JOC Article
pubs.acs.org/joc

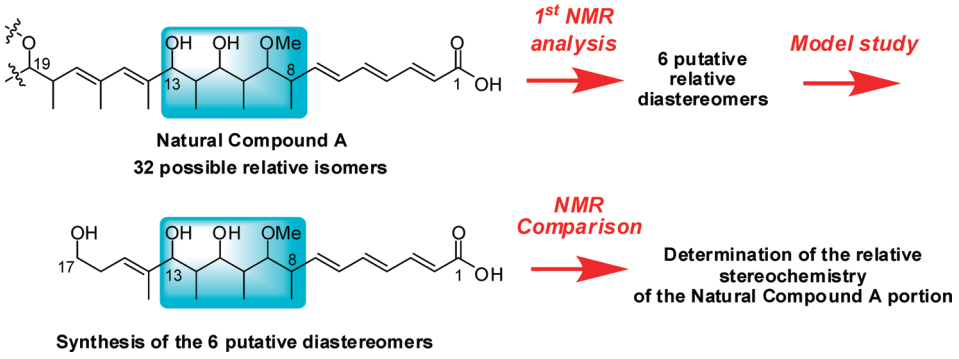
Relative Stereochemical Determination and Synthesis of the C1−C17 Fragment of a New Natural Polyketide

Etienne Fleury,[†] Marie-Isabelle Lannou,[†] Olivia Bistri,[†] François Sautel,[‡] Georges Massiot,[‡] Ange Pancrazi,*[,†] and Janick Ardisson*[,†]

[†]*CNRS UMR 8638, Faculté de Pharmacie, Université Paris Descartes, 4 avenue de l'observatoire, 75270 Paris cedex 06, France, and* [‡]*CNRS/Pierre Fabre UMS 2597, Laboratoire Pierre Fabre, 3 rue des satellites, BP 94244, 31402 Toulouse cedex 4, France*

janick.ardisson@parisdescartes.fr; ange.pancrazi@parisdescartes.fr

Received June 19, 2009



The challenging determination of the relative stereochemistry of a complex natural polyketide portion was achieved. After careful NMR analysis, a concise synthesis of a set of possible relative diastereomers (only 6 diastereomers out of the 32 initially envisioned) has been carried out using a common strategy based on enantioselective aldol reactions. With a high predictability, final NMR comparison established the relative stereochemistry of the C1−C17 fragment of this natural product.

Introduction

For more than a century, polyketides have been of great interest for the scientific community. Natural compounds of this family are produced by various organisms (such as bacteria, sponge invertebrates, fungi or plants) and exhibit a wide range of biological activity (antibiotic, antitumoral, antifungic, or immunomodulatory action) along with a great molecular complexity.[1] Many of them include polypropionate motifs, reflecting their common biosynthesis from propionates.[2]

In general, the low abundance of these natural polyketides requires their total synthesis to deliver significant quantities of pure material for extensive testing. Moreover, in numerous cases, the stereochemistry of these natural products can only be established by stereocontrolled synthesis of putative structures, especially when analytical methods do not permit full assignment.

(1) (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313. (b) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847–2849. (c) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (d) Omura, S. *Macrolide Antibiotics*; Academic Press Inc.: New York, 1984.

(2) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477–493.

(3) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142. (c) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821–1830. (d) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314. (e) For a recent review, see Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525.

(4) (a) Brown, H.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 3701–3702. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570–1576. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348. (d) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359. (e) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806–3813. (f) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572–4573. (g) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475–12476. (h) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995–3998. (i) BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 3029–3031. (j) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948. (k) de Lemos, E.; Porée, F.-H.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.-I.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Chem.—Eur. J.* **2008**, *14*, 11092–11112.

Published on Web 08/20/2009 DOI: 10.1021/jo9012833

© 2009 American Chemical Society

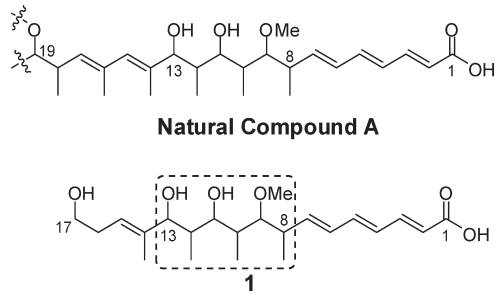


FIGURE 1. Structure of natural product **A** and model compound **1**.

Elaboration of these polypropionates is challenging, considering the number of contiguous stereogenic centers. Therefore, numerous stereocontrolled approaches (such as aldol[3] and allylation/crotylation[4] reactions) have been developed in the past three decades.

In this context, natural compound **A**, a complex polyketide recently isolated by Pierre Fabre laboratories in association with IRD (Institut de Recherche pour le Développement), has been subjected to extensive work in our group (Figure 1).[5] Its full structure elucidation is still under investigation, but the planar structure of the C1−C19 region was well-characterized as a three-propionate subunit (hexad) bordered with polyunsaturated chains. However, the stereochemical information was limited since the very low extraction yield prevented from any derivatization or degradation. The relative configurations of the stereogenic centers in the acyclic C8−C13 subunit were therefore not assigned (32 possible relative diastereomers). To solve this problem, a model compound **1**, close enough to the natural compound to enable NMR comparison, was selected for synthesis (Figure 1).[6]

An extension of Kishi's NMR database method based on a statistical approach was first considered.[7] However, the C9 methyl ether led to internal perturbations that could not be circumvented. Fortunately, a careful NMR data analysis provided an interesting indication. A surprisingly low ^{13}C NMR chemical shift ($\delta = 7.6$ ppm) was noticed for the sole C12 methyl group and this characteristic value is consistent with a *syn*−*syn* stereotriad, whether substituted or not.[8] Consequently, the C11−C13 motif was assigned as a *syn*−*syn* stereotriad, and the C9−C11 motif as a *syn*−*anti*, *anti*−*syn*, or *anti*−*anti* stereotriad.

As a result of these considerations, only 6 relative diastereomers (**1a**−**f**) out of the 32 initially envisioned could potentially correspond to natural product **A** (Figure 2). We set out to synthesize these 6 compounds (**1a**−**f**) to determine the correct relative stereochemistry of the natural product.

Results and Discussion

As outlined in Scheme 1, the deconvolution of target **1** into three fragments **2**, **3**, and **4** has been envisaged.

Noteworthy, all the required stereovariations will occur in the central fragment **4**. This subunit presents five of the six contiguous stereogenic centers of the C8−C13 hexad, the C13 carbonyl group being subsequently reduced. The final set up of the adjacent unsaturations will be achieved through a nucleophilic addition and a Horner−Wadsworth−Emmons olefination (Scheme 1).

Phosphonate **2** was readily accessible from sorbic acid **5** in three steps. The carboxylic acid function was protected as a trimethylsilylethyl ester.[9] Indeed, a fluorine-cleavable protecting group proved to be necessary at this position since classical saponification methods[10] of the corresponding ethyl ether failed to regenerate the acid in advanced stages of the synthesis. A cross metathesis/Arbuzov sequence developed by Cossy[11] was then applied to **6** to yield phosphonate **2** with a high selectivity (95% de, estimated by NMR analysis of the crude reaction mixture; Scheme 2).

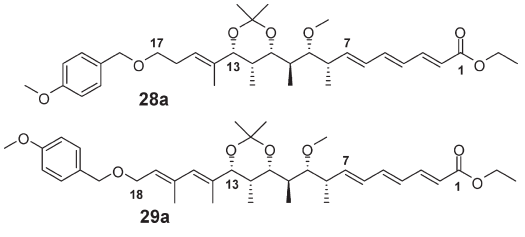
Compound **3** was efficiently prepared, with a total selectivity, from commercial 2,3-dihydrofuran **7** using a cuprate transposition developed by Kocienski[12] and recently applied in total synthesis in our laboratory.[4k,13] The resulting vinyl tin species **8** was protected at the C17 position as a *tert*-butyldiphenylsilyl ether and a Sn/Br or Sn/I exchange step was performed to lead to vinyl bromide **3a** or vinyl iodide **3b** (Scheme 3).

The central fragment **4** features the polypropionate pattern of **1** and therefore constitutes the portion where the stereovariation must take place to access all diastereomers **4a**−**f** (Figure 3) and, consequently, **1a**−**f**. We designed a straightforward strategy that could provide the six isomers using common intermediates and featuring a minimum number of steps.

Stereocontrolled installation of the C11−C12 and C9−C10 hydroxy-methyl patterns would arise from iterative boron-mediated aldol reactions, involving aldehydes **9** and **10**, respectively. The C8 stereocenter would derive from Roche ester **11**, commercially available in its (*R*) or (*S*) configuration (Scheme 4).

(5) The C1−C19 portion represented in Figure 1 features approximatively half of the actual natural molecule.

(6) The relevant choice of a vinyl C14−C15 motif instead of the C14−C17 diene (like in the natural compound **A**) was proved by preliminary NMR studies: no significant NMR differences were observed for the C8−C13 sequence between the two products **28a** and **29a** shown below (see Supporting Information for synthesis and NMR data of these two compounds).



(7) (a) Fleury, E.; Lannou, M.-I.; Bistri, O.; Sautel, F.; Massiot, G.; Pancrazi, A.; Ardisson, J. *Eur. J. Org. Chem.* **2009**, in press. (b) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180. (c) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2181–2184. (d) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076–2078.

(8) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980–3992.

(9) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772–1783.

(10) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028–15029.

(11) (a) Amans, D.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5870–5874. (b) Ferrié, L.; Amans, D.; Reymond, S.; Bellosta, V.; Capdevielle, P.; Cossy, J. *J. Organomet. Chem.* **2006**, *691*, 5456–5465. (c) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509–5512. (d) Schöning, K.-U.; Wittenberg, R.; Kirschning, A. *Synlett* **1999**, 1624–1626.

(12) (a) Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363–2365. (b) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933–1940. (c) Le Ménez, P.; Fargeas, V.; Berque, I.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592–3599. (d) Fargeas, V.; Le Ménez, P.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613–6634.

(13) de Lemos, E.; Porée, F.-H.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1917–1921.

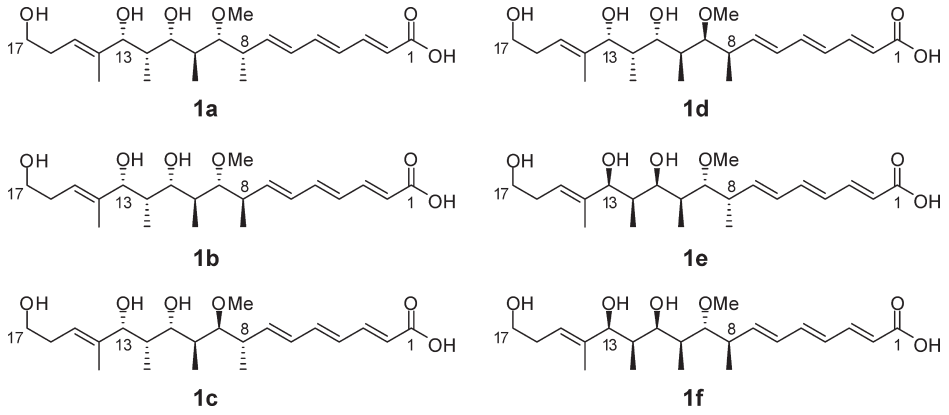
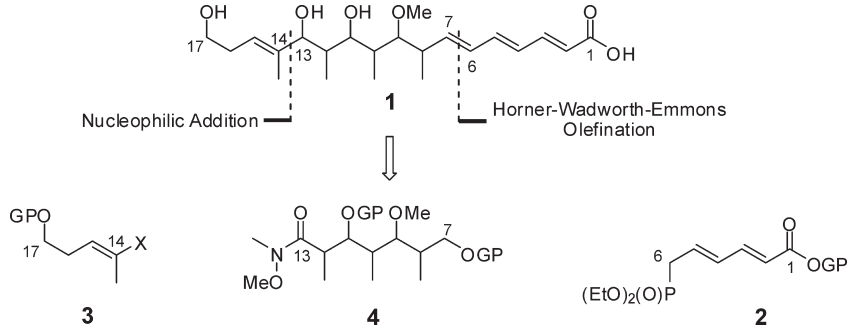
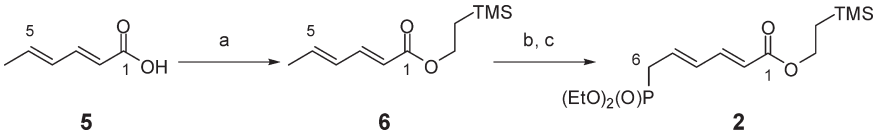


FIGURE 2. Structure of the six putative relative diasteromers **1a**−**f** corresponding to natural product **A**.

