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Synthesis of Two Bioactive Natural Products: FR252921 and Pseudotrienic Acid B

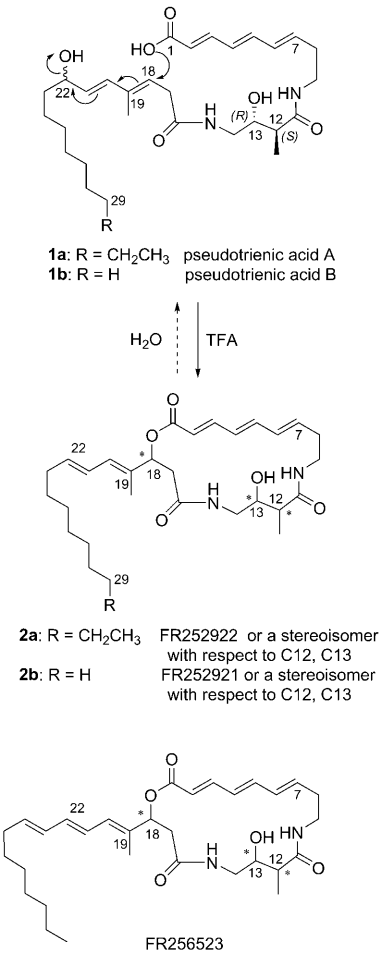
Dominique Amans, Véronique Bellosta, and Janine Cossy*[a]

Abstract: Concise and highly convergent syntheses of the immunosuppressive agent FR252921 and the related antimicrobial natural product pseudotrienic acid B were achieved from a common intermediate by using optically active titanium complexes to control the configuration of the stereogenic centers, a highly stereo- and regioselective cross-metathesis to generate the triene moieties, and a Stille cross-coupling to install the dienic units.

Keywords: asymmetric catalysis · cross-coupling · metathesis · natural products · polyenes

Introduction

From 2003–2005, five structurally related natural products were discovered: two antimicrobial agents pseudotrienic acids A (**1a**) and B (**1b**) isolated from *Pseudomonas* sp. MF 381-IODS[1] and three novel immunosuppressive agents FR252921 (**2b**), FR252922 (**2a**) and FR256523 incorporating a 19-membered lactone isolated from the culture broth of *Pseudomonas fluorescens* No 408813 (Scheme 1).[2] The overall backbone structure of the three 19-membered macrolactones FR252921, FR252922 and FR256523 was clearly established by Fujine et al. but the absolute stereochemistry of their three stereogenic centers remained unknown.[2] On the other hand, while pseudotrienic acids A and B were isolated as a 1:1 mixture of epimers at C22, the absolute configuration at C12 and C13 were well defined as (*S*) and (*R*), respectively.[1] The molecular architecture of pseudotrienic acids A and B is further characterized by a (*E*,*E*,*E*)-trienic conjugated acid, two amide bonds and a trisubstituted conjugated (*E*,*E*)-diene. Interestingly, Pohanka et al. observed that pseudotrienic acids A and B were prone to macrolactonization upon treatment with trifluoroacetic acid, leading to



Scheme 1. Pseudotrienic acids A and B and macrolactones FR252921, FR252922 and FR256523.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802649: Experimental procedures and characterization data for compounds (*S*,*S*)-**11**, **13**–**17**, (*S*)-**21**, (*S*)-**22**, **25**, (*S*)-**27**, (*S*)-**28**, (*S*)-**29**, (*S*,*S*)-**30**, (*S*,*R*)-**31**, (*S*,*S*)-**31**, (*S*,*R*)-**32**, **33**, **37**, **38**, **41** and **42**.

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the formation of the naturally occurring lactones FR252922 and FR252921 respectively (Scheme 1).[1] On the basis of this transformation, it seemed reasonable to assume that the absolute configuration of FR252921 was (*S*) at C12, and (*R*) at C13, but the absolute configuration of the stereogenic center at C18 remained unknown. In 2007 and during our studies, Falck et al. unequivocally established, by chemical synthesis, that the absolute configuration of FR252921 is (12*S*,13*R*,18*R*).[3]

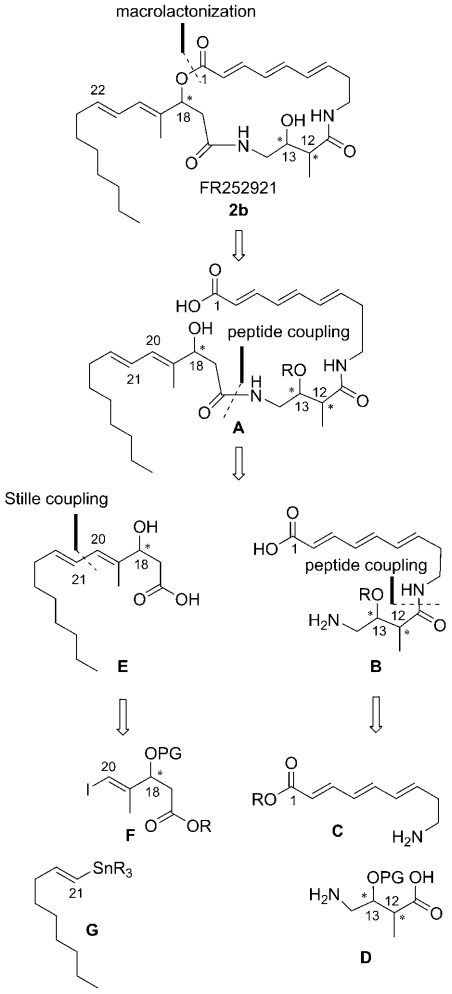
Herein, we describe the full account of a program directed toward the synthesis and the elucidation of the absolute configuration of FR252921. These efforts culminated in an expedient and stereocontrolled synthesis of both FR252921[4] and pseudotrienic acid B.[5]

Results and Discussion

Total synthesis of FR252921: FR252921 displayed significant immunosuppressive activity against murine splenocyte proliferation stimulated with lipopolysaccharide (LPS) or anti-CD3 mAb in vitro without blocking T-cell activation. Further studies also revealed that FR252921 inhibits protein-1 (AP-1) transcription activity and acts dominantly against antigen-presenting cells (APC) compared to T-cells. Importantly, it was shown that FR252921 strongly synergizes the effects of FK506 in vitro and in vivo. It is worth noting that the site and mechanism of action of this new immunosuppressive agent seem to be distinct from those of FK-506 and cyclosporin A, thus making it a good candidate for rejection control in clinical use.[2] Due to its unique pharmacological profile and challenging structure and, in order to unambiguously suppress the uncertainties surrounding its stereochemical assignment, we were as other groups[3,6] interested in the total synthesis of FR252921.

As the absolute configuration of the three stereogenic centers of FR252921 was unknown when we started our studies, a flexible and versatile strategy was devised in order to provide access to all possible diastereoisomers. The overall approach employed to achieve our goal is depicted retrosynthetically in Scheme 2. It relied on a macrolactonization of *seco*-acid **A** to form the 19-membered ring lactone **2b**. The diamide **A** would result from a peptide coupling between carboxylic acid **E** and amino alcohol **B**, which in turn would be synthesized via an additional peptide coupling between trienic amine **C** and carboxylic acid **D**. A palladium-catalyzed cross-coupling between vinyl iodide **F** and alkenyl metal **G** would allow the elaboration of the (*E*,*E*)-dienic side chain **E**. The absolute configuration of the three stereogenic centers at C12, C13 and C18 would be controlled by using highly face-selective allyl- and crotylmetal complexes.

