allylmagnesium chloride (1.71 mL, 2.0 M in THF, 3.42 mmol, 1.4 equiv). After 2.5 h at 0 °C, the solution was cooled to −78 °C, and a solution of the above crude aldehyde in dry Et_2O (10 mL) was added by syringe. After 16 h at −78 °C, deionized water (15 mL) was added, and the reaction mixture was stirred at rt for 3 days. Celite was added and the mixture was filtered on Celite (washing with Et_2O). The resulting solution was dried over $MgSO_4$, filtered, and concentrated. The residue was diluted with pentane, and the white precipitate [(*R*,*R*)-TADDOL] was sonicated and filtered. Pentane was evaporated, and the residue was purified by silica gel chromatography (toluene/Et_2O 95:5 to 90:10) to afford the homoallylic alcohol **37** (918 mg, 78%): $[\alpha]_D^{20}$ +26.4 (*c* 0.69, $CHCl_3$); IR (neat) 3436, 3000−2800, 1641, 1462, 1382, 1252, 1073, 1073, 970, 911, 834, 775 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, $J = 17.3$, 10.2, 7.1 Hz, 1H), 5.52 (dt, $J = 15.3$, 7.1 Hz, 1H), 5.40 (ddt, $J = 15.3$, 6.9, 1.2 Hz, 1H), 5.14−5.06 (m, 2H), 4.19 (ddd, $J = 9.0$, 7.0, 3.5 Hz, 1H), 4.03 (m, 1H), 3.83 (dtd, $J = 9.3$, 6.1, 2.5 Hz, 1H), 3.70 (m, 1H), 3.34 (m, 1H), 3.37 (s, 3H), 3.20 (br s, 1H, OH), 2.23 (m, 2H), 1.97−1.74 (m, 5H), 1.69 (ddd, $J = 14.4$, 9.4, 7.7 Hz, 1H), 1.66−1.54 (m, 3H), 1.53−1.40 (m, 3H), 1.38−1.25 (m, 2H), 0.99−0.86 (m, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (d), 134.9 (d), 128.9 (d), 117.4 (t), 77.8 (d), 72.4 (d), 70.7 (d), 69.8 (d), 68.7 (d), 56.1 (q), 42.3 (t), 41.5 (t), 40.8 (t), 40.0 (t), 38.8 (t), 35.4 (d), 29.0 (t), 28.4 (d), 27.3 (t), 25.9 (q, 3C), 22.4 (q), 22.2 (q), 18.3 (s), 18.2 (q), −3.9 (q), −4.6 (q); MS (EI), 283 (5), 227 (7), 209 (4), 199 (3), 187 (4), 171 (4), 145 (7), 131 (7), 95 (9), 75 (100); HRMS (ESI) calcd for $C_{28}H_{54}O_4Si + Na^+$ 505.3684, found 505.3679.

7-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}-6-methoxyheptane-1,2,4-triol (38). To a solution of olefin **37** (857 mg, 1.77 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide (198.6 mg, 1.95 mmol, 1.1 equiv) in a mixture of *t*-BuOH (20 mL) and H_2O (10 mL) at 0 °C was added a solution of OsO_4 (900 μL, 2.5 wt % in *t*-BuOH, 0.071 mmol, 0.04 equiv), and the solution was stirred at 0 °C for 18 h. After 30 min at rt, the reaction mixture was quenched by addition of $Na_2S_2O_3$, and the solution was stirred for 30 min. The solution was diluted with EtOAc, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ EtOAc 20:80 to 0:100) to afford the diol **38** (603 mg, 66%) in a 1:1 ratio of diastereoisomers and the unreacted starting material **37** (149 mg, 17%): IR (neat) 3368, 3000−2800, 1461, 1381, 1251, 1075, 971, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.51 (dt, $J = 15.2$, 6.8 Hz, 1H), 5.40 (dd, $J = 15.2$, 7.0 Hz, 1H), 4.24−3.94 (m, 4H), 3.73−3.60 (m, 2.5H), 3.60−3.46 (m, 1.5H), 3.38 (s, 1.5H), 3.37 (s, 1.5H), 3.31 (m, 1H), 1.96−1.28 (m, 18H), 0.91−0.85 (m, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.0 (d), 129.1 (d), 129.1 (d), 78.9 (d), 78.6 (d), 77.2 (d), 77.4 (d), 73.0 (d), 72.9 (d), 70.9 (d), 70.8 (d), 69.0 (d), 68.9 (d), 68.9 (3d), 66.7 (t), 56.2 (q), 56.1 (q), 41.5 (t), 40.0 (3t), 38.5 (t), 38.3 (t), 35.5 (2d), 29.0 (2t), 28.3 (d), 27.2 (2t), 25.9 (q), 22.4 (q), 22.3 (q), 18.3 (2s), 18.2 (q), −3.9 (2q), −4.6 (2q); HRMS (ESI) $C_{28}H_{56}O_6Si + Na^+$ 539.3739, found 539.3733.