SCHEME 1. Retrosynthetic Analysis of Target Compound 1

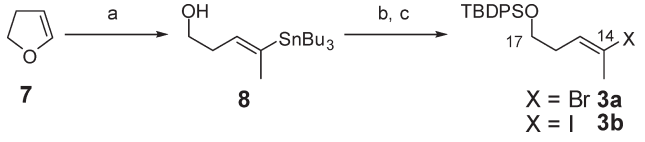


SCHEME 2. Synthesis of Fragment 2[a]



[a]Reagents and conditions: (a) $TMSCH_2CH_2OH$, PPh_3, DIAD, THF, 0 °C → r.t., 18 h, 83%; (b) allyl bromide, Grubbs−Hoveyda second generation catalyst 3 mol %, CH_2Cl_2, r.t., 24 h, 62%; (c) $P(OEt)_3$, 120 °C, 1 h, 96%.

SCHEME 3. Synthesis of Fragment 3[a]



[a]Reagents and conditions: (a) (i) *t*-BuLi, THF, −78 °C → 0 °C, 50 min, (ii) $(Bu_3Sn)_2CuLi \cdot LiCN$, Et_2O, −78 °C → 0−5 °C, 90 min, (iii) MeI, −30 °C → r.t., 5 h, 92%; (b) TBDPSCl, imidazole, DMF, r.t., 90 min, 99%; (c) (i) for **3a**: NBS, CH_2Cl_2, 0 °C, 45 min, quant., (ii) for **3b**: I_2, CH_2Cl_2, 0 °C, quant.

The first goal was to synthesize aldehydes **9a**−**d**. To this aim, Paterson's boron-mediated aldol reaction turned out to be the most appropriate, because all of the four possible relative configurations of the C8−C10 stereotriad were accessible from only two aldehydes (***S*)-10** and (***R*)-10** and two known ketones **12** and **13** derived from ethyl (*S*)-lactate **14** (Scheme 5).[14] Noteworthy, Paterson's boron-mediated aldol reaction leads to the *E*- or *Z*-enolate formation and consequently to the *anti* or *syn* aldol product

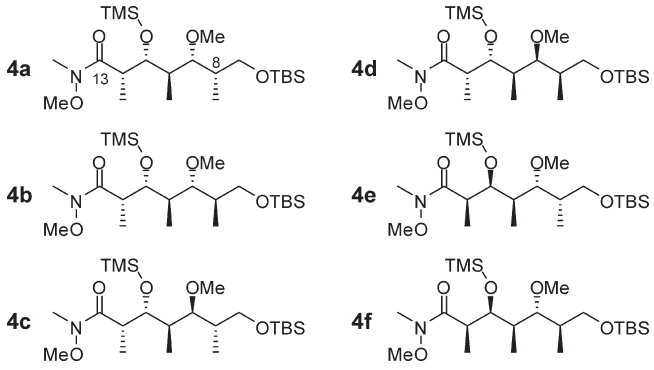
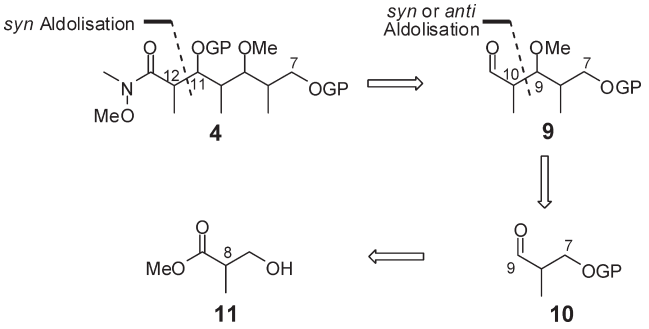


FIGURE 3. Structure of the six diastereomers **4a**−**f**.

(14) (a) Paterson, I. *Synthesis* **1998**, 639–652. (b) Goodman, J. M.; Paterson, I. *Tetrahedron Lett*. **1992**, *33*, 7223–7226. (c) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett*. **1994**, *35*, 9083–9086. (d) Paterson, I.; Wallace, D. J. *Tetrahedron Lett*. **1994**, *35*, 9087–9090. (e) Paterson, I.; Wallace, D. J. *Tetrahedron Lett*. **1994**, *35*, 9477–9480. (f) Paterson, I.; Chen, D. Y.-K.; Acena, J. L.; Franklin, A. S. *Org. Lett*. **2000**, *2*, 1513–1516. (g) Paterson, I.; Collett, L. A. *Tetrahedron Lett*. **2001**, *42*, 1187–1191. (h) Crossman, J. S.; Perkins, M. V. *J. Org. Chem*. **2006**, *71*, 117–124.

SCHEME 4. Retrosynthetic Analysis of Fragment 4



15a−**d** according to the hydroxyl protecting group (Bz or Bn) of the starting ketones (**12** or **13**) and the enolization conditions.

Commercially available (*S*)-Roche ester (***S***)-**11** was converted into aldehyde (***S***)-**10** by silylation of the C7 alcohol function, ester reduction and subsequent Swern oxidation of the C9 alcohol.[4c] This aldehyde was then engaged in a substrate-controlled aldol coupling with the *E*-dicyclohexylboroenolate derived from α-chiral ketone **12** to give the *anti* aldol product **15a** with an excellent diastereoselectivity (>95% de, estimated by NMR; Scheme 6).[15]

The C9 hydroxyl group of the resulting α-keto alcohol **15a** was subsequently methylated to provide compound **16a**. The most efficient method consisted in the use of methyl trifluoromethanesulfonate with 2,6-di-*tert*-butyl-4-methylpyridine in refluxing dichloromethane.[16] The reduction of both ketone and ester functionalities with lithium borohydride led to the corresponding diol, which was then cleaved by treatment with sodium periodate to yield aldehyde **9a**.

Synthesis of diastereomer **9b** was performed in an identical manner, starting from (*R*)-Roche ester (***R***)-**11** (Scheme 6). As before, the aldol reaction was achieved with a high diastereoselectivity.

Finally, for the synthesis of aldehyde **9c**, the aldol reaction starting from α-chiral ketone **13** generated the *syn* aldol product **15c** (over 90% de, estimated by NMR). After reduction of the ketone, the benzyl ether was cleaved by hydrogenolysis and subsequent oxidative cleavage with sodium periodate afforded aldehyde **9c**. Synthesis of diastereomer **9d** was performed in an identical manner (similar de was obtained), starting from (***R***)-**11** (Scheme 7).

Having the four possible relative diastereomers of the C7−C11 segment in hand, the synthesis of the six diastereomers **1a**−**f** was now possible through the setting up of the *syn* C11−C12 hydroxy-methyl core. First studies showed that Paterson's boron-mediated aldol reaction failed to give the expected aldol product. Fortunately, Evans aldol reaction, starting from (***S***)-**17**,[17] successfully led to **18a** (with over 95% de, estimated by NMR).[18] After conversion of the oxazolidine moiety into a Weinreb amide functionality,[19] the C11 alcohol was protected as a trimethylsilyl ether **4a**.

This synthetic pathway was performed in an identical manner to afford diastereomers **4b**−**f**, with similar selectivities (Scheme 8).

The synthesis of the six diastereomers **1a**−**f** was now possible through the coupling of fragments **2** and **3** with **4a**−**f** (Scheme 9).

Vinyl bromide **3a** was treated with *tert*-butyllithium to generate the corresponding lithiated species, which could successfully be coupled to Weinreb amide **4a**.[20] Surprisingly, we found that lithiation of the vinyl iodide **3b** only led to the degradation of amide **4a**.

The C11 alcohol function was then deprotected and the C13 stereocenter was set up through a 1,3 diastereoselective reduction. The best result was obtained with zinc borohydride, and the *syn*−*syn* C11−C12−C13 stereotriad of **19a** was generated in 91% yield and high diastereoselectivity (over 90% de, NMR estimation).[21] The C7 primary alcohol function was then deprotected and the corresponding triol was treated with triethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine. Differentiation between the triethylsilyl ethers was achieved by selective oxidation of the protected primary alcohol function into aldehyde **20a**.[22]

This aldehyde was further involved in a Horner−Wadsworth−Emmons olefination[23] with phosphonate **1** to generate the C6−C7 double bond with over 95:5 *E* stereoselectivity (^{1}H NMR analysis). Final deprotection was performed with *tris*(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) to afford acid **1a**.[24]

Finally, the five other diastereomers **1b**−**f** were synthesized, following the same sequence as depicted in Scheme 9.

NMR Comparison

A direct comparison between natural product **A** and the six synthesized diastereomers **1a**−**f** was performed. Concerning

(15) Aldol product **15a** was already described, see (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535–9544. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377−380. The stereochemistry assignment of other aldol products **15** was achieved through NOESY experiments of corresponding δ-lactols **30** generated by cleavage of the silyl ether (see Solsona, J. G.; Romea, P.; Urpi, F. *Tetrahedron Lett.* **2005**, *45*, 5379−5382 and Supporting Information).

(16) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583–3586.

(17) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176–5183.

(18) Kangani, C. O.; Brückner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379–382.

(19) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.-X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433–15442.

(20) (a) Raimundo, B. C.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 27–28. (b) Marumoto, S.; Kogen, H.; Naruto, S. *Tetrahedron* **1999**, *55*, 7145–7156. (c) Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058–5060. (d) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643–1645. (e) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett.* **2000**, *41*, 621–624.