In order to establish the absolute and relative configuration of the stereogenic centers present in FR252921, we decided to synthesize the four *syn*,*syn*-, *syn*,*anti*-, *anti*,*syn*- and *anti*,*anti*-diastereomers of *seco*-acid **A** possessing the (*S*)-configuration at C12 (Scheme 3). Macrocyclization of one of these four diastereomers should in principle provide either



Scheme 2. Retrosynthetic analysis of FR252921.

FR252921 or its enantiomer, thus establishing the stereochemistry of the natural product.

The synthesis of the amino-trienic ester of type **C** was achieved by using the methodology developed in our laboratory for the chemo- and stereoselective synthesis of conjugated 1,3-dienes by cross-metathesis.[7] Thus, cross-metathesis between methyl sorbate **3** and an excess of allylbromide (5 equiv), in the presence of the Grubbs–Hoveyda catalyst [Ru]-**I**[8] (5 mol%), in CH_2Cl_2 at RT, furnished the desired dienic allylic bromide **4** in 48% yield and with excellent stereoselectivity [(*E*,*E*)/(*E*,*Z*) > 95:5].[9] Subsequent treatment of **4** under Michaelis–Arbuzov conditions led to the desired diethylphosphonate **5** in near quantitative yield. It is worth mentioning that dienic phosphonate **5** can be directly obtained by cross-metathesis between commercially available diethyl allylphosphonate and methyl sorbate **3** in a similar yield. However, this procedure resulted in a diminished [(*E*,*E*)/(*E*,*Z*)] selectivity [(*E*,*E*)/(*E*,*Z*) 85:15] as well as difficulties associated with the removal of ruthenium by-products from phosphonate **5**.[7]

A Horner–Wadsworth–Emmons olefination between the *N*-Boc protected amino aldehyde **6** and the lithium salt of

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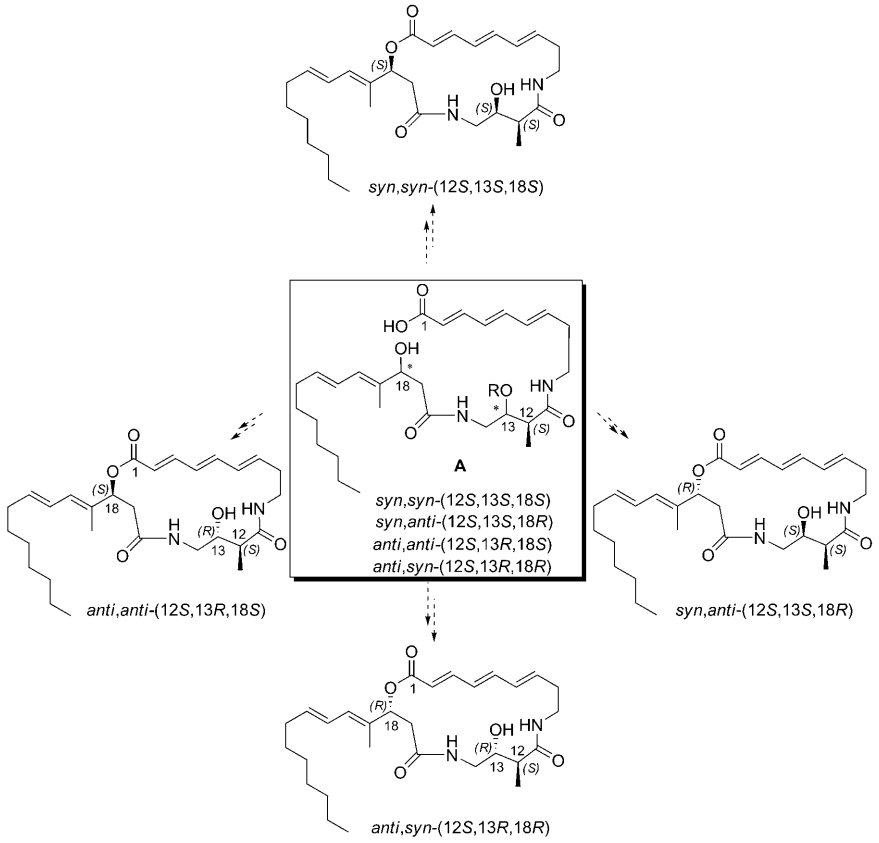


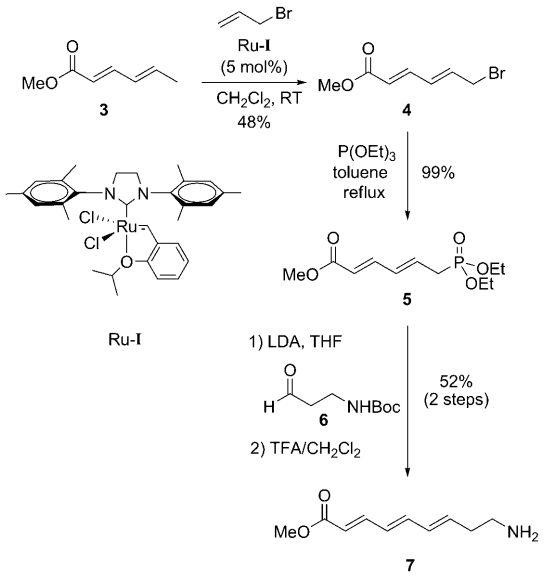
Scheme 3. FR252921 or *ent*-FR252921 possible stereoisomers.

allylic phosphonate **5** allowed the stereoselective formation of the corresponding (*E*,*E*,*E*)-trienic ester. Subsequent TFA-mediated deprotection of the *tert*-butoxycarbonyl group ultimately furnished the desired free amine **7** (52%, two steps). Thus, trienic ester **7** (compound of type **C**) was efficiently prepared in four steps from the commercially available methyl sorbate **3** in 25% overall yield (Scheme 4).

Preparation of both *syn* and *anti* diastereoisomers of the amino alcohol of type **D**, incorporating two contiguous stereogenic centers at C12 and C13, was then considered.

The synthesis of the amino acids of type **D**, possessing the *anti*-relationship between the two substituents at C12 and C13, has been achieved starting from the *N*-Boc protected glycine methyl ester **8**. The latter was carefully transformed into the corresponding aldehyde **9** upon reduction with DIBAL-H (CH_2Cl_2, −78°C),[10] and then directly treated with the highly enantioselective crotyltitanium complex (*S*,*S*)-**II**,[11] which gave rise to the corresponding homoallylic amino alcohol (*R*,*R*)-**10** (57% yield) with the requisite *anti*-relationship between the methyl and the hydroxy substituents at C12 and C13 (dr > 95:5), and with high enantioselectivity for the major isomer (*ee* > 95%).[12] Subsequent protection of the resulting amino alcohol as *N*,*O*-acetonide followed by ruthenium-catalyzed oxidative cleavage of the terminal olefin ($RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$)[13] led to the desired carboxylic acid (*S*,*R*)-**11** with an overall yield of 75% for the two steps (Scheme 5).