9-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}-8-methoxynon-1-ene-4,6-diol (39). To a solution of **38** (595 mg, 1.153 mmol, 1 equiv) and *n*-Bu_4NCl (57 mg, 0.346 mmol, 0.3 equiv) in a mixture of THF (20 mL) and H_2O (10 mL) was added a solution of $NaIO_4$ (10 mL, 0.6 M in H_2O, 5.77 mmol, 5 equiv), and the reaction mixture was stirred for 30 min at rt. Celite was added, and the reaction mixture was filtered on a pad of Celite and eluted with Et_2O. The ethereal solution was dried over Na_2SO_4, filtered on a pad of silica gel eluting with Et_2O, and concentrated. The crude aldehyde was used in the next step without further purification. To a solution of allylTMS (4 mmol, 634 μL) in CH_2Cl_2 (10 mL) was added $SnCl_4$ (4 mmol, 460 μL), and the solution was stirred for 18 h at rt to prepare a solution of allyl$SnCl_3$ (0.36 M).

To a solution of the above crude aldehyde in CH_2Cl_2 (3 mL) at −78 °C was added allyl$SnCl_3$ (4.75 mL, 0.36 M in CH_2Cl_2, 1.73 mmol, 1 equiv), and the solution was stirred for 1 h at −78 °C. The reaction mixture was quenched by the addition of MeOH (0.5 mL) and stirred for 30 min at −78 °C. A saturated aqueous solution of NH_4Cl was then added (3 mL) with apparition of a white precipitate. After warming at rt, the white mixture was filtered on Celite, and the aqueous layer was extracted with Et_2O, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/AcOEt 75:25) to afford the diol **39** (448 mg, 74%): $[\alpha]_D^{20}$ +25.8 (*c* 0.87, $CHCl_3$); IR (neat) 3400, 3000−2800, 1642, 1461, 1407, 1382, 1251, 1075, 971, 913, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, $J = 17.1$, 10.3, 7.1 Hz, 1H), 5.51 (dt, $J = 15.3$, 7.1 Hz, 1H), 5.40 (dd, $J = 15.3$, 6.9 Hz, 1H), 5.13−5.05 (m, 2H), 4.19 (ddd, $J = 9.0$, 7.4, 3.5 Hz, 1H), 4.07−3.99 (m, 2H), 3.92 (m, 1H), 3.66 (m, 1H), 3.35 (s, 3H), 3.28−3.37 (m, 1H), 2.30−2.15 (m, 2H), 1.96−1.70 (m, 6H), 1.40−1.67 (m, 8H), 1.39−1.25 (m, 2H), 0.87 (s, 9H), 0.90−0.85 (m, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.1 (d), 134.9 (d), 129.0 (d), 117.4 (t), 78.1 (d), 72.8 (d), 71.8 (d), 71.6 (d), 70.8 (d), 68.9 (d), 56.1 (q), 42.8 (t), 42.2 (t), 42.1 (d), 41.5 (t), 39.9 (t), 38.4 (t), 35.5 (d), 29.0 (t), 28.3 (d), 27.2 (t), 25.9 (q), 22.4 (q), 22.2 (q), 18.3 (q), 18.1 (s), −3.9 (q), −4.6 (q); HRMS (ESI) calcd for $C_{30}H_{58}O_5Si + Na^+$ 549.3946, found 549.3938.