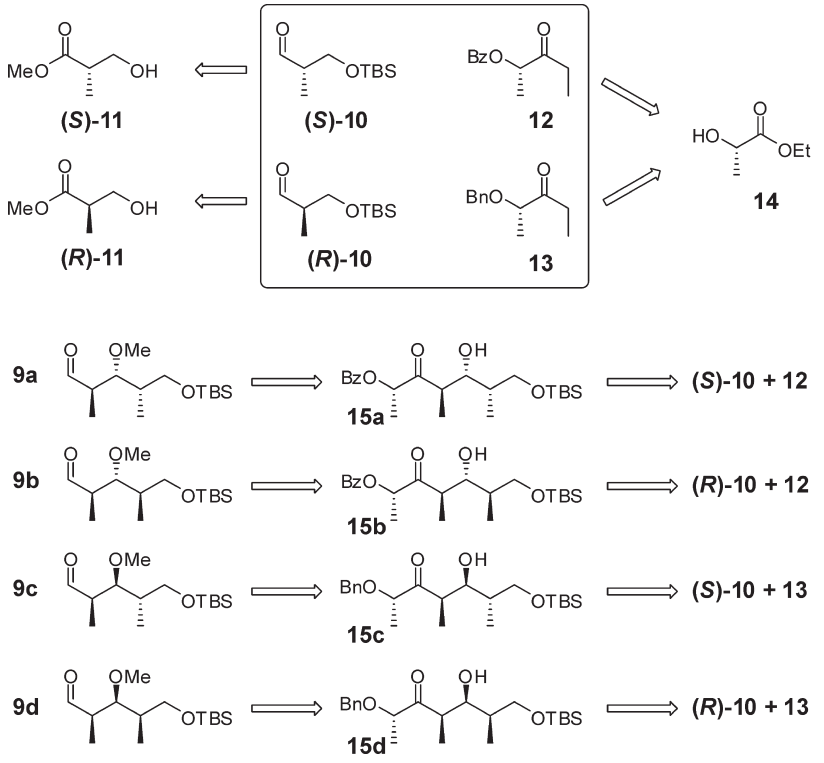
(21) This diol **19a** was converted into the corresponding acetonide compound **28a** (see Supporting Information). ^{13}C NMR analysis according to the Rychnovsky method confirmed the presence of a C11−C12−C13 *syn*−*syn* relationship.

(22) (a) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161–5164. (b) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J.; Lee, T. H. *Tetrahedron* **2001**, *57*, 25–37. (c) Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Rassu, G.; Pinna, L.; Auzzas, L.; Zambrano, V.; Casiraghi, G. *Eur. J. Org. Chem.* **2002**, 1956–1964. (d) Hübner, J.; Liebscher, J.; Pätzel, M. *Tetrahedron* **2002**, *58*, 10485–10500.

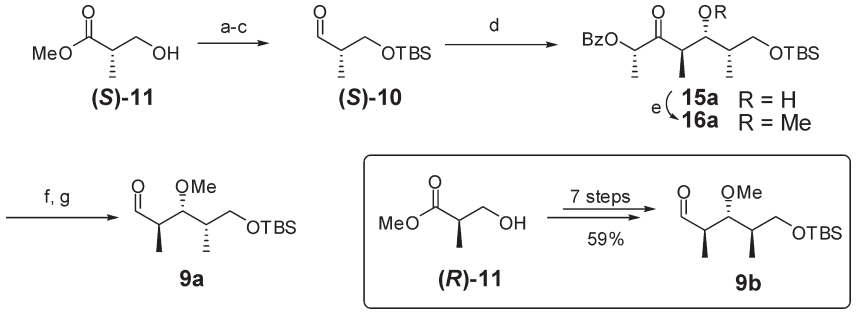
(23) (a) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899–10905. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696.

(24) For all this sequence, the choice of hydroxyl and acid protecting groups was imposed by problems of selectivity and stability of the different synthetic intermediates.

SCHEME 5. Retrosynthetic Analysis of Aldehydes 9a−d

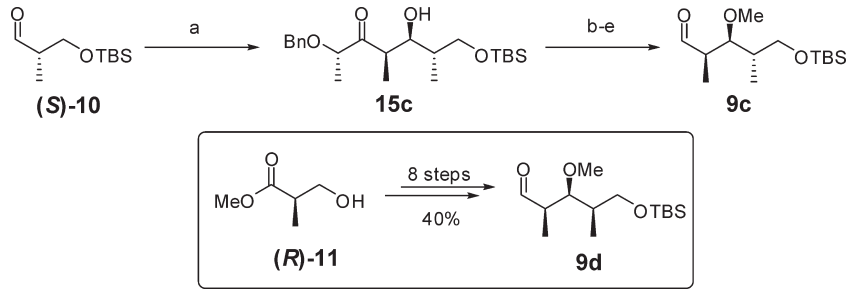


SCHEME 6. Synthesis of Aldehydes 9a and 9b[a]



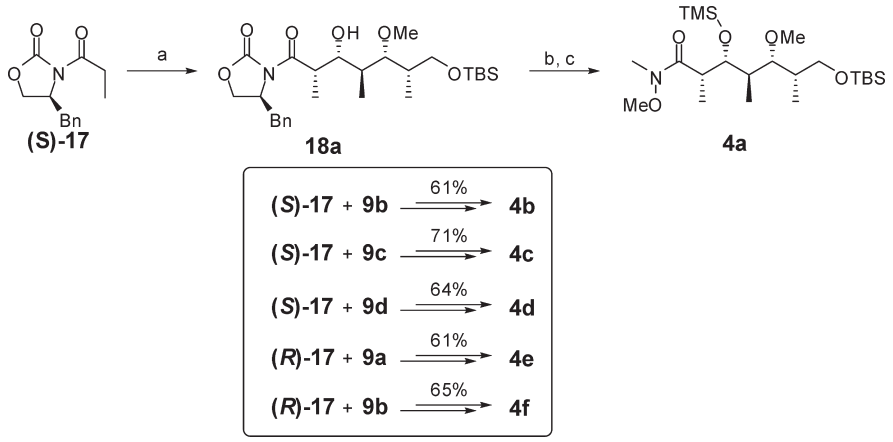
[a]Reagents and conditions: (a) TBSCl, imidazole, DMF, r.t., 18 h; (b) DIBAL-H, CH_2Cl_2, −40 °C → −20 °C, 3 h, 98% over 2 steps; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −55 °C, 1 h, (ii) Et_3N, r.t., 1 h, 100%; (d) (i) **12**, $ClB(Cy)_2$, Me_2NEt, Et_2O, 0 °C, 2 h, (ii) (**S**)-**10**, −78 °C → −25 °C, 16 h, 98%; (e) MeOTf, DTBMP, CH_2Cl_2, 45 °C, 24 h, 76%; (f) $LiBH_4$, THF, −78 °C → r.t., 16 h; (g) $NaIO_4$, MeOH, r.t., 20 min, 84% over two steps.

SCHEME 7. Synthesis of Aldehydes 9c and 9d[a]



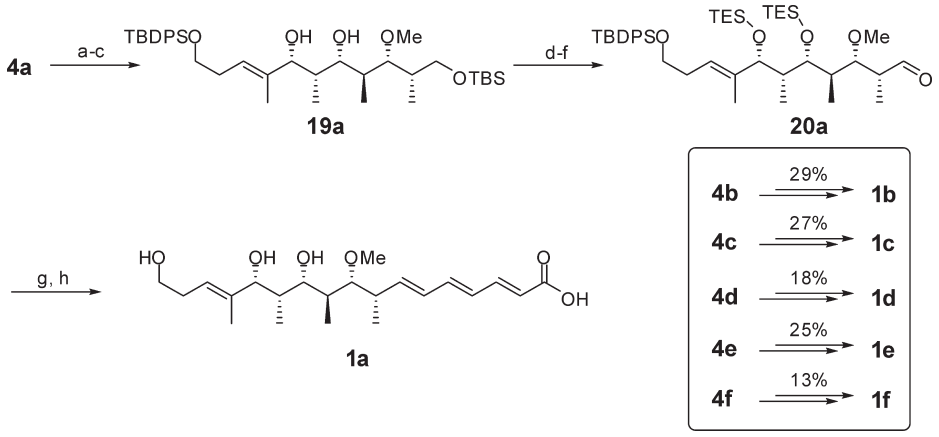
[a]Reagents and conditions: (a) (i) **13**, $ClB(Cy)_2$, Et_3N, Et_2O, −78 °C, 2 h, (ii) (**S**)-**10**, −78 °C → −25 °C, 16 h, 84%; (b) MeOTf, DTBMP, CH_2Cl_2, 45 °C, 24 h, 75%; (c) $LiBH_4$, THF, −78 °C → r.t., 16 h; (d) Pd/C, H_2 (1 atm), EtOH, r.t., 16 h; (e) $NaIO_4$, MeOH, r.t., 20 min, 65% over three steps.

SCHEME 8. Synthesis of Weinreb Amides 4a−f[a]



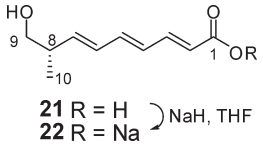
[a]Reagents and conditions: (a) (i) (**S**)-**17**, *n*-BuOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, (ii) **9a**, −78 °C → 0 °C, 90 min, 91%; (b) MeONHMe·HCl, $AlMe_3$, CH_2Cl_2, −20 °C → r.t., 16 h, 75%; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C, 1 h, 93%.

SCHEME 9. Synthesis of the Four Diastereomers 1a−f[a]



[a]Reagents and conditions: (a) (i) **3**, *t*-BuLi, Et_2O, −90 °C, 10 min, (ii) **4a**, −78 °C → −50 °C, 1 h; (b) Amberlyst-15, MeOH, r.t., 30 min, 85% over two steps; (c) $Zn(BH_4)_2$, Et_2O, CH_2Cl_2, −78 °C → −50 °C, 5 h, 91%; (d) AcOH, THF, H_2O, r.t., 16 h, 88%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 45 min, 99%; (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −80 °C → −55 °C, 1 h, (ii) Et_3N, −80 °C → r.t., 1 h; (g) (i) **2**, LDA, THF, −78 °C, 15 min, (ii) **20a**, −78 °C → 0 °C, 45 min, 59% over two steps; (h) TAS-F, DMF, 0 °C, r.t., 9 h, 67%.

SCHEME 10. Synthesis of Model Compounds 21 and 22



the trienic portion, an inconsistency was immediately noticed. Indeed, a large difference in ^{13}C and ^{1}H NMR chemical shifts was observed between compound **A** and all diastereomers with a decreasing impact from position 1 to 7 (Figure 4).

A dilution effect was first assumed to explain this difference, but subsequent experiences ruled out this hypothesis. The observed chemical shift differences were then supposed to be attributed to the presence of a carboxylate salt in natural product **A**. To prove this assumption and to determine whether this could affect the polypropionate section or not, a model compound **21** was synthesized[25] and converted into its corresponding sodium carboxylate salt **22** (Scheme 10).

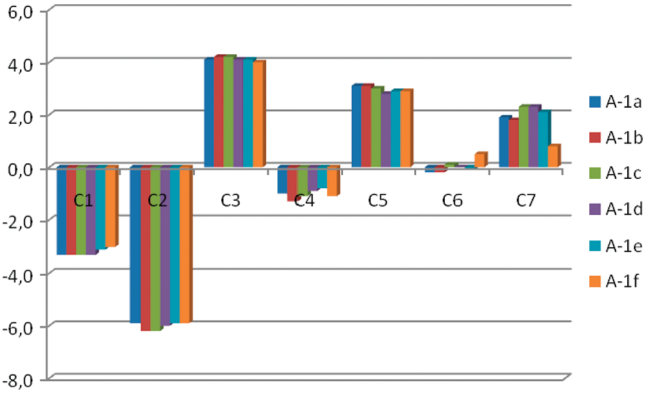


FIGURE 4. $\Delta\delta$ ^{13}C (ppm) between **A** and **1a−f** for carbons 1 to 7.

(25) Model compound **21** was prepared from the aldehyde (***R***)-**10** and phosphonate **2** (through the same sequence as the one described in Scheme 9).