In order to obtain the enantiopure amino alcohol of type **D** with the *syn* relationship between the two substituents at C12 and C13, the use of a configurationally stable optically active crotylmetal complex of *Z* configuration was required.[14] We therefore considered to use the configurationally stable (*Z*)-configured optically active crotylboranes derived from α-pinene, developed by Brown et al.[15] Thus, addition of (*Z*)-(−)-crotylbis(isopinocampheyl)borane (−)-Ipc-**III** generated in situ, on the *Si* face of aldehyde **9**, allowed the formation of the corresponding homoallylic alcohol (*R*,*S*)-**10** possessing the *syn*-relationship between the methyl and the hydroxy substituents present at C12 and C13 (dr > 95:5, *ee* > 95%) in 53% yield. Conversion of the amino alcohol (*R*,*S*)-**10** into the required carboxylic acid (*S*,*S*)-**11** was accomplished in an analogous fashion as for the synthesis of its diastereoisomer (*S*,*R*)-**11** (77% yield, two steps) (Scheme 5).



Scheme 4. Synthesis of the amino-trienic ester **7**.

We then turned our attention toward the synthesis of the optically active β-hydroxyester **F**. The latter could be ac-

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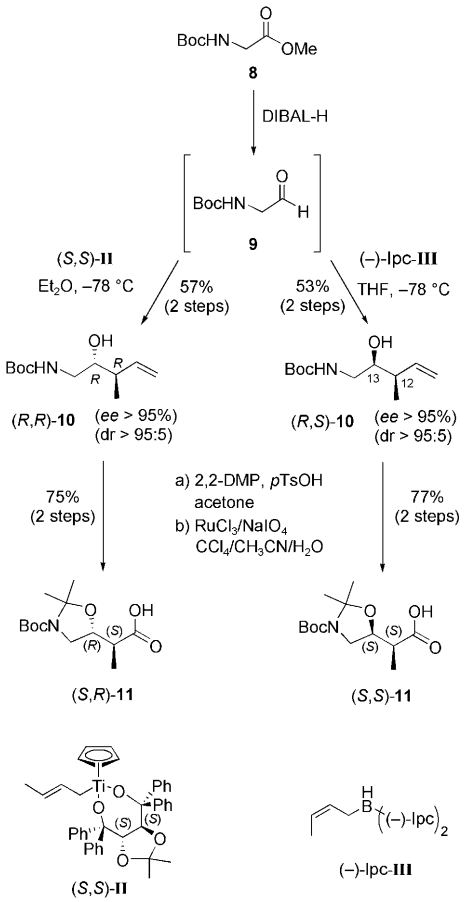
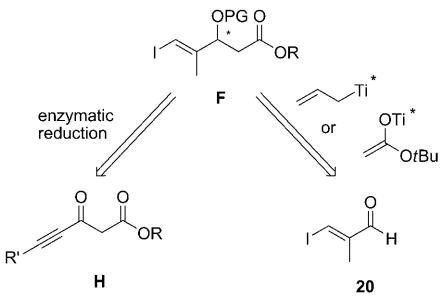


Scheme 5. Synthesis of the amino acids (*S*,*R*)-**11** and (*S*,*S*)-**11**.

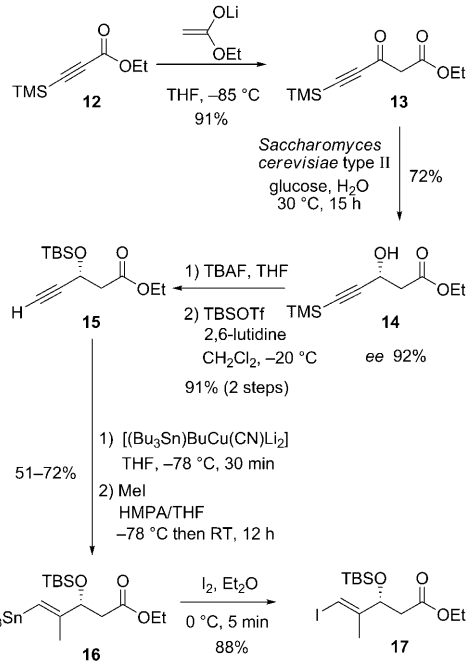
cessed by performing an enzymatic reduction of a β-ketoester of type **H**. Alternatively, addition of a chiral allyltitanium complex or an optically active titanium enolate onto aldehyde **20** would also provide the required enantiopure β-hydroxyester **F** (Scheme 6).

The enzymatic reduction of β-ketoester **13** (of type **H**), was first explored. The synthesis of β-ketoester **13** was readily accomplished by performing a Claisen condensation between the lithium enolate of ethyl acetate and the commercially available ethyl trimethylsilylpropiolate (**12**) (−85 °C, THF, 91 % yield). The resulting β-ketoester **13** was subjected to an enantioselective enzymatic reduction on treatment



Scheme 6. Retrosynthetic analysis of the β-hydroxyester of type **F**.

with *Saccharomyces cerevisiae* (type II) in the presence of glucose (H_2O/EtOH, 30 °C) to afford the optically active secondary alcohol **14** of *R* configuration in 72 % yield with an enantiomeric excess of 92 %.[16,17] It is worth mentioning that the stereochemical outcome of this reaction is controlled by the presence of the trimethylsilyl group at the acetylenic position. Indeed, it has been shown that the enzymatic reduction of the corresponding terminal alkyne, in similar conditions, would deliver the *S* enantiomer of β-hydroxyester **14**.[18] Removal of the acetylenic trimethylsilyl group in **14** under standard conditions followed by protection of the propargylic alcohol as its *tert*-butyldimethylsilyl ether afforded the resulting terminal alkyne **15**. The latter was then subjected to a stannylcupration–methylation sequence [$Bu(Bu_3Sn)Cu(CN)Li_2$, THF, −78 °C then MeI, HMPA/THF, −78 °C to RT][19] to give the trisubstituted (*E*)-configured alkenyl stannane **16** (51–72 % yield). A subsequent iododestannylation (I_2, Et_2O, 0 °C) ultimately furnished the required (*E*)-vinyl iodide **17** in 88 % yield (Scheme 7).



Scheme 7. Synthesis of vinyl iodide **17** by enzymatic reduction.

While vinyl iodide **17** could be obtained efficiently from ethyl trimethylsilylpropiolate **12** in six steps and in 10 % yield, this route turned out to be not amenable for large-scale preparation. Consequently, we decided to explore a more practical route which would allow the access to both *R* and *S* enantiomers of β-hydroxyester of type **F** on a large scale.

To this end, the enantioselective addition of allyltitanium reagents onto aldehyde **20** was considered in order to control the configuration of the C18 stereogenic center. The requisite aldehyde **20** was obtained by MnO_2 oxidation of the known allylic alcohol **19**,[20] prepared by performing a