10-{6-[2-(*tert*-Butyldimethylsilanyloxy)-6-methylhept-3-enyl]-3-methyltetrahydropyran-2-yl}-5,7-dihydroxy-9-methox-dec-2-enoic Acid Methyl Ester (40). To a solution of olefin **39** (0.195 mmol, 102.5 mg, 1 equiv) and methyl acrylate (1.95 mmol, 168 mg, 10 equiv) in CH_2Cl_2 (1 mL) was added Grubbs−Hoveyda catalyst Ru−**III** (18.3 mg, 29.5 μmol, 0.15 equiv). After being stirred for 18 h, the reaction mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography (petroleum ether/AcOEt 70:30) to afford the unsaturated ester **40** (96.0 mg, 84%): $[\alpha]_D^{20}$ +16.2 (*c* 1.04, $CHCl_3$); IR (neat) 3433, 3000−2800, 1726, 1658, 1461, 1436, 1365, 1251, 1075, 972, 938, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.00 (dt, $J = 15.7$, 7.4

Hz, 1H), 5.89 (d, J = 15.7 Hz, 1H), 5.50 (dt, J = 15.2, 7.0 Hz, 1H), 5.40 (dd, J = 15.2, 7.0 Hz, 1H), 4.30−4.13 (m, 2H), 4.08−3.98 (m, 3H), 3.72 (s, 3H), 3.67 (m, 1H), 3.35 (s, 3H), 3.27 (m, 1H), 2.45−2.28 (m, 2H), 1.96−1.68 (m, 6H), 1.66−1.40 (m, 8H), 1.35−1.20 (m, 2H), 0.90−0.83 (m, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8 (s), 145.6 (t), 135.0 (d), 129.0 (d), 123.1 (d) 78.3 (d), 72.9 (d), 71.9 (d), 71.0 (d), 70.8 (d), 68.9 (d), 56.0 (q), 51.4 (q), 42.9 (t), 42.1 (d), 41.5 (t), 40.4 (t), 39.9 (t), 38.2 (t), 35.5 (d), 29.0 (t), 28.3 (d), 27.2 (t), 25.9 (q, 3C), 22.4 (q), 22.2 (q), 18.3 (q), 18.1 (s), −3.9 (q), −4.7 (q); HRMS (ESI) calcd for $C_{32}H_{60}O_7Si + Na^+$ 607.4001, found 607.3993.

(4-Hydroxy-6-{3-[6-(2-hydroxy-6-methylhept-3-enyl)-3-methyltetrahydropyran-2-yl]-2-methoxypropyl}tetrahydropyran-2-yl)acetic Acid Methyl Ester (42). To a solution of the unsaturated ester **40** (46.9 mg, 80 μmol, 1 equiv) in THF (10 mL) at 0 °C was added *t*-BuOK (80 μmol, 1 mg, 0.1 equiv), and the solution was stirred for 1 h. A second portion of *t*-BuOK (0.1 equiv) was then added, and the reaction was stirred for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl, the aqueous layer was extracted with AcOEt, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford the THP ring **41** in a 3/1 (**41**-*cis*/ **41**-*trans*) ratio.