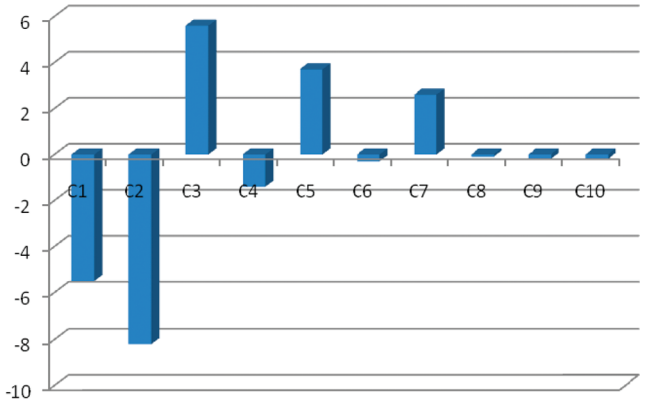


FIGURE 5. $\Delta\delta$ ^{13}C (ppm) between **21** and **22** for carbons 1−10.

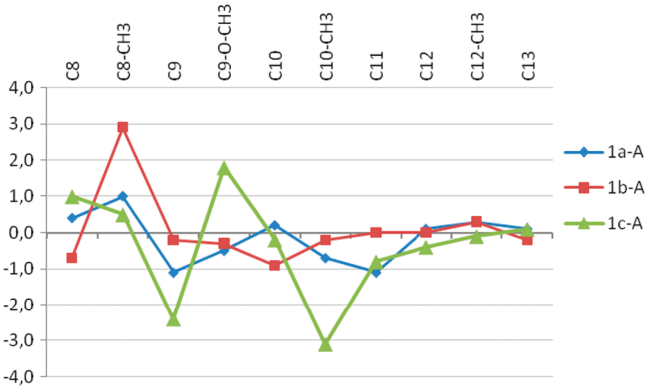


FIGURE 6. $\Delta\delta$ ^{13}C (ppm) between **A** and **1a**−**c** for the C8−C13 subunit.

A chemical shift deviation profile was observed for carbons C1−C7 by ^{13}C NMR data comparison between compounds **21** and **22**. Because this deviation was similar to that observed between diastereomers **1a**−**f** and **A**, natural compound **A** was then deduced to be extracted as a carboxylate salt, but the nature of the counterion could not be determined.

Unfortunately, the available quantity of natural compound **A** did not allow its conversion into the corresponding carboxylic acid. However, it is interesting to note that this salt effect does not affect the saturated portion (see C8, C9, and C10 in Figure 5). An NMR comparison of the central polyketide portion C8−C13 of **1a**−**f** with natural compound **A** was therefore possible.

The differences in the ^{13}C NMR spectra are highlighted in Figures 6 and 7 by plotting the chemical shift difference observed for each carbon of the C8−C13 portion between natural product **A** and **1a**−**f**.

There is a significant difference ($\Delta\delta$ > 1 ppm) in the chemical shift of a number of peaks for compounds **1c**−**f**, most notably at positions C9, C9-O-CH$_3$, and C10-CH$_3$ for **1c** and **1d** and at positions C12, C12-CH$_3$, and C13 for **1e** and **1f**. Consequently, these structures could not be correlated with the natural product **A**.

For compounds **1a** and **1b**, the difference in ^{13}C NMR chemical shifts is low ($\Delta\delta$ < 1 ppm), except for the C8-CH$_3$ position of **1b** ($\Delta\delta$ = 2.8 ppm). We turned to ^{1}H NMR comparison to clearly distinguish the two compounds (Figure 8).

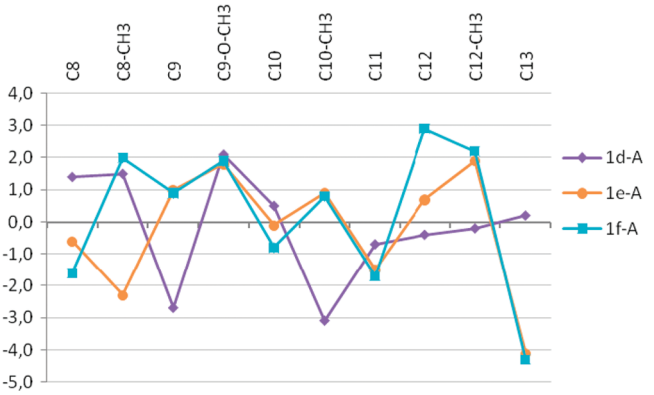


FIGURE 7. $\Delta\delta$ ^{13}C (ppm) between **A** and **1d**−**f** for the C8−C13 subunit.

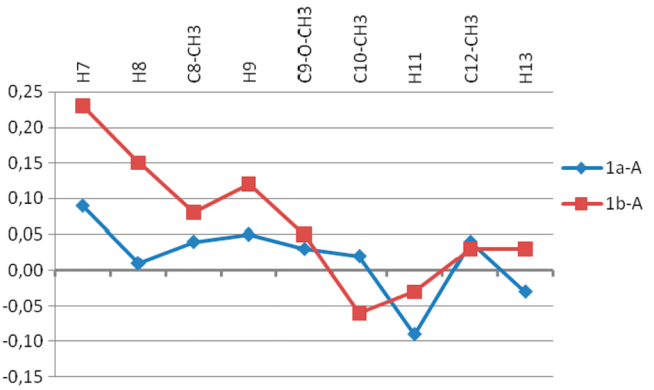


FIGURE 8. $\Delta\delta$ ^{1}H (ppm) between **A** and **1a** and **1b** for the C7−C13 subunit.

TABLE 1. Comparison of the ^{1}H and ^{13}C NMR Data for Natural Compound A and Isomer 1a

	compound A		isomer **1a**	
carbon No.	δH, m, ^{3}J [Hz]	δC	δH, m, ^{3}J [Hz]	δC
C8	2.53, m	41.5	2.54, m	41.8
C8-CH$_3$	1.07, d, 6.7	17.2	1.10, d, 6.7	18.1
C9	3.27, dd, 6.7, 4.6	88.3	3.32, dd, 7.4, 3.6	87.3
C9-O-CH$_3$	3.38, s	59.6	3.41, s	59.1
C10		40.1	2.03, m	40.3
C10-CH$_3$	0.85, d, 7.0	13.0	0.86, d, 6.9	12.4
C11	3.57, dd, 9.6, 2.0	75.5	3.49, dd, 10.1, 1.7	74.5
C12		38.5	1.78, m	38.6
C12-CH$_3$	0.93, d, 7.0	7.6	0.96, d, 7.0	7.9
C13	3.99, d, 7.3	82.1	3.97, d, 8.1	82.2

In this case, a much closer correlation with natural product **A** is observed for compound **1a**, especially with regard to protons H7, H8, C8-CH$_3$, and C9-OCH$_3$. The small variations ($\Delta\delta_{max}$ = 0.08 ppm for the C8−C13 portion) can be explained by the structural differences between our model and the natural compound. On this basis, the relative configuration of the natural compound **A** is assigned as isomer **1a** (see Table 1 for full NMR comparison between **A** and **1a** and Supporting Information for full NMR comparison between **A** and **1b**−**f**).[26]

(26) Analysis of the coupling constants also displays a good correlation between **1a** and **A**.

Conclusion

In summary, the relative stereochemistry of the six contiguous stereogenic centers of the C8−C13 segment of a recently isolated natural compound was convincingly determined. A relevant initial NMR analysis allowed us to decrease the number of putative relative isomers from 32 to 6. The next step consisted in designing a synthetic model of the C1−C19 part of **A**, whose isomers were prepared through a highly convergent strategy. With a high predictability, a final thorough comparison of the ^{13}C and ^{1}H NMR data of the natural compound with those of the model isomers enabled the full relative structural assignment of this large part of the natural compound.

Experimental Section

(2*E*,4*E*)-2-(Trimethylsilyl)ethyl Hexa-2,4-dienoate 6. To a cooled (0 °C) solution of sorbic acid **5** (1.0 g, 8.9 mmol, 1.0 equiv) in THF (60 mL) were added successively trimethylsilylethanol (1.7 mL, 11.6 mmol, 1.3 equiv), triphenylphosphine (4.7 g, 17.8 mmol, 2.0 equiv), and DIAD (3.5 mL, 17.8 mmol, 2 equiv). The mixture was stirred at this temperature for 3 h. The solvent was then removed in vacuo, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc 100:0 to 85:15) to yield ester **6** (1.6 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.01 (m, 2H), 1.84 (d, J = 5.5 Hz, 3H), 4.22 (m, 2H), 5.75 (d, J = 15.9 Hz, 1H), 6.05−6.25 (m, 2H), 7.23 (dd, J = 15.9, 9.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.4 ($3CH_3$), 17.3 (CH_2), 18.6 (CH_3), 62.3 (CH_2), 119.2 (CH), 129.8 (CH), 139.1 (CH), 144.7 (CH), 167.4 (C). IR (Film) ν 2981, 1721, 1644, 1245, 1192, 1147, 1111 cm^{-1}.

(2*E*,4*E*)-2-(Trimethylsilyl)ethyl 6-(Diethoxyphosphoryl)hexa-2,4-dienoate 2. Ester **6** (1.6 g, 7.4 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (70 mL). The solution was flushed with argon for 10 min. Allylbromide (3.2 mL, 36.9 mmol, 5.0 equiv) and Grubbs−Hoveyda catalyst second generation (0.1 g, 0.2 mmol, 3 mol %) were then added successively. The mixture was stirred at room temperature for 2 days. The solvent was then removed under reduced pressure and the residue was purified by chromatography on silica gel (cyclohexane/Et_2O 97.5:2.5−80:20) to afford the expected bromide (1.3 g, 62% yield) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.02 (m, 2H), 4.03 (d, J = 7.2 Hz, 2H), 4.25 (m, 2H), 5.92 (d, J = 15.3 Hz, 1H), 6.23 (dt, J = 15.6, 7.2 Hz, 1H), 6.38 (dd, J = 15.6, 10.8 Hz, 1H), 7.24 (dd, J = 15.3, 10.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5 ($3CH_3$), 17.3 (CH_2), 31.3(CH_2), 62.8 (CH_2), 123.5 (CH), 131.9 (CH), 136.4 (CH), 142.3 (CH), 166.6 (C). IR (Film) ν 2985, 1712, 1642, 1330, 1252, 1191, 1147, 832 cm^{-1}.

The previous bromide (1.2 g, 4.3 mmol, 1.0 equiv) was dissolved in triethylphosphite (5.0 mL, 29.9 mmol, 7.0 equiv) and the mixture was heated at 120 °C for 1 h. The solution was then cooled down to 70 °C and the excess triethylphosphite was removed under reduced pressure (∼1 mmHg). The crude product **2** (1.5 g, 100% yield) was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.97−1.05 (m, 2H), 1.27−1.36 (m, 6H), 2.71 (dd, J = 24.0, 7.7 Hz, 2H), 4.05−4.15 (m, 4H), 4.19−4.26 (m, 2H), 5.83 (d, J = 15.5 Hz, 1H), 6.05 (dq, J = 15.9, 7.7 Hz, 1H), 6.30 (ddd, J = 15.9, 11.0, 4.9 Hz, 1H), 7.23 (dd, J = 15.5, 11.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5 ($3CH_3$), 16.4 (d, $2CH_3$, $^{3}J_{C/P}$ = 5.9 Hz), 17.3 (CH_2), 31.3 (d, CH_2, $^{1}J_{C/P}$ = 139.5 Hz), 62.2 (d, $2CH_2$, $^{2}J_{C/P}$ = 6.8 Hz), 62.6 (CH_2), 121.5 (d, CH, $^{5}J_{C/P}$ = 4.1 Hz), 131.3 (d, CH, $^{3}J_{C/P}$ = 12.6 Hz), 132.9 (d, CH, $^{2}J_{C/P}$ = 14.5 Hz), 167.1 (C), 143.3 (d, CH, $^{4}J_{C/P}$ = 4.7 Hz). IR (Film) ν 2954, 1720, 1251, 1168, 1027, 977, 838 cm^{-1}.