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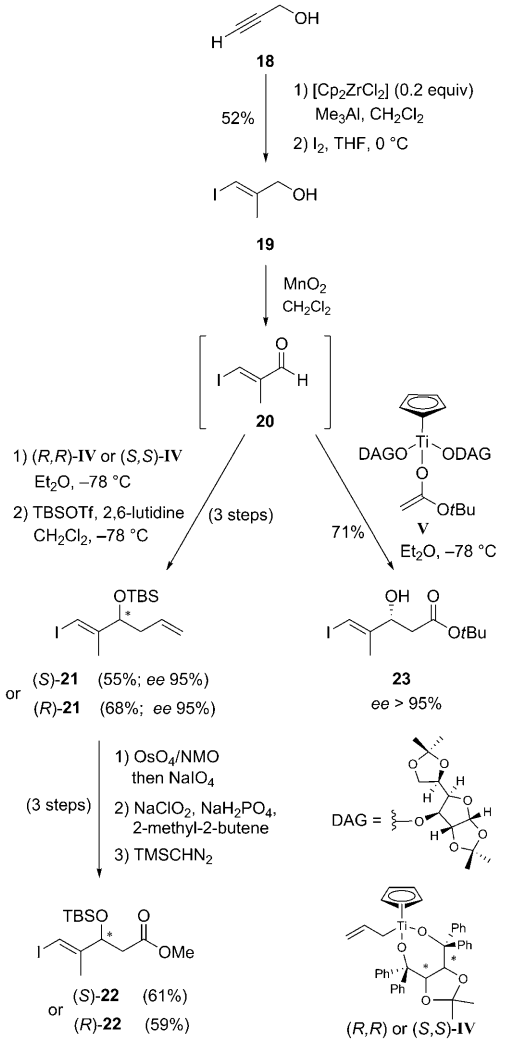
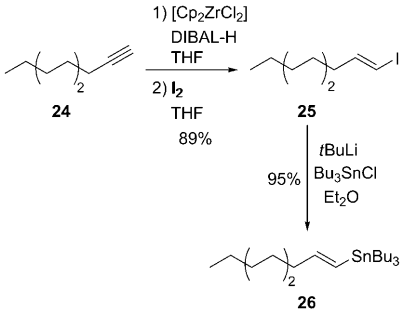
stereo- and regioselective zirconium-assisted carboalumination of propargylic alcohol **18** followed by iodolysis.[21] The resulting aldehyde **20** was directly submitted to an enantioselective allylmetalation with allyltitanium complexes[11] (*R*,*R*)-**IV** or (*S*,*S*)-**IV** to produce, after TBS protection, compounds (*S*)-**21** and (*R*)-**21**, respectively, in good yield and high enantioselectivity (*ee* > 95%). A three-step sequence [regioselective oxidative cleavage of the terminal double bond (OsO_4/NMO then $NaIO_4$), oxidation of the resulting aldehyde into a carboxylic acid ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene),[22] esterification with trimethylsilyldiazomethane], applied to each enantiomer of **21** provided access to both enantiomers (*S*)-**22** and (*R*)-**22** in satisfactory yield (61 and 59%, respectively) (Scheme 8). This alternative approach, undoubtedly more efficient than the previous one, allowed the synthesis of both enantiomers of the β-hydroxyesters of type **F** in synthetically useful quantities.

While the synthetic sequence outlined above provided efficient access to both enantiomers (*S*)-**21** and (*R*)-**21**, it could be even shortened by treating aldehyde **20** with the optically active titanium enolate **V**,[23] generated in situ from *tert*-butylacetate lithium enolate and $CpTi(ODAG)_2Cl$ titanium complex derived from D-glucose, which directly furnished β-hydroxyester (*R*)-**23** in 71% yield and with high optical purity (*ee* > 95%)[24] (Scheme 8). This protecting group free strategy provides a very short and efficient access to the desired β-hydroxyester of *R* configuration, but this method is unfortunately not suitable for the preparation of the *S* enantiomer since the non-natural L-diacetone glucofuranose is not readily available.



Scheme 8. Enantioselective syntheses of vinyl iodides of type **F** involving chiral titanium complexes.

The synthesis of the final fragment, vinyl stannane of type **G**, was needed to build the dienic side chain of FR252921. Its preparation involved a stereo- and regioselective hydrozirconation of non-1-yne **24** by the Schwartz reagent Cp_2ZrHCl, generated in situ ($[Cp_2ZrCl_2]$, DIBAL-H, THF),[25] followed by iodolysis (I_2, THF) to give (*E*)-alkenyl iodide **25** as a single stereoisomer in 89% yield. Subsequent halogen–metal exchange with *t*BuLi, followed by trapping the resulting vinyl lithium species with tri-*n*-butyltin chloride gave rise to the required vinyl stannane **26** (compound of type **G**) in 95% yield (Scheme 9).



Scheme 9. Synthesis of vinyl stannane **26**.

Having established efficient syntheses of fragments **C**, **D**, **F** and **G**, we turned our attention to their coupling into FR252921. The order in which these four fragments would be assembled needed to be considered. In order to minimize the risk of β-elimination of the extremely labile C18 hydroxy group, we reasoned that fragment **E**, resulting from the coupling between vinyl iodide **F** and vinyl stannane **G**, should be introduced at the late stage of the synthesis.

Coupling of vinyl stannane **26** and alkenyl iodide (*S*)-**22** was achieved by performing a $[PdCl_2(CH_3CN)_2]$-catalyzed Stille cross-coupling in DMF, which successfully led to (*E*,*E*)-diene (*S*)-**27**. Deprotection of the TBS ether with TBAF followed by saponification with LiOH resulted in the formation of hydroxycarboxylic acid (*S*)-**29** in 89% yield over the two steps. Its enantiomer (*R*)-**29** was obtained in an identical fashion, and in similar yields (Scheme 10).

It was also possible to perform the Pd-catalyzed Stille coupling under the previously described conditions between alkenyl stannane **26** and vinyl iodide (*R*)-**23** which possesses a free hydroxy group. After saponification of the *tert*-butyl

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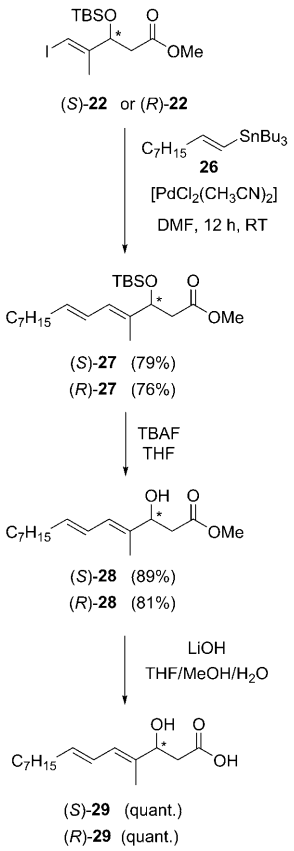
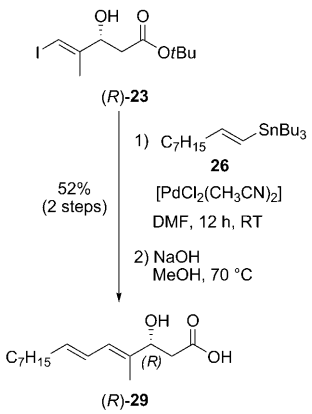


Scheme 10. Synthesis of dienes (*S*)-**29** and (*R*)-**29**.

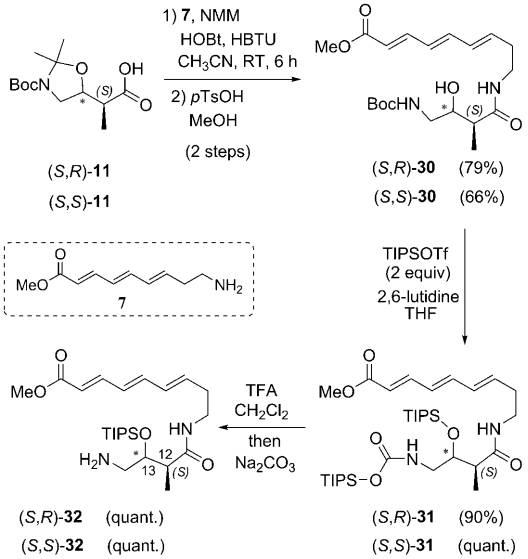
ester (NaOH, MeOH, 70 °C), the dienic β-hydroxyacid (*R*)-**29** was isolated in 52 % yield (two steps) (Scheme 11).