To a solution of the above crude residue in THF (10 mL) was added TBAF (1.6 mL, 1.6 mmol, 1.0 M in THF, 20 equiv), and the reaction mixture was stirred for 24 h. The reaction was quenched by addition saturated $NaHCO_3$ solution, extracted with AcOEt, dried over Na_2SO_4, filtered, and concentrated. The residue was first purified by silica gel chromatography (AcOEt) to afford a mixture of the two diastereoisomers *cis*-**42** and *trans*-**42** THP (19.8 mg, 52%, *cis/trans*: 3/1) and (*Z*,*E*)-dienoic acid **43** (31%). This mixture of diastereoisomers was purified by silica gel chromatography (petroleum ether/AcOEt 20:80) to afford *cis*-**42** THP isomer (14.8 mg, 38%)[28] and *trans*-**42** THP isomer (5.0 mg, 13%): $[\alpha]_D^{20}$ +21.3 (*c* 0.075, $CHCl_3$); IR (neat) 3338, 3000−2800, 1737, 1460, 1379, 1256, 1164, 1087, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.65 (dtd, J = 15.3, 7.2, 1.0 Hz, 1H), 5.49 (ddt, J = 15.3, 6.2, 1.1 Hz, 1H), 4.35 (m, 1H), 4.26−4.18 (m, 2H), 4.00 (m, 1H), 3.85 (m, 1H), 3.66 (s, 3H), 3.60 (m, 1H), 3.53 (m, 1H), 3.30 (s, 3H), 3.20 (br s, 1H, OH), 2.50 (dd, J = 15.1, 8.5 Hz, 1H), 2.37 (dd, J = 15.1, 4.9 Hz, 1H), 1.95−1.16 (m, 18H), 1.00 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (s, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9 (s), 134.5 (d), 129.2 (d), 74.8 (d), 73.2 (d), 68.9 (d), 68.6 (d), 68.4 (d), 66.9 (d), 64.5 (d), 56.4 (q), 51.7 (q), 41.6 (t), 41.1 (t), 40.6 (t), 40.2 (t), 38.7 (t), 38.1 (t), 37.9 (t), 33.3 (d, C_{12}), 28.3 (d), 27.7 (t), 26.2 (t), 22.3 (q), 22.2 (q), 18.5 (q); HRMS (ESI) calcd for $C_{26}H_{46}O_3Si + Na^+$ 493.3141, found 493.3130.

2,4,6-Trichlorobenzoic Acid ester of "Macrocyclic Core of Leucascandrolide A" (48). To a solution of the ester *cis*-**42** (11.0 mg, 23.4 μmol, 1 equiv) in Et_2O (5 mL) was added TMSOK (10.0 mg, 70 μmol, 3 equiv). After being stirred for 16 h, the reaction mixture was diluted with CH_2Cl_2 and quenched by addition of an aqueous solution of $KHSO_4$ 0.1 N until pH 2. The aqueous layer was extracted with CH_2Cl_2 (6 × 30 mL), and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude carboxylic acid **47** was dried by azeotropic removal of water with toluene (2 × 20 mL) and used in the next step without further purification.

To a solution of the above carboxylic acid in toluene (25 mL) was added Et_3N (73 μL, 526 μmol, 15 equiv), followed by 2,4,6-trichlorobenzoyl chloride (83 μL, 526 μmol, 15 equiv) and DMAP (113 mg, 936 μmol, 40 equiv). After 24 h of stirring at 60 °C, the reaction mixture was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (30 mL) and water (20 mL). After stirring for 20 min, the aqueous layer was extracted with AcOEt (20 mL), and the combined organic layers were washed with aqueous $KHSO_4$ 0.1 N (30 mL). The last acidic aqueous phase was extracted with AcOEt (20 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (AcOEt/petroleum ether 40:60) to afford the unexpected 2,4,6-trichlorobenzoic acid ester of leucascandrolide A macrolactone **48** (11.0 mg, 72%) as an oil: $[\alpha]_D^{20}$ +35.8 (*c* 0.45, $CHCl_3$); IR (neat) 3000−2800, 1738, 1579, 1547, 1460, 1369, 1270, 1193, 1160, 1117, 1080, 1058, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1.5H), 7.34 (s, 0.5H), 5.69 (dt, J = 14.3, 7.3 Hz, 1H), 5.47 (t, J = 3.0 Hz, 1H), 5.40−5.30 (m, 2H), 4.09 (t_{app}, J = 11.1 Hz, 1H), 3.88 (d_{app}, J = 12.1, 1H), 3.66 (t_{app}, J = 11.8 Hz 1H), 3.52 (m, 2H), 3.35 (s, 3H), 2.53 (dd, J = 13.1, 3.7 Hz, 1H), 2.33 (m, 1H), 2.35 (dd, J = 13.1, 11.5 Hz, 1H), 2.05−1.20 (m, 15H), 1.16 (d, J = 7.1 Hz, 3H), 0.99 (m, 1H), 0.87 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3 (s), 163.2 (s), 136.3 (s), 132.5 (d), 132.4 (s, 2C), 132.1 (s), 130.0 (d), 128.2 (d, 2C), 73.6 (d), 73.2 (d), 71.2 (d), 70.9 (d), 69.9 (d), 69.6 (d), 63.0 (d), 57.3 (q), 43.1 (t), 42.8 (t), 41.6 (t), 39.1 (t), 35.5 (t), 35.2 (t), 35.1 (t), 30.9 (d), 28.1 (d), 27.1 (t), 24.2 (t), 22.2 (q, 2C), 18.2 (q); HRMS (ESI) calcd for $C_{32}H_{43}O_7Cl_3 + Na^+$ 667.1967, found 667.1962.