(*E*)-4-(Tributylstannyl)pent-3-en-1-ol 8. To a solution of $(Bu_3Sn)_2$ (19.7 mL, 50.3 mmol, 1.9 equiv) in THF (20 mL) at −40 °C was slowly added *n*-BuLi (1.6 M solution in hexanes, 33.1 mL, 31.7 mmol, 2.0 equiv). The mixture was stirred for 15 min at −40 °C before being added via cannula to a suspension of CuCN (2.4 g, 26.5 mmol, 1.0 equiv) in Et_2O (40 mL). The yellow solution was stirred for 1 h between −30 °C and −20 °C. In parallel, to a solution of commercial 2,3-dihydrofuran **7** (2.0 mL, 26.5 mmol, 1.0 equiv) in THF (18 mL) at −60 °C was added *tert*-BuLi (1.5 M solution in pentane, 21.2 mL, 31.7 mmol, 1.2 equiv). The yellow solution was stirred for 10 min at −60 °C then for 50 min at 0 °C. The solution of lithio-dihydrofuran, prepared above, was then added via cannula to the cyanocuprate and the reaction mixture was stirred at −5 °C for 90 min. At −30 °C was added freshly distilled MeI (11.5 mL, 185.0 mmol, 7.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 5 h. Finally the reaction mixture was poured into a mixture of a saturated aqueous NH_4Cl solution and concentrated ammonia (4:1) at 0 °C and stirring was maintained for 1 h at 20 °C before extraction with diethyl ether. The organic layer was washed with water, brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on basic silica gel (cyclohexane/EtOAc 100:0−70:30) to give 9.13 g (92% yield) of the title compound **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−1.01 (m, 15H), 1.20−1.40 (m, 6H), 1.42−1.57 (m, 6H), 1.87 (d, J = 1.8 Hz, 3H), 2.42 (q, J = 6.4 Hz, 2H), 3.66 (t, J = 5.9 Hz, 2H), 5.51 (qd, J = 7.3, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 ($3CH_2$), 13.7 ($3CH_3$), 19.3 (CH_3), 27.4 ($3CH_2$), 29.2 ($3CH_2$), 31.7 (CH_2), 62.3 (CH_2), 135.7 (CH), 142.5 (C). HRMS (EI+) m/z Calcd for $C_{17}H_{36}OSn$ (M^+): 376.1788. Found: 376.1776. IR (Film) ν 3340, 2958, 2925, 2871, 2853, 1463, 1046 cm^{-1}.

(*E*)-(4-Bromopent-3-enyloxy)(*tert*-butyl)diphenylsilane 3a. Alcohol **8** (3.0 g, 8.0 mmol, 1.0 equiv) was dissolved in dry DMF (10 mL) at room temperature. To this solution were successively added imidazole (1.7 g, 24.8 mmol, 3.1 equiv) and TBDPSCl (3.3 g, 12.0 mmol, 1.5 equiv). After stirring for 1.5 h, the mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography on basic silica gel (cyclohexane/Et_2O 100:0−90:10) to give 4.9 g (100% yield) of the silyl ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−0.94 (m, 15H), 1.06 (s, 9H), 1.26−1.37 (m, 6H), 1.45−1.55 (m, 6H), 1.82 (s, 3H), 2.42 (q, J = 6.7 Hz, 2H), 3.69 (t, J = 6.7 Hz, 2H), 5.61 (t, J = 6.7 Hz, 1H), 7.35−7.45 (m, 6H), 7.66−7.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0 ($3CH_2$), 13.7 ($3CH_3$), 19.2 (C+CH_3), 26.8 ($3CH_3$), 27.4 ($3CH_2$), 29.2 ($3CH_2$), 31.6 (CH_2), 63.5 (CH_2), 127.6 (4CH), 129.5 (2CH), 134.1 (2C), 135.6 (4CH), 136.8 (CH), 140.0 (C). HRMS (EI+) m/z Calcd for $C_{33}H_{54}OSiSn$ (M^+): 614.2966. Found: 614.3002. IR (film) ν 2956, 2927, 2856, 1463, 1428, 1111, 701 cm^{-1}.

NBS (2.8 g, 16.0 mmol, 2.0 equiv) was added to a solution of the silyl ether (4.9 g, 8.0 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) at 0 °C. After 1 h at 0 °C, the mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100:0−70:30) to afford vinyl bromide **3a** (3.2 g, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.18 (s, 3H), 2.24 (q, J = 6.7 Hz, 2H), 3.66 (t, J = 6.7 Hz, 2H), 5.86 (t, J = 6.7 Hz, 1H), 7.35−7.45 (m, 6H), 7.65−7.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1 (C), 23.3 (CH_3), 26.8 ($3CH_3$), 32.9 (CH_2), 62.6 (CH_2), 121.0 (C), 127.7 (4CH), 128.8 (CH), 129.7 (2CH), 133.7 (2C), 135.6 (4CH). IR (film) ν 3070, 2956, 2930, 2857, 1427, 1111, 701 cm^{-1}.

(2*S*,4*R*,5*R*,6*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4,6-dimethyl-3-oxoheptan-2-yl Benzoate 15a. To a cooled solution of $ClB(Cy)_2$ (5 mL, 22.8 mmol, 1.5 equiv) in anhydrous Et_2O (40 mL) at −78 °C were added dropwise freshly distilled Me_2NEt (3.0 mL, 27.4 mmol, 1.8 equiv) followed by ketone **12** (3.1 g,

15.2 mmol, 1.0 equiv) in anhydrous Et_2O (15 mL). The resulting milky mixture was stirred at 0 °C for 2 h. The solution was then cooled to −78 °C before dropwise addition of aldehyde (*S*)-**10**[4c] (4.6 g, 22.8 mmol, 1.5 equiv). The solution was stirred for 2 h at −78 °C. The mixture was then maintained overnight at −25 °C without stirring. After one night, the mixture was stirred for 30 min at 0 °C. The reaction was then quenched by addition of MeOH (50 mL), pH 7 phosphate buffer (50 mL), and H_2O_2 (35%, 50 mL). The mixture was stirred for 1 h at room temperature, before being partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/Et_2O 90:10−80:20) to afford aldol **15a** (6.1 g, 98% yield) as colorless oil. **RN**: 261968-17-6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 0.93 (d, J = 7.3 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.57 (d, J = 6.9 Hz, 3H), 1.63−1.83 (m, 1H), 2.99 (dq, J = 9.6, 6.9 Hz, 1H), 3.06 (d, J = 2.3 Hz, 1H), 3.68 (dd, J = 9.6, 4.6 Hz, 1H), 3.79 (dd, J = 9.6, 3.7 Hz, 1H), 4.11 (dt, J = 9.6, 2.3 Hz, 1H), 5.43 (q, J = 6.9 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.57 (tt, J = 7.3, 1.4 Hz, 1H), 8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7 (CH_3), −5.6 (CH_3), 8.9 (CH_3), 13.7 (CH_3), 15.4 (CH_3), 18.2 (C), 25.8 ($3CH_3$), 35.3 (CH), 45.8 (CH), 68.5 (CH_2), 75.3 (CH), 75.6 (CH), 128.4 (2CH), 129.7 (C), 129.8 (2CH), 133.1 (CH), 165.9 (C), 211.0 (C). HRMS (EI+) m/z Calcd for $C_{22}H_{36}O_5Si$ (M^+): 408.2332. Found: 408.2293. $[\alpha]_D$ = +5.0 (c = 0.8, $CHCl_3$). IR (film) ν 3505, 2932, 2855, 1720 cm^{-1}.

(2*R*,3*R*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-methoxy-2,4-dimethylpentanal 9a. Aldol **15a** (4.2 g, 10.1 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (120 mL) at room temperature. To this solution was added 2,6-di-*tert*-butyl-4-methylpyridine (25.0 g, 121.9 mmol, 12.0 equiv) followed by methyl trifluoromethanesulfonate (6.9 mL, 61.0 mmol, 6.0 equiv). The solution was heated to reflux of CH_2Cl_2 for 8 h, and then 6.0 equiv of methyl trifluoromethanesulfonate were further added. The solution was refluxed overnight. The mixture was then cooled to 0 °C and a 7 M aqueous solution of NH_4OH (17.0 mL, 120 mmol, 12.0 equiv) diluted in water (120 mL) was added dropwise very carefully. Finally, the mixture was extracted with Et_2O, dried over $MgSO_4$, and solvents were removed in vacuo. The residue was purified by column chromatography (cyclohexane/Et_2O 100:0−90:10) to afford the methylated aldol product **16a** (3.3 g, 76% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 1.07 (d, J = 6.9 Hz, 3H), 1.56 (d, J = 7.3 Hz, 3H), 1.70−1.90 (m, 1H), 3.05 (dq, J = 10.1, 6.9 Hz, 1H), 3.27 (s, 3H), 3.41−3.61 (m, 2H), 3.75 (dd, J = 10.1, 1.8 Hz, 1H), 5.41 (q, J = 7.3 Hz, 1H), 7.44 (m, 2H), 7.57 (tt, J = 7.3, 0.9 Hz, 1H), 8.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (CH_3), −5.3 (CH_3), 9.2 (CH_3), 14.2 (CH_3), 14.9 (CH_3), 18.2 (C), 25.9 ($3CH_3$), 37.4 (CH), 45.1 (CH), 60.8 (CH_3), 65.2 (CH_2), 75.2 (CH), 81.6 (CH), 128.4 (2CH), 129.7 (C), 129.8 (2CH), 133.1 (CH), 165.8 (C), 210.2 (C). HRMS (EI+) m/z Calcd for $C_{23}H_{38}O_5Si$ (M^+): 422.2489. Found: 422.2508. $[\alpha]_D$ = +22.1 (c = 1.7, $CHCl_3$). IR (film) ν 2958, 2935, 2898, 2858, 1664, 1462, 1385, 1251, 1130, 1075, 1056, 997, 890, 838, 775 cm^{-1}.

The methylated aldol compound **16a** (3.7 g, 8.7 mmol, 1.0 equiv) was dissolved in THF (40 mL) at −78 °C before addition of $LiBH_4$ (2.0 M solution in THF, 87.0 mL, 174.0 mmol, 20.0 equiv). The solution was allowed to warm to room temperature and stirred overnight. At 0 °C, water (100 mL) was added slowly followed by a saturated aqueous solution of Rochelle salt (100 mL). The mixture was stirred for 1 h at room temperature before being partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $MgSO_4$ and solvents were removed in vacuo. The residue was directly used in the next step without further purification.