The amino acids of type **D**, (*S*,*R*)-**11** and (*S*,*S*)-**11**, were then coupled with the aminotrienic ester **7** [*N*-hydroxybenzotriazole (HOBt), *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and *N*-methylmorpholine (NMM) in acetonitrile] to produce, after cleavage of the *N*,*O*-dimethyloxazolidine under acidic conditions, the corresponding *N*-Boc-amino alcohols (*S*,*R*)-



Scheme 11. Synthesis of diene (*R*)-**29**.

30 and (*S*,*S*)-**30**. Subsequent protection of the free hydroxyl group at C13 as a TIPS ether (2 equiv of TIPSOTf; 2,6-lutidine) led to the amino alcohols (*S*,*R*)-**31** and (*S*,*S*)-**31** in excellent yields. It is worth mentioning that under these conditions, the *tert*-butoxycarbamate was transformed into a TIPS carbamate,[26] which was merely cleaved upon treatment with TFA in CH_2Cl_2 to furnish the corresponding free amines (*S*,*R*)-**32** and (*S*,*S*)-**32** quantitatively (Scheme 12).



Scheme 12. Synthesis of amino alcohols (*S*,*R*)-**32** and (*S*,*S*)-**32**.

Possessing now the two diastereomeric amino alcohols of type **B**, (*S*,*R*)-**32** and (*S*,*S*)-**32**, as well as the two enantiomers of the dienic β-hydroxy acids of type **E**, we were in a favorable position to synthesize the four diastereomers of *seco*-acid **A**, one of which being the precursor of the natural product FR252921 (or its enantiomer).

Being aware of the structural analogy existing between FR252921 and pseudotrienic acid B of (12*S*,13*R*) configuration, the synthesis of both *anti*,*syn*-(12*S*,*13R*,18*R*) and *anti*,*anti*-(12*S*,13*R*,18*R*) diastereoisomers was first considered. Thus, (*S*,*R*)-**32** was assembled with (*R*)-**29** under classical peptide coupling conditions (HOBt, HBTU, NMM) to give after saponification the corresponding *anti*,*anti*-(12*S*,13*R*,18*R*) *seco*-acid **33** in 71 % yield (Scheme 13). With hydroxy-acid **33**, the stage was set for the crucial macrolactonization step.[27] To this end, we decided to explore in a first place the macrolactonization of *seco*-acid **33** under Mitsunobu conditions. Unfortunately, when a solution of diisopropyl azodicarboxylate (DIAD) was slowly added to a dilute solution of hydroxy acid **33** and triphenylphosphine in benzene ($c = 0.0035$ M), no trace of the desired macrolactone **34** could be detected. Alternative protocols based on the activation of the carboxylic acid in **33** were also attempted, to no avail. Concerned about the risk of a β-elimination of the hydroxy group at C18 under basic conditions, camphorsulfonic acid-catalyzed macrolactonization involving an ethoxy-

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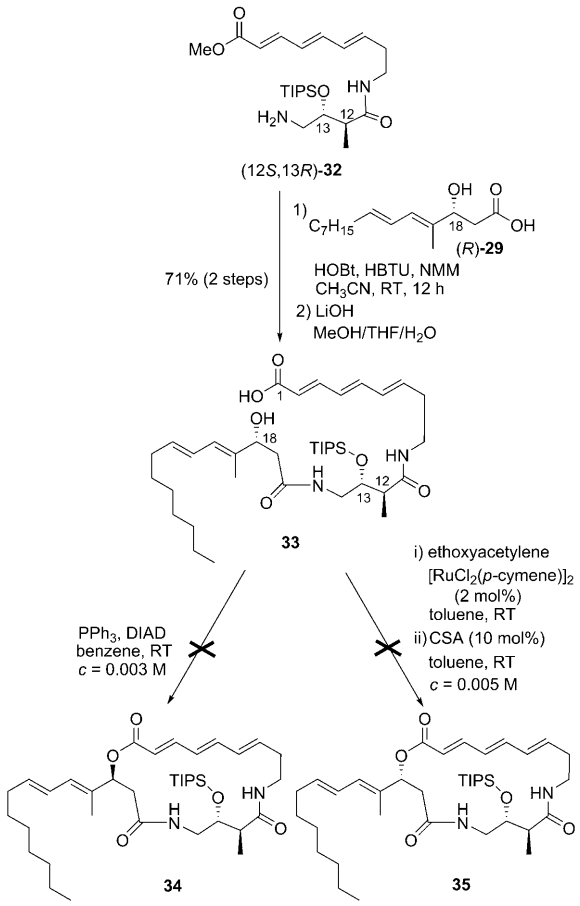
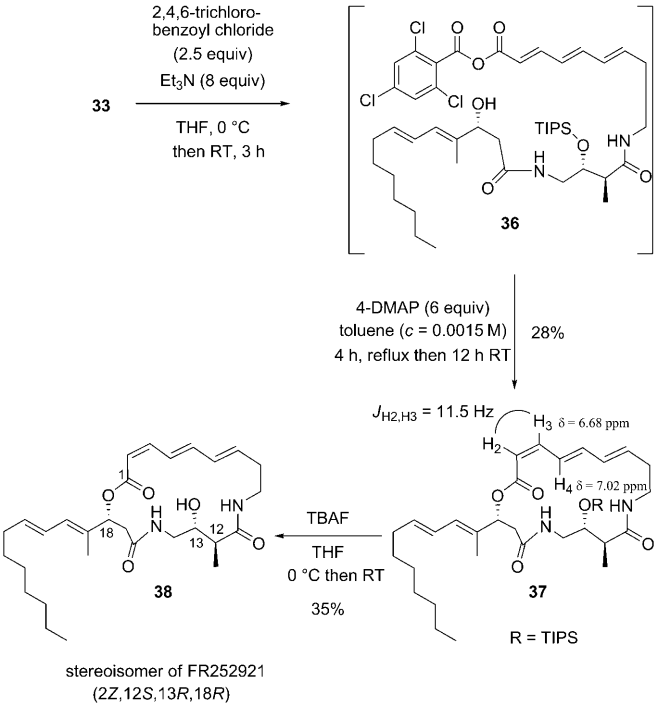


Scheme 13. Synthesis of *seco*-acid **33** and first attempts of macrolactonization.



Scheme 14. Synthesis of (2*Z*,12*S*,13*R*,18*R*)-macrolactone **38**.

vinyl ester, readily obtained from the corresponding carboxylic acid, was examined.[28] Along these lines, the *seco*-acid **33** was treated with ethoxyacetylene, in the presence of a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$,[29] to provide the corresponding sensitive ethoxyvinyl ester. This compound was not purified but directly added to a dilute solution of CSA in toluene ($c = 0.005$ M). Unfortunately, the desired macrolactone **35** was not obtained under these conditions (Scheme 13).

On the basis of these negative results, more forcing conditions were assayed for the macrolactonization. To our delight, under classical Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP, toluene, $c = 0.0015$ M, 65 °C)[30] *seco*-acid **33** underwent macrolactonization. However, close examination of the NMR spectra revealed the formation of unexpected macrolactone **37**, the result of an isomerization of the C2–C3 double bond initially of *E* configuration into a *Z* olefin. Indeed, COSY ^1H–^1H correlation showed that the most deshielded proton, which was usually attributed to H3 since it is localized in the deshielding plane of the carbonyl group, turned out to be H4 and more strikingly the value of the coupling constant between H2 and H3 was 11.5 Hz, which is abnormally small for a *E*-configured double bond. These results confirmed the hypothesis of an isomerization of the C2–C3 double bond into a *Z* olefin. The subsequent fluoride-mediated cleavage of the TIPS-ether proceeded uneventfully and furnished the trienic macrolactone **38** of (2*Z*,12*S*,13*R*,18*R*) configuration, stereoisomer of FR252921 (Scheme 14).