Macrocyclic Core of Leucascandrolide A (1). To a solution of the ester *cis*-**42** (10.0 mg, 21.3 μmol, 1 equiv) in Et_2O (5 mL) was added TMSOK (8.2 mg, 64 μmol, 3 equiv). After being stirred for 16 h, the reaction mixture was diluted with CH_2Cl_2 and quenched by addition of an aqueous solution of $KHSO_4$ 0.1 N until pH 2. The aqueous layer was extracted with CH_2Cl_2 (6 × 30 mL), and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude carboxylic acid **47** was dried by azeotropic removal of water with toluene (2 × 20 mL) and used in the next step without further purification.

To a solution of the above carboxylic acid in toluene (100 mL) was added Et_3N (130 μL, 937 μmol, 44 equiv), followed by 2,4,6-trichlorobenzoyl chloride (133 μL, 852 μmol, 40 equiv) and DMAP (25.8 mg, 213 μmol, 10 equiv). After stirring for 1 h at rt, a second portion of DMAP (10 equiv) was added, and the reaction was stirred for 48 h. The reaction mixture was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (30 mL) and water (20 mL). After stirring for 20 min, the aqueous layer was extracted with AcOEt (20 mL), and the combined organic layers were washed with aqueous $KHSO_4$ 0.1 N (30 mL). The last acidic aqueous phase was extracted with AcOEt (20 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (AcOEt/petroleum ether 50:50) to afford the leucascandrolide A macrolactone **1** (7.0 mg, 75%) as an oil: $[\alpha]_D^{20}$ +58.5 (*c* 0.205, EtOH); IR (neat) 3429, 3000−2800, 1738, 1461, 1385, 1272, 1238, 1195, 1167, 1142, 1111, 1076, 1034, 1004, 964 cm^{-1}; ^{1}H NMR (C_5D_5N, 400 MHz) δ 6.38 (br s, 1H, OH), 5.81−5.70 (m, 2H), 5.53 (dd, J = 15.4, 6.9 Hz, 1H), 4.62 (t_{app}, J = 11.6 Hz, 1H), 4.41 (m, 1H), 4.17 (t_{app}, J = 11.3 Hz, 1H), 4.05 (d_{app}, J = 10.9, 1H), 3.91 (t_{app}, J = 10.5 Hz, 1H), 3.74 (t_{app}, J = 10.7 Hz, 1H), 3.36 (s, 3H), 2.67 (dd, J = 12.9, 3.8 Hz, 1H), 2.57−2.42 (m, 2H), 2.10 (app t, J = 12.5 Hz, 1H), 1.95−1.13 (m, 14H), 1.06 (d, J = 7.0 Hz, 3H), 1.12−0.99 (m, 2H), 0.77 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR (C_5D_5N, 100 MHz) δ 170.3 (s), 131.9 (d), 131.5 (d), 73.9 (d), 73.8 (d), 70.9 (d), 69.9 (d), 69.7 (d), 63.8 (d), 63.1 (d), 56.7 (q), 43.9 (t), 43.4 (t), 41.7 (t), 39.9 (t), 39.6 (t), 39.5 (t), 35.9 (t), 31.4 (d), 28.3 (d), 27.4 (t), 24.2 (t), 22.3 (q), 22.2 (q), 18.4 (q); HRMS (ESI) calcd for $C_{25}H_{42}O_6 + Na^+$ 461.2874, found 461.2870.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3**−**10**, **12**−**19**, **22**−**25**, **27**−**29**, **30**−**32**, **34**−**40**, **42**, **1**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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