Crude diols were diluted in MeOH (40 mL) and water (20 mL) at room temperature. $NaIO_4$ (11.2 g, 52.5 mmol, 6.0 equiv) was added and the mixture was stirred for 25 min. The resulting milky solution was quenched by addition of water (80 mL) and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (cyclohexane/Et_2O 95:5−85:15) to afford aldehyde **9a** (2.0 g, 84% yield over two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 1.02 (d, J = 7.3 Hz, 3H), 1.72−1.90 (m, 1H), 2.65 (qd, J = 7.3, 2.3 Hz, 1H), 3.41 (s, 3H), 3.42−3.62 (m, 2H), 3.56 (dd, J = 7.8, 3.7 Hz, 1H), 9.80 (d, J = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5 (CH_3), −5.4 (CH_3), 10.7 (CH_3), 11.1 (CH_3), 18.2 (C), 25.9 ($3CH_3$), 38.2 (CH), 49.2 (CH), 60.5 (CH_3), 64.8 (CH_2), 82.1 (CH), 204.9 (C). HRMS (EI+) m/z Calcd for $C_{14}H_{30}O_3Si$ (M^+): 274.1964. Found: 274.1972. $[\alpha]_D$ = −15.1 (c = 0.7, $CHCl_3$). IR (Film) ν 2955, 2930, 2895, 2857, 1725, 1461, 1091, 836, 775 cm^{-1}.

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*R*,6*S*)-7-(*tert*-butyldimethylsilyloxy)-3-hydroxy-5-methoxy-2,4,6-trimethylheptanoyl)oxazolidin-2-one 18a. (*S*)-4-Benzyl-3-propionyl-2-oxazolidinone (*S*)-**17** (595 mg, 2.6 mmol, 1.4 equiv) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. *n*-Bu_2BOTf (1.0 M solution in CH_2Cl_2, 2.8 mL, 2.8 mmol, 1.55 equiv) was added over 5 min, followed by freshly distilled Et_3N (585 μL, 4.2 mmol, 2.3 equiv). After 30 min, the solution was cooled to −78 °C and aldehyde **9a** (500 mg, 1.8 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added via cannula. The mixture was stirred at −78 °C for 90 min then at 0 °C for 1 h. The reaction was quenched at 0 °C by addition of pH 7 phosphate buffer (3 mL), MeOH (7 mL), and MeOH/35% H_2O_2 (4 mL, 2:1). The mixture was stirred for 1 h before being partitioned between Et_2O and saturated aqueous NaCl. The combined organic layers were dried over $MgSO_4$ and solvents were removed in vacuo. The crude residue was purified by column chromatography (cyclohexane/Et_2O 80:20−50:50) to afford imide **18a** (2.4 g, 91% yield) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.84 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 1.24 (d, J = 6.9 Hz, 3H), 1.78−1.82 (m, 1H), 1.90 (sext d, J = 6.9, 2.3 Hz, 1H), 2.76 (dd, J = 13.3, 9.6 Hz, 1H), 3.37 (dd, J = 13.3, 2.7 Hz, 1H), 3.44 (dd, J = 5.9, 2.3 Hz, 1H), 3.45 (s, 3H), 3.50 (d, J = 6.9 Hz, 2H), 4.02−3.92 (m, 2H), 4.17 (dd, J = 9.2, 2.7 Hz, 1H), 4.21 (dd, J = 9.2, 6.9 Hz, 1H), 4.36 (s, 1H), 4.70 (ddt, J = 9.6, 6.9, 2.7 Hz, 1H), 7.19−7.24 (m, 2H), 7.26−7.37 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (CH_3), −5.3 (CH_3), 8.7 (CH_3), 10.5 (CH_3), 13.6 (CH_3), 18.3 (C), 26.0 ($3CH_3$), 37.8 (CH_2), 38.4 (CH), 38.7 (CH), 41.0 (CH), 56.0 (CH), 60.7 (CH_3), 66.0 (CH_2), 66.2 (CH_2), 74.3 (CH), 86.0 (CH), 127.4 (2CH), 129.0 (CH), 129.6 (2CH), 135.6 (C), 153.4 (C), 175.7 (C). HRMS (EI+) m/z Calcd for $C_{27}H_{45}NO_6Si$ (M^+): 507.3016. Found: 507.3024. $[\alpha]_D$ = +39.2 (c = 2.0, $CHCl_3$). IR (Film) ν 2955, 2929, 2857, 1782, 1702, 1455, 1387, 1210, 1093, 837, 776 cm^{-1}.

(2*S*,3*R*,4*R*,5*R*,6*S*)-7-(*tert*-Butyldimethylsilyloxy)-*N*-5-dimethoxy-*N*-2,4,6-tetramethyl-3-(trimethylsilyloxy)heptanamide 4a. *N*,*O*-Dimethylhydroxylamine hydrochloride (0.56 g, 5.8 mmol, 2.5 equiv) was suspended in CH_2Cl_2 (20 mL) and cooled to 0 °C. $AlMe_3$ (2 M solution in heptane, 2.9 mL, 5.8 mmol, 2.5 equiv) was added dropwise over 5 min and the resulting clear solution was stirred at room temperature for 1 h. Imide **18a** (1.17 g, 2.3 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise at −20 °C over 5 min. The reaction mixture was allowed to stir at room temperature overnight and was then transferred via cannula onto a vigorously stirred aqueous tartaric acid 1 M solution (60 mL) at 0 °C. The mixture was stirred for 5 h until two layers appeared. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with

brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (cyclohexane/EtOAc 90:10−70:30) to afford the corresponding Weinreb amide (676 mg, 75% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.85 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 1.17 (d, J = 6.9 Hz, 3H), 1.88−1.94 (m, 1H), 1.94−2.02 (m, 1H), 2.95−3.10 (m, 1H), 3.19 (s, 3H), 3.41 (s, 3H), 3.45−3.65 (m, 3H), 3.71 (s, 3H), 3.80−3.86 (m, 1H), 4.08 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 ($2CH_3$), 10.3 (CH_3), 11.6 (CH_3), 12.7 (CH_3), 18.3 (C), 25.9 ($3CH_3$), 32.2 (CH_3), 37.0 (CH), 37.6 (CH), 38.2 (CH), 59.5 (CH_3), 61.3 (CH_3), 66.6 (CH_2), 73.3 (CH), 83.1 (CH), 177.9 (C). HRMS (EI+) m/z Calcd for $C_{19}H_{41}NO_5Si$ (M^+): 391.2754. Found: 391.2746. $[\alpha]_D$ = +5.1 (c = 2.5, $CHCl_3$). IR (Film) ν 3454, 2957, 2932, 2858, 1641, 1462, 1399, 1255, 1090, 837, 775 cm^{-1}.

This Weinreb amide (1.3 g, 3.3 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (35 mL) and the reaction mixture was cooled to −30 °C. 2,6-Lutidine (1.6 mL, 13.3 mmol, 4.0 equiv) was added, followed by TMSOTf (1.2 mL, 6.6 mmol, 2.0 equiv). After stirring for 1 h at −30 °C, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl at −30 °C and the mixture was allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude residue was purified by column chromatography (cyclohexane/EtOAc 90:10−75:25) to afford title compound **4a** (1.4 mg, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.15 (s, 9H), 0.68 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 1.63−1.72 (m, 2H), 3.16 (s, 3H), 3.39 (s, 3H), 3.49−3.41 (m, 4H), 3.72 (s, 3H), 3.92−3.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (CH_3), −5.3 (CH_3), 0.9 ($3CH_3$), 9.5 (CH_3), 16.1 (CH_3), 17.4 (CH_3), 18.2 (C), 25.9 ($3CH_3$), 32.0 (CH_3), 38.1 (CH), 38.9 (CH), 40.8 (CH), 59.3 (CH_3), 61.3 (CH_3), 65.5 (CH_2), 77.3 (CH), 80.3 (CH), 177.7 (C). HRMS (EI+) m/z Calcd for $C_{22}H_{49}NO_5Si_2$ (M^+): 463.3149. Found: 463.3161. $[\alpha]_D$ = +22.1 (c = 1.7, $CHCl_3$). IR (Film) ν 2958, 2935, 2898, 2858, 1664, 1462, 1385, 1251, 1130, 1075, 1056, 97, 890, 838, 775 cm^{-1}.

(9*R*,10*S*,11*S*,12*S*,13*R*,14*S*,*E*)-13-Methoxy-2,2,8,10,12,14,-17,17,18,18-decamethyl-3,3-diphenyl-4,16-dioxa-3,17-disilanonadec-7-ene-9,11-diol 19a. Vinyl bromide **3a** (1.60 g, 3.98 mmol, 3.0 equiv) was diluted in Et_2O (20 mL). To remove dissolved O_2, the mixture was frozen at −196 °C under argon and then allowed to melt in vacuo. This procedure was repeated three times. At −78 °C, under argon, *t*-BuLi (1.7 M solution in pentane, 4.70 mL, 7.96 mmol, 6.0 equiv) was added dropwise. The mixture was stirred at this temperature for 10 min, then amide **4a** (615 mg, 1.33 mmol, 1.0 equiv) was quickly added, and the mixture was stirred at −50 °C for 1 h. After this time, the reaction mixture was quenched by addition of 4 mL of MeOH at −50 °C. The mixture was then extracted with Et_2O (2×), and the combined organic layers were washed with a saturated aqueous solution of NH_4Cl, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100:0−70:30) to afford the expected enone which could not be separated from the excess of reduced vinyl compound.

This enone was dissolved in MeOH (15 mL) at room temperature and 50 beads of Amberlyst-15 were added. The reaction was monitored by thin layer chromatography and the mixture was filtered as soon as the starting material was totally consumed. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc 100:0−80:20) to give 735 mg (85% yield over two steps) of the desired β-keto alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.81 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 1.05 (s, 9H), 1.13 (d, J = 7.0 Hz, 3H), 1.76 (s, 3H), 1.80−1.95 (m, 2H), 2.50 (dt, J = 7.3, 6.3 Hz, 2H), 3.37−3.40 (m, 1H), 3.40 (s, 3H), 3.45 (dd, J = 6.3, 2.7 Hz, 1H), 3.46 (dd, J = 9.9, 6.2 Hz, 1H), 3.51 (dd, J = 9.9, 7.5 Hz, 1H), 3.79 (t, J = 6.3 Hz, 2H), 3.83−3.90 (m, 1H), 3.94 (d, J = 2.1 Hz, 1H), 6.71 (t, J = 7.3 Hz, 1H), 7.35−7.47 (m, 6H), 7.63−7.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4 ($2CH_3$), 11.2 (CH_3), 11.3 (CH_3), 11.9 (CH_3), 13.4 (CH_3), 18.3 (C), 19.2 (C), 25.9 ($3CH_3$), 26.8 ($3CH_3$), 32.5 (CH_2), 37.9 (CH), 38.7 (CH), 41.4 (CH), 59.8 (CH_3), 62.4 (CH_2), 66.4 (CH_2), 74.0 (CH), 83.9 (CH), 127.7 (4CH), 129.8 (2CH), 133.5 (2C), 135.5 (4CH), 137.5 (C), 138.6 (CH), 205.9 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{38}H_{62}O_5Si_2$ (M + Na^+): 677.4034. Found: 677.4048. $[\alpha]_D$ = +2.0 (c = 2.4, $CHCl_3$). IR (Film) ν 2955, 2929, 2857, 2359, 2341, 1651, 1471, 1428, 1091, 701 cm^{-1}.