Considering these results, we wondered whether the relative configuration at C12, C13 and C18 could influence the cyclization process since some conformational restrictions could be the result of the relative orientation of the substituents located on these three stereogenic centers. Therefore, the *anti*,*anti*- and *syn*,*anti*-diastereomers of the *seco*-acid **33** were also synthesized by using the same two-step procedure and subsequently underwent macrolactonization under Yamaguchi conditions to provide the *anti*,*anti*-*seco*-acid (12*S*,13*R*,18*S*)-**39** in 71% yield [2 steps from (12*S*,13*R*)-**32** and (*S*)-**29**] and *syn*,*anti*-*seco*-acid (12*S*,13*S*,18*R*)-**40** in 76% yield [two steps from (12*S*,13*S*)-**32** and (*R*)-**29**]. As previously, Yamaguchi macrolactonization of *seco*-acids **39** and **40** followed by cleavage of the TIPS ether by TBAF furnished the macrolactones **41** and **42** respectively (Scheme 15). Unfortunately, isomerization of the C2–C3 double bond into a *Z* olefin was observed in these cases as well. Based on these observations, we concluded that the isomerization of the C2–C3 double bond was not related to the configuration of the three stereogenic centers, but rather to the conditions used for the macrolactonization (Scheme 15).[31] We believe that the use of excess DMAP at elevated temperatures could be responsible for the observed isomerization of the C2–C3 double bond, presumably involving a ketene intermediate.[32,33]

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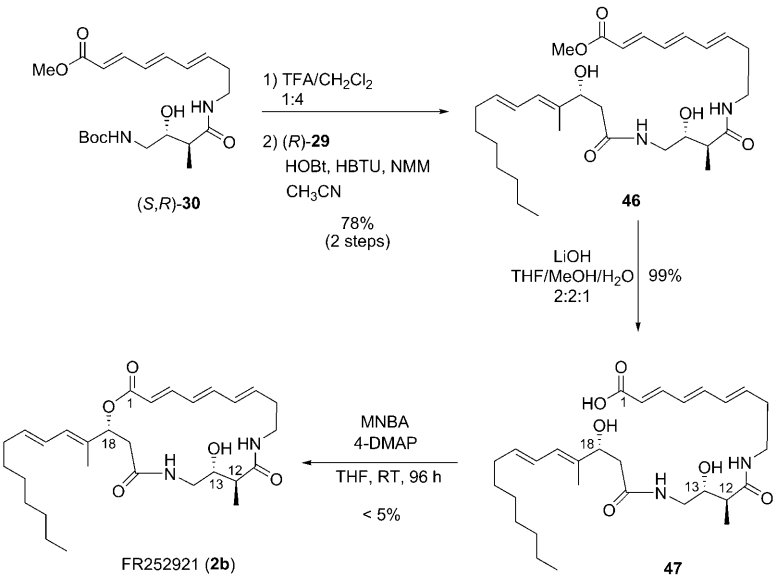
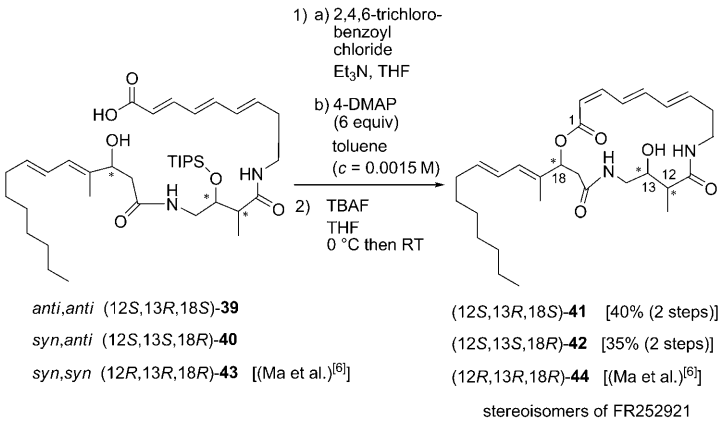
These results allowed us to conclude that the presence of the bulky TIPS ether at C13 could be indirectly responsible for the displacement of the thermodynamic equilibrium toward the formation of the putative more stable lactone of (2*Z*,4*E*,6*E*)-configuration, which would consequently prevent the formation of the natural product FR252921. In order to test this hypothesis, the macrolactonization without any protecting group for the alcohol at C13 was considered.

Being aware at that time of the results published by Falck et al., who disclosed the total synthesis of FR252921 from the corresponding *seco*-acid with a free hydroxy group at C13,[3] we embarked in the synthesis of the *seco*-acid of (12*S*,13*R*,18*R*)-configuration.



Scheme 16. Total synthesis of FR252921.



Scheme 15. Synthesis of stereomeric lactones of FR252921.

Along these lines, treatment of *N*-Boc-amino alcohol (*S*,*R*)-**30** with TFA in CH_2Cl_2, followed by peptide coupling with (*R*)-**29** (HOBt, HBTU, NMM, CH_3CN) gratifyingly furnished diamide **46** in 78% over two steps. Saponification of **46** with LiOH resulted in *seco*-acid **47**, precursor of FR252921, in near quantitative yield (Scheme 16). It should be noted that the NMR spectral data of *seco*-acid **47** are highly dependent on sample concentration (in particular for the chemical shifts of H2, H3, C1, C2, C5) and fortunately one of our NMR ^1H spectra was in total agreement with one of the NMR spectra provided by Falck et al.[34] Furthermore, the optical rotation value of our *seco*-acid **47** corresponds to the one published by Falck.

The completion of the total synthesis of FR252921 was performed according to the protocol described by Falck et al. involving the macrolactonization of *seco*-acid **47** under Shiina's conditions.[35] Thus, treatment of the previously obtained hydroxy-acid **47** by 2-methyl-6-nitrobenzoic anhydride (MNBA), in the presence of 4-DMAP in a highly diluted THF solution ($c = 0.0006$ M), allowed the formation of FR252921 in poor yield ($\approx 5\%$) accompanied by significant impurities, which could only be separated from the natural product by reverse phase chromatography (Scheme 16).[36–38]

Total synthesis of pseudotrienic acid B: Due to the structural similarities between pseudotrienic acid B and FR252921, a straightforward synthesis of pseudotrienic acid B was envisaged starting from a common intermediate, compound (*S*,*R*)-**30**. The strategy employed to synthesize pseudotrienic acid B relied on a palladium-catalyzed Stille cross-coupling between vinyl iodide **57** and the alkenyl stannane **56** to generate the (*E*,*E*)-diene. Compound **57** would be obtained through amide bond formation between carboxylic acid **52** and amino alcohol (*S*,*R*)-**30** that we previously obtained in the course of the total synthesis of FR252921 (Scheme 17).

We therefore needed to synthesize vinyl iodide **52** and alkenyl stannane **56**. The required (*E*)-vinyl iodide **52**, which corresponds to the C16–C19 fragment of pseudotrienic acid B, was synthesized in three steps from the commercially available pent-3-yn-1-ol **48** as outlined in Scheme 18. A regio- and stereoselective stannylcupration using the mixed higher order cuprate $[(Bu_3Sn)BuCu(CN)Li_2]$[19] in the presence of MeOH[39] afforded the vinyl stannanes **49** and **50** in a 9:1 ratio with a combined yield of 74%. These two regioisomers were easily separated by flash chromatography on silica gel and the desired (*E*)-vinyl stannane **49** was subsequently subjected to iododestannylation (I_2, Et_2O) to give alkenyl iodide **51** in good yield (94% yield). Oxidation of the primary alcohol with Jones reagent ($CrO_3 \cdot H_2SO_4$, acetone) successfully led to the desired carboxylic acid **52** in 92% yield (Scheme 18).

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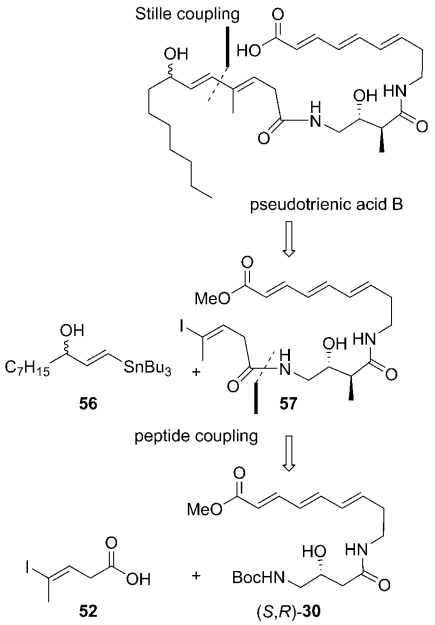
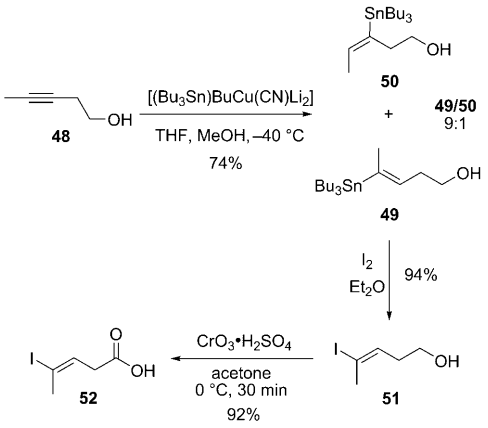


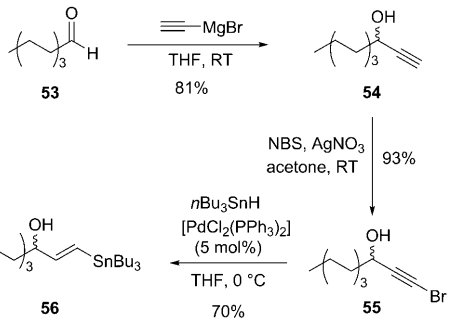
Scheme 17. Retrosynthetic analysis for pseudotrienic acid B.



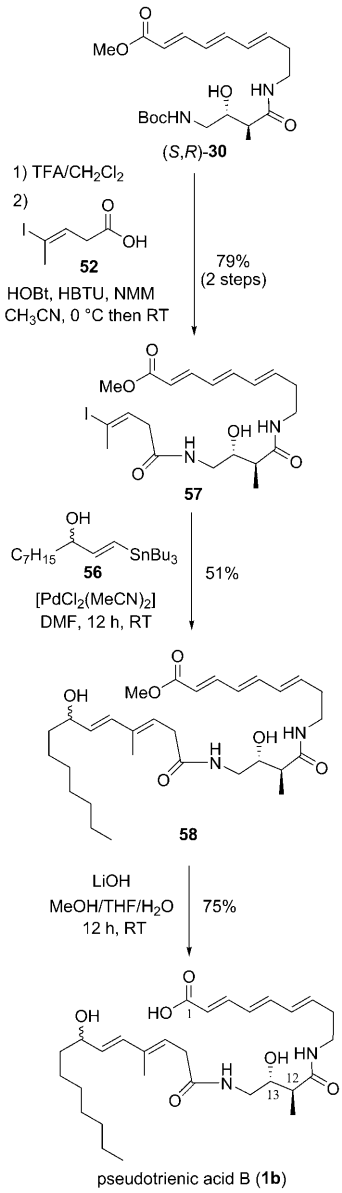
Scheme 18. Synthesis of alkenyl iodide **52**.

The last fragment, vinyl stannane **56** (C20–C29 fragment), was prepared in three steps from octanal **53**. After addition of ethynylmagnesium bromide (THF, 0°C), the resulting propargylic alcohol **54** (81% yield) was exposed to *N*-bromosuccinimide (NBS) in the presence of $AgNO_3$ to give the bromoalkyne **55** in 93% yield.[40] A regio- and stereocontrolled [>95% *E* isomer] palladium-mediated hydrostannylation of bromoalkyne **55** {[$PdCl_2(PPh_3)_2$], nBu_3SnH, THF, 0°C} afforded the desired (*E*)-configured alkenyl stannane **56** in 70% yield (Scheme 19).

With the four fragments at hand, the coupling reactions were performed as shown in Scheme 20. Treatment of *N*-Boc-amino alcohol (*S*,*R*)-**30** with TFA in CH_2Cl_2, followed by a coupling with carboxylic acid **52** under classical peptide coupling conditions (HOBt, HBTU, NMM, CH_3CN) furnished amide **57** in 79% yield (two steps). The vinyl



Scheme 19. Synthesis of vinyl stannane **56**.



Scheme 20. Total synthesis of pseudotrienic acid B.

iodide **57** was subsequently involved in a Pd-catalyzed Stille cross-coupling {[$PdCl_2(MeCN)_2$], DMF, 12 h} with vinyl

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stannane **56** bearing a non-protected hydroxy group, which successfully gave rise to the core structure of pseudotrienic acid B, ester **58**, as a mixture of two epimers at C20 (51% yield). It is worth mentioning that only one set of NMR signals is observed, which suggests that these two epimers cannot be distinguished by NMR spectroscopy. Finally, after saponification of **58** with LiOH, the expected pseudotrienic acid B was isolated in 75% yield. The spectroscopic data were in total agreement with those reported in the literature for the natural product (Scheme 20).[1,41]

Conclusion

In conclusion, a short and highly convergent strategy allowed us to achieve the total synthesis of FR252921 from methyl sorbate **3** in ten steps (longest linear sequence), as well as three potentially useful analogues for biological evaluation. This work illustrates the crucial role that total synthesis plays in the structural assignment of natural products, and also highlights the difficulties associated with a macrolactonization strategy toward this type of constrained polyenic macrolide. Moreover, a concise, efficient and highly convergent stereoselective synthesis of related pseudotrienic acid B has been achieved from methyl sorbate **3** in 5.8% overall yield over ten steps (longest linear sequence) which constitutes, to our knowledge, the first total synthesis of this naturally-occurring molecule.

Experimental Section

General methods: TLC was performed on Merck $60F_{254}$ silica gel plates and visualized either with a UV lamp (254 nm), or by using a solution of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH followed by heating.

Flash chromatography was performed with Merck Geduran Si60 silica gel (40–63μm).

Infrared (IR) spectra were recorded on a Perkin-Elmer 298 or on a Bruker TENSOR 27 (IRFT), wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet or overlap of non equivalent resonances), integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz or on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Mass spectra with electronic impact (MS) were recorded from a Hewlett-Packard tandem 5890 A GC (12 m capillary column), 5971 MS (70 eV). High resolution mass spectra (HRMS) were performed by the Groupe de Spectrométrie de Masse de l'Université Pierre et Marie Curie (Paris).