To a cooled (−78 °C) solution of this β-keto alcohol (715 mg, 1.10 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added dropwise $Zn(BH_4)_2$ (0.15 M solution in Et_2O, 36.0 mL, 5.50 mmol, 5.0 equiv.). The mixture was stirred at −60 °C for 1 h, then the temperature was allowed to warm to −40 °C. After 4 h at −40 °C, the reaction was quenched by addition of MeOH (5 mL) at this temperature. The mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with a saturated aqueous solution of NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 90:10−50:50) to afford diol **19a** (655 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.75 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 1.04 (s, 9H), 1.52 (s, 3H), 1.72−1.78 (m, 1H), 1.80−1.92 (m, 2H), 2.34 (q, J = 7.0 Hz, 1H), 2.37 (q, J = 7.0 Hz, 1H), 3.38−3.52 (m, 3H), 3.48 (s, 3H), 3.68 (t, J = 7.0 Hz, 2H), 3.77 (br d, J = 10.0 Hz, 1H), 4.16 (br s, 1H), 4.20 (br s, 1H), 4.74 (br s, 1H), 5.52 (t, J = 7.0 Hz, 1H), 7.31−7.42 (m, 6H), 7.62−7.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 (CH_3), −5.4 (CH_3), 4.2 (CH_3), 10.4 (CH_3), 13.6 ($2CH_3$), 18.3 (C), 19.2 (C), 25.9 ($3CH_3$), 26.9 ($3CH_3$), 31.4 (CH_2), 36.2 (CH), 38.3 (CH), 38.6 (CH), 60.8 (CH_3), 63.7 (CH_2), 65.9 (CH_2), 79.8 (CH), 80.4 (CH), 86.2 (CH), 120.3 (CH), 127.6 (4CH), 129.5 (2CH), 134.1 (2C), 135.6 (4CH), 136.6 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{38}H_{64}O_5Si_2$ (M + Na^+): 679.4190. Found: 679.4173. $[\alpha]_D$ = +1.4 (c = 0.2, $CHCl_3$). IR (Film) ν 3445, 2928, 2857, 1471, 1427, 1255, 1111, 1089, 701 cm^{-1}.

(2*R*,3*S*,4*R*,5*R*,6*S*,7*R*,*E*)-11-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-2,4,6,8-tetramethyl-5,7-bis(triethylsilyloxy)undec-8-enal 20a. Diol **19a** (550 mg, 0.84 mmol, 1.0 equiv) was dissolved in THF (20 mL) at room temperature. Water (10 mL) followed by acetic acid (30 mL) were then added. The mixture was stirred at room temperature for 18 h. The solution was diluted in Et_2O and carefully washed with saturated aqueous solution of $NaHCO_3$ (2×). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc 80:20−40:60) to give the wanted triol (400 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H), 1.52 (s, 3H), 1.71−1.81 (m, 1H), 1.87−1.99 (m, 2H), 2.29−2.40 (m, 2H), 3.40 (dd, J = 6.9, 3.0 Hz, 1H), 3.47 (s, 3H), 3.53 (dd, J = 10.5, 8.1 Hz, 1H), 3.62 (dd, J = 10.5, 5.1 Hz, 1H), 3.68 (t, J = 6.8 Hz, 2H), 3.77 (dd, J = 9.5, 1.7 Hz, 1H), 4.19 (br s, 1H), 5.50 (t, J = 7.3 Hz, 1H), 7.33−7.45 (m, 6H), 7.64−7.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.3 (CH_3), 11.4 (CH_3), 13.6 (CH_3), 14.0 (CH_3), 19.1 (C), 26.8 ($3CH_3$), 31.3 (CH_2), 36.1 (CH), 37.8 (CH), 38.2 (CH), 60.4 (CH_3), 63.6 (CH_2), 66.2 (CH_2), 79.2 (CH), 80.6 (CH), 86.5 (CH), 120.6 (CH), 127.6 (4CH), 129.5 (2CH), 134.0 (2C), 135.6 (4CH), 136.7 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{32}H_{50}O_5Si$ (M + Na^+): 565.3325. Found: 565.3334. $[\alpha]_D$ = +2.3 (c = 0.5, $CHCl_3$). IR (Film) ν 3418, 2932, 1462, 1427, 1111, 702 cm^{-1}.

2,6-Lutidine (178 μL, 1.53 mmol, 12.0 equiv) and TESOTf (261 μL, 1.15 mmol, 9.0 equiv) were added to a solution of the

previous triol (69 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min before being quenched by addition of a saturated aqueous solution of NH_4Cl. The mixture was then extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc 100:0−80:20) to afford the expected silyl ether (111 mg, 99% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47−0.65 (m, 18H), 0.79 (d, J = 6.8 Hz, 3H), 0.83−1.03 (m, 33H), 1.06 (s, 9H), 1.49 (s, 3H), 1.75−1.85 (m, 1H), 1.86−1.98 (m, 2H), 2.20−2.40 (m, 2H), 3.30 (s, 3H), 3.35 (dd, J = 8.9, 1.9 Hz, 1H), 3.46 (dd, J = 9.6, 6.7 Hz, 1H), 3.56 (dd, J = 9.6, 8.0 Hz, 1H), 3.62−3.66 (m, 1H), 3.66 (t, J = 7.5 Hz, 2H), 3.95 (d, J = 5.8 Hz, 1H), 5.40 (t, J = 6.7 Hz, 1H), 7.34−7.44 (m, 6H), 7.66−7.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.4 ($3CH_2$), 5.0 ($3CH_2$), 5.7 ($3CH_2$), 6.8 ($3CH_3$), 7.0 ($3CH_3$), 7.2 ($3CH_3$), 10.0 (CH_3), 10.9 (CH_3), 12.7 (CH_3), 15.4 (CH_3), 19.1 (C), 26.8 ($3CH_3$), 31.3 (CH_2), 38.3 (CH), 39.6 (2CH), 59.4 (CH_3), 63.5 (CH_2), 65.8 (CH_2), 76.4 (CH), 79.3 (CH), 81.0 (CH), 121.9 (CH), 127.6 (4CH), 129.5 (2CH), 134.0 (2C), 135.5 (4CH), 138.7 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{50}H_{92}O_5Si_4$ (M + Na^+): 907.5920. Found: 907.5883. $[\alpha]_D$ = −1.1 (c = 2.2, $CHCl_3$). IR (Film) ν 2956, 2876, 1459, 1427, 1239, 1094, 1008, 822, 757, 701 cm^{-1}.

To a cooled (−78 °C) solution of oxalyl chloride (49 μL, 0.57 mmol, 5.0 equiv) in CH_2Cl_2 (2 mL) was added dropwise DMSO (87 μL, 1.13 mmol, 10.0 equiv). After 10 min at −78 °C, a solution of the TES ether (100 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was slowly added. The mixture was stirred at −78 °C for 20 min and then at −40 °C for 20 min. At −78 °C, triethylamine (284 μL, 2.03 mmol, 18.0 equiv) was added dropwise and the mixture was allowed to warm to room temperature over 2 h. The resulting white and milky solution was diluted in Et_2O and washed successively with a saturated aqueous solution of NH_4Cl and water. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude aldehyde **20a** (100 mg) was directly used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48−0.66 (m, 12H), 0.85−1.00 (m, 24H), 1.05 (s, 9H), 1.09 (d, J = 7.0 Hz, 3H), 1.48 (s, 3H), 1.76−1.86 (m, 1H), 1.89−2.01 (m, 1H), 2.20−2.35 (m, 2H), 3.42−3.54 (m, 1H), 3.07 (s, 3H), 3.65 (t, J = 7.5 Hz, 1H), 3.70−3.80 (m, 3H), 3.89 (d, J = 7.2 Hz, 1H), 5.39 (t, J = 7.1 Hz, 1H), 7.33−7.44 (m, 6H), 7.63−7.70 (m, 4H), 9.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0 ($3CH_2$), 5.7 ($3CH_2$), 6.6 (CH_3), 7.1 ($3CH_3$), 7.2 ($3CH_3$), 11.0 (CH_3), 12.0 (CH_3), 14.2 (CH_3), 19.1 (C), 26.8 ($3CH_3$), 31.3 (CH_2), 39.1 (CH), 40.4 (CH), 49.0 (CH), 58.0 (CH_3), 63.4 (CH_2), 74.1 (CH), 80.0 (CH), 80.5 (CH), 122.8 (CH), 127.6 (4CH), 129.5 (2CH), 133.9 (2C), 135.5 (4CH), 138.4 (C), 204.8 (C).

(2*E*,4*E*,6*E*,8*S*,9*R*,10*S*,11*S*,12*S*,13*R*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1a. *n*-BuLi (1.6 M solution in hexanes, 622 μL, 0.99 mmol, 1.7 equiv) was added to a solution of diisopropylamine (140 μL, 0.99 mmol, 1.7 equiv) in THF (3 mL) at −78 °C. The resulting pale yellow solution was stirred at −78 °C for 5 min and then at 0 °C for 15 min. A solution of phosphonate **2** (347 mg, 0.99 mmol, 1.7 equiv) in THF (5 mL) was slowly added at −78 °C. The resulting dark-brown solution was stirred for 15 min at −78 °C before addition of aldehyde **20a** (450 mg, 0.58 mmol, 1.0 equiv) in THF (5 mL). The mixture was stirred for 15 min at −78 °C then 30 min at 0 °C. The mixture was then extracted with Et_2O (2×) and washed with a saturated aqueous solution of NH_4Cl. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100:0−90:10) to afford the desired ester (330 mg, 59% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.45−0.65 (m, 12H), 0.85−0.95 (m, 27H), 0.99−1.05 (m, 2H), 1.06 (s, 9H), 1.47 (s, 3H), 1.80−1.95 (m, 2H), 2.20−2.40 (m, 2H), 2.40−2.52 (m, 1H), 3.03 (dd, J = 7.0, 3.7 Hz, 1H), 3.25 (s, 3H), 3.62−3.66 (m, 1H), 3.66 (t, J = 7.7 Hz, 2H), 3.86 (d, J = 7.5 Hz, 1H), 4.20−4.27 (m, 2H), 5.41 (t, J = 6.4 Hz, 1H), 5.82 (d, J = 15.5 Hz, 1H), 5.94 (dd, J = 15.1, 7.3 Hz, 1H), 6.10 (dd, J = 15.1, 10.2 Hz, 1H), 6.20 (dd, J = 14.5, 11.4 Hz, 1H), 6.50 (dd, J = 14.5, 10.2 Hz, 1H), 7.28 (dd, J = 15.5, 11.4 Hz, 1H), 7.33−7.44 (m, 6H), 7.65−7.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5 ($3CH_3$), 5.0 ($3CH_2$), 5.8 ($3CH_2$), 6.9 ($3CH_3$), 7.2 ($3CH_3$), 10.9 (CH_3), 12.4 (CH_3), 14.1 (CH_3), 15.2 (CH_3), 17.3 (CH_2), 19.1 (C), 26.8 ($3CH_3$), 31.3 (CH_2), 39.3 (CH), 39.4 (CH), 39.9 (CH), 59.6 (CH_3), 62.4 (CH_2), 63.4 (CH_2), 76.8 (CH), 84.0 (CH), 87.6 (CH), 120.5 (CH), 122.8 (CH), 127.6 (4CH), 127.7 (CH), 128.7 (CH), 129.6 (2CH), 133.9 (2C), 135.5 (4CH), 138.6 (C), 140.9 (CH), 144.3 (CH), 144.4 (CH), 167.3 (C).