All the reactions were performed under an argon atmosphere.

Methyl (2*E*,4*E*)-6-bromohexa-2,4-dienoate (4): Grubbs–Hoveyda catalyst [Ru]-**I** (18.5 mg, 0.030 mmol, 0.025 equiv) was added to a solution of methyl sorbate **3** (150 mg, 1.2 mmol, 1.0 equiv) and allylbromide (6.0 mmol, 5.0 equiv) in CH_2Cl_2 (15 mL). After 24 h of stirring at RT, another portion of Grubbs–Hoveyda catalyst [Ru]-**I** was added (18.5 mg, 0.030 mmol, 0.025 equiv). Stirring was continued for 24 h, and silica was added to the reaction mixture. The volatiles were removed in vacuo and the residue was purified by flash column chromatography (PE/EtOAc 98:2 → 95:5) to give diene **4** (118 mg, 48%) as a mixture of diastereoisomers [(*E*,*E*)-**4**/(*E*,*Z*)-**4** 32:1], contaminated by traces of methyl 8-bromoocta-2,4,6-trienoate. $R_f \approx 0.25$ (PE/EtOAc 95:5); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.19$ (dd, 1H, $J = 15.4$, 11.0 Hz), 6.32 (dd, 1H, $J = 15.0$, 11.0 Hz), 6.18 (dt, 1H, $J = 15.0$, 7.5 Hz), 5.87 (d, 1H, $J = 15.4$ Hz), 3.97 (d, 2H, $J = 7.5$ Hz), 3.69 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9 (s), 142.8 (d), 136.7 (d), 131.9 (d), 122.8 (d), 51.8 (q), 31.2 ppm (t); IR (neat): $\tilde{\nu} = 2950$, 1713, 1643, 1614, 1434, 1336, 1249, 1194, 1147, 1113, 995 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 206 (15) [$M(^{81}Br)^+$], 204 (15) [$M(^{79}Br)^+$], 175 (15) [$M(^{81}Br)-OMe^+$], 173 (15) [$M(^{79}Br)-OMe^+$], 147 (3), 145 (4), 125 (100), 97 (12), 94 (23), 93 (57), 79 (14), 66 (50), 65 (37).

Methyl (2*E*,4*E*)-6-(diethoxyphosphoryl)hexa-2,4-dienoate (5): Triethylphosphite (29 mL, 170 mmol, 12.0 equiv) was added dropwise to a solution of bromodiene **4** (3.10 g, 14.2 mmol, 1.0 equiv) in toluene (29 mL). The mixture was heated to reflux for 1 h, was then allowed to reach RT and the volatiles were removed in vacuo. Purification of the crude residue by flash chromatography on silica gel (PE/EtOAc 50:50 → 20:80) furnished the desired phosphonate (3.65 g, 99%) as a colorless oil. $R_f \approx 0.2$ (EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (dd, 1H, J = 15.5, 11.0 Hz), 6.32 (ddd, 1H, $J = 15.5$, 11.0, $J_{H,P} = 5.2$ Hz), 6.07 (m, 1H), 5.86 (dd, 1H, $J = 15.5$, 2.4 Hz), 4.11 (m, 4H), 3.74 (s, 3H), 2.72 (dd, 2H, $J_{H,P} = 23.1$, 7.6 Hz), 1.32 ppm (t, 6H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (s), 143.7 (d), 132.6 (d, $J_{C,P} = 20.1$ Hz), 131.7 (d, $J_{C,P}$ = 20.1 Hz), 120.7 (d), 62.1 (2t), 51.5 (q), 31.2 (t, $J_{C,P} = 140.9$ Hz), 16.4 ppm (2q); IR (neat): $\tilde{\nu} = 3467$, 2983, 2982, 1716, 1644, 1617, 1436, 1340, 1247, 1149, 1025, 957, 791, 729 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 262 (16) [M^+], 247 (10) [$M-OMe^+$], 233 (2), 231 (8), 191 (7), 175 (9), 125 (12), 124 (100), 111 (18), 109 (32), 94 (11), 93 (11), 91 (10), 81 (21), 66 (18), 65 (13), 59 (7); HRMS (CI^+, NH_3): *m*/*z*: calcd for $C_{11}H_{20}O_5P$: 263.1048; found: 263.1044 $[M+H]^+$.

***tert*-Butyl 2-formylethylcarbamate (6)**: A solution of Dess–Martin periodinane (1.36 g, 6.27 mmol, 1.1 equiv) in CH_2Cl_2 (15 mL) was added dropwise to a solution of *N*-Boc-aminopropan-1-ol (1.0 g, 5.70 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 0°C. After 2 h at RT, the reaction mixture was diluted with Et_2O (30 mL) and then hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$ containing solid $Na_2S_2O_3$ (5 g). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (2×30 mL), brine (2×30 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude aldehyde **6** was immediately used in the next step without purification.

Methyl (2*E*,4*E*,6*E*)-9-aminonona-2,4,6-trienoate (7)

Methyl (2*E*,4*E*,6*E*)-9-(*tert*-butoxycarbonylamino)nona-2,4,6-trienoate: *n*BuLi (2.8 mL, 7.4 mmol, 1.3 equiv) was added dropwise to a solution of diisopropylamine (1.1 mL, 7.4 mmol, 1.3 equiv) in THF (6 mL) at 0°C. After 20 min of stirring, the reaction mixture was cooled down to −78°C and a solution of phosphonate **5** (2.05 g, 7.4 mmol, 1.3 equiv) in THF (10 mL) was added dropwise. After 15 min, a solution of the crude aldehyde **6** (5.70 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and stirring was continued for 15 min at −78°C, then 15 min at 0°C. The reaction mixture was hydrolyzed by adding a saturated aqueous solution of NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 85:15) furnished methyl (2*E*,4*E*,6*E*)-9-(*tert*-butoxycarbonylamino)nona-2,4,6-trienoate (944 mg, 55%) as a yellow oil which solidified upon standing in the fridge at −20°C. $R_f \approx 0.25$ (PE/EtOAc 80:20); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (dd, 1H, $J = 15.4$, 12.1 Hz), 6.52 (dd, 1H, J = 14.8, 10.8 Hz), 6.24 (dd, 1H, $J = 14.8$, 11.3 Hz), 6.19 (dd, 1H, $J = 15.2$, 10.8 Hz), 5.87 (d, 1H, $J = 15.2$ Hz), 5.86 (m, 1H), 4.65 (brs, 1H, NH), 3.74 (s, 3H), 3.22 (m, 2H), 2.34 (m, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.5$ (s), 155.9 (s), 144.7 (d), 139.2 (d), 135.4 (d), 131.9 (d), 128.7 (d), 119.8 (d), 79.3 (s), 51.5 (q), 39.8 (t), 33.6 (t), 28.4 ppm (3q); IR (neat): $\tilde{\nu} = 3297$, 2978, 2949, 2932, 1701, 1680, 1618, 1531, 1277, 1246, 1171, 1135, 1007, 994, 877, 850 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 281 (1), 225 (38), 208 (19), 207 (19), 194 (13), 139 (54), 176 (21),

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164 (47), 152 (66), 151 (15), 148 (10), 133 (14), 132 (45), 131 (19), 120 (28), 119 (57), 118 (12), 105 (71), 104 (20), 98 (21), 93 (24), 92 (31), 91 (100), 79 (16), 78(13), 77 (20), 66 (16), 65 (15), 59