To a solution of this ester (75 mg, 0.08 mmol, 1.0 equiv) in dry DMF at 0 °C (0.7 mL) was added a solution of TAS-F (150 mg, 0.42 mmol, 7.0 equiv) in dry DMF (0.2 mL). The resulting purple solution was stirred at 0 °C for 15 min then at room temperature for 9 h. The mixture was then diluted with EtOAc and washed with an aqueous pH 2−3 HCl solution. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were washed (4×) with small quantities of a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/MeOH 100:0−80:20) to give title compound **1a** (20 mg, 67% yield). ^{1}H NMR (300 MHz, MeOD) δ 0.87 (d, J = 7.1 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H), 1.54 (s, 3H), 1.73−1.83 (m, 1H), 1.98−2.08 (m, 1H), 2.33 (q, J = 6.7 Hz, 2H), 2.48−2.60 (m, 1H), 3.30−3.34 (m, 1H), 3.41 (s, 3H), 3.48 (dd, J = 10.1, 1.7 Hz, 1H), 3.66 (t, J = 6.7 Hz, 2H), 3.96 (d, J = 8.2 Hz, 1H), 5.50 (t, J = 6.7 Hz, 1H), 5.90 (d, J = 15.2 Hz, 1H), 5.95 (dd, J = 15.3, 9.2 Hz, 1H), 6.23 (dd, J = 15.3, 10.7 Hz, 1H), 6.37 (dd, J = 14.8, 11.3 Hz, 1H), 6.65 (dd, J = 14.8, 10.7 Hz, 1H), 7.36 (dd, J = 15.2, 11.3 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 7.9 (CH_3), 11.9 (CH_3), 12.4 (CH_3), 18.1 (CH_3), 32.4 (CH_2), 38.6 (CH), 40.3 (CH), 41.8 (CH), 59.1 (CH_3), 62.8 (CH_2), 74.5 (CH), 82.2 (CH), 87.3 (CH), 121.7 (CH), 125.6 (CH), 129.7 (CH), 130.7 (CH), 139.0 (C), 142.9 (CH), 144.7 (CH), 146.8 (CH), 170.8 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2418. $[\alpha]_D$ = −2.5 (c = 0.3, $CHCl_3$). IR (Film) ν 3370, 2932, 1688, 1612, 1260, 1078, 1007, 702 cm^{-1}.

(2*E*,4*E*,6*E*,8*R*,9*R*,10*S*,11*S*,12*S*,13*R*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1b. ^{1}H NMR (300 MHz, MeOD) δ 0.79 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.62 (s, 3H), 1.75−1.87 (m, 1H), 2.04−2.15 (m, 1H), 2.38 (q, J = 7.1 Hz, 2H), 2.63−2.72 (m, 1H), 3.39 (dd, J = 5.4, 3.2 Hz, 1H), 3.43 (s, 3H), 3.54 (dd, J = 10.0, 1.6 Hz, 1H), 3.65 (t, J = 7.1 Hz, 2H), 4.02 (d, J = 8.1 Hz, 1H), 5.53 (t, J = 7.1 Hz, 1H), 5.90 (d, J = 14.9 Hz, 1H), 6.09 (dd, J = 15.3, 8.3 Hz, 1H), 6.18 (dd, J = 15.3, 9.6 Hz, 1H), 6.34 (dd, J = 14.5, 11.1 Hz, 1H), 6.64 (dd, J = 14.5, 9.6 Hz, 1H), 7.33 (dd, J = 14.9, 11.1 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 7.9 (CH_3), 12.0 (CH_3), 12.8 (CH_3), 20.1 (CH_3), 32.4 (CH_2), 38.5 (CH), 39.2 (CH), 40.8 (CH), 59.3 (CH_3), 62.8 (CH_2), 75.5 (CH), 81.9 (CH), 88.1 (CH), 121.4 (CH), 125.0 (CH), 129.4 (CH), 130.7 (CH), 139.2 (C), 142.9 (CH), 144.6 (CH), 146.9 (CH), 170.8 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2400. $[\alpha]_D$ = −28.3 (c = 0.6, $CHCl_3$). IR (Film) ν 3368, 2932, 1688, 1611, 1260, 1078, 1007, 702 cm^{-1}.

(2*E*,4*E*,6*E*,8*S*,9*S*,10*S*,11*S*,12*S*,13*R*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1c. ^{1}H NMR (300 MHz, MeOD) δ 0.80 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.64 (s, 3H), 1.72−1.82 (m, 1H), 1.80−1.89 (m, 1H), 2.34 (q, J = 7.1 Hz, 2H), 2.43−2.59 (m, 1H), 3.41 (s, 3H), 3.46 (dd, J = 8.6, 1.7 Hz,

1H), 3.53 (dd, J = 11.3, 1.3 Hz, 1H), 3.61 (t, J = 7.1 Hz, 2H), 4.04 (d, J = 7.7 Hz, 1H), 5.54 (t, J = 7.1 Hz, 1H), 5.89 (d, J = 15.1 Hz, 1H), 6.08 (dd, J = 15.1, 8.2 Hz, 1H), 6.28 (dd, J = 15.1, 10.4 Hz, 1H), 6.37 (dd, J = 14.8, 11.3 Hz, 1H), 6.69 (dd, J = 14.8, 10.4 Hz, 1H), 7.35 (dd, J = 15.1, 11.3 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 7.4 (CH_3), 10.0 (CH_3), 12.1 (CH_3), 17.6 (CH_3), 32.3 (CH_2), 38.1 (CH), 39.9 (CH), 42.5 (CH), 61.5 (CH_3), 62.8 (CH_2), 74.7 (CH), 82.2 (CH), 85.9 (CH), 121.4 (CH), 124.8 (CH), 129.6 (CH), 131.0 (CH), 139.2 (C), 142.8 (CH), 145.1 (CH), 146.9 (CH), 170.8 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2408. $[\alpha]_D$ = −13.5 (c = 0.4, $CHCl_3$). IR (Film) ν 3370, 2932, 1688, 1612, 1260, 1078, 1007, 702 cm^{-1}.

(2*E*,4*E*,6*E*,8*R*,9*S*,10*S*,11*S*,12*S*,13*R*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1d. ^{1}H NMR (300 MHz, MeOD) δ 0.76 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.64 (s, 3H), 1.66−1.76 (m, 1H), 1.76−1.86 (m, 1H), 2.34 (q, J = 7.1 Hz, 2H), 2.45−2.61 (m, 1H), 3.47 (dd, J = 8.9, 1.9 Hz, 1H), 3.50−3.52 (m, 1H), 3.52 (s, 3H), 3.61 (t, J = 7.1 Hz, 2H), 4.03 (d, J = 7.7 Hz, 1H), 5.54 (t, J = 7.1 Hz, 1H), 5.86 (dd, J = 15.2, 9.3 Hz, 1H), 5.89 (d, J = 15.0 Hz, 1H), 6.25 (dd, J = 15.2, 10.6 Hz, 1H), 6.37 (dd, J = 14.9, 11.2 Hz, 1H), 6.64 (dd, J = 14.9, 10.6 Hz, 1H), 7.33 (dd, J = 15.0, 11.2 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 7.4 (CH_3), 9.9 (CH_3), 12.1 (CH_3), 18.7 (CH_3), 32.3 (CH_2), 38.1 (CH), 40.6 (CH), 42.9 (CH), 61.8 (CH_3), 62.8 (CH_2), 74.8 (CH), 82.3 (CH), 85.6 (CH), 121.6 (CH), 124.8 (CH), 129.8 (CH), 130.9 (CH), 139.2 (C), 142.6 (CH), 143.7 (CH), 146.8 (CH), 170.8 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2415. $[\alpha]_D$ = +8.4 (c = 0.5, $CHCl_3$). IR (Film) ν 3397, 2933, 1689, 1614, 1261, 1078, 1007, 705 cm^{-1}.

(2*E*,4*E*,6*E*,8*S*,9*R*,10*S*,11*R*,12*R*,13*S*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1e. ^{1}H NMR (300 MHz, MeOD) δ 0.94 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.63 (s, 3H), 1.73−1.84 (m, 1H), 1.95−2.04 (m, 1H), 2.35 (q, J = 7.1 Hz, 2H), 2.53−2.66 (m, 1H), 3.20 (dd, J = 6.2, 5.1 Hz, 1H), 3.47 (s, 3H), 3.61 (t, J = 7.1 Hz, 2H), 3.85 (dd, J = 6.7, 3.5 Hz, 1H), 4.02 (d, J = 3.6 Hz, 1H), 5.53 (t, J = 7.1 Hz, 1H), 5.89 (d, J = 15.1 Hz, 1H), 6.07 (dd, J = 15.2, 7.9 Hz, 1H), 6.29 (dd, J = 15.2, 10.4 Hz, 1H), 6.39 (dd, J = 14.7, 11.2 Hz, 1H), 6.68 (dd, J = 14.7, 10.4 Hz, 1H), 7.34 (dd, J = 15.1, 11.2 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 9.5 (CH_3), 11.7 (CH_3), 13.9 (CH_3), 14.9 (CH_3), 32.3 (CH_2), 39.1 (CH), 39.9 (CH), 40.9 (CH), 61.4 (CH_3), 62.9 (CH_2), 73.9 (CH), 78.0 (CH), 89.3 (CH), 121.7 (CH), 122.2 (CH), 129.9 (CH), 130.7 (CH), 139.4 (C), 142.7 (CH), 144.9 (CH), 146.7 (CH), 170.9 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2420. $[\alpha]_D$ = +10.0 (c = 0.6, $CHCl_3$). IR (Film) ν 3391, 2933, 1688, 1614, 1261, 1078, 1007 cm^{-1}.

(2*E*,4*E*,6*E*,8*R*,9*R*,10*S*,11*R*,12*R*,13*S*,14*E*)-11,13,17-Trihydroxy-9-methoxy-8,10,12,14-tetramethylheptadeca-2,4,6,14-tetraenoic Acid 1f. ^{1}H NMR (300 MHz, MeOD) δ 0.93 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.62 (s, 3H), 1.70−1.80 (m, 1H), 1.89−1.97 (m, 1H), 2.35 (q, J = 7.0 Hz, 2H), 2.52−2.64 (m, 1H), 3.19 (dd, J = 7.3, 3.3 Hz, 1H), 3.52 (s, 3H), 3.61 (t, J = 7.0 Hz, 2H), 3.82 (dd, J = 7.1, 3.2 Hz, 1H), 4.01 (d, J = 4.4 Hz, 1H), 5.51 (t, J = 7.0 Hz, 1H), 5.88 (d, J = 15.4 Hz, 1H), 6.06 (dd, J = 15.2, 8.6 Hz, 1H), 6.25 (dd, J = 15.2, 10.4 Hz, 1H), 6.35 (dd, J = 14.7, 11.3 Hz, 1H), 6.65 (dd, J = 14.7, 10.4 Hz, 1H), 7.33 (dd, J = 15.4, 11.3 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ 9.7 (CH_3), 10.6 (CH_3), 10.9 (CH_3), 13.6 (CH_3), 32.1 (CH_2), 39.2 (CH), 39.8 (CH), 41.2 (CH), 61.3 (CH_3), 62.8 (CH_2), 73.6 (CH), 77.7 (CH), 89.1 (CH), 122.0 (CH), 122.1 (CH), 129.5 (CH), 131.2 (CH), 139.3 (C), 142.4 (CH), 143.0 (CH), 146.3 (CH), 171.1 (C). HRMS (TOF MS ES$^+$) m/z Calcd for $C_{22}H_{36}O_6$ (M + Na^+): 419.2404. Found: 419.2416. $[\alpha]_D$ = +2.1 (c = 0.1, $CHCl_3$). IR (Film) ν 3391, 2933, 1688, 1614, 1261, 1078, 1007 cm^{-1}.

Acknowledgment. We thank Pierre Fabre Laboratories and CNRS for a doctoral fellowship for E.F.

Supporting Information Available: Full data analysis of ^{13}C and ^{1}H NMR values for all examples. This material is available free of charge via the Internet at http://pubs.acs.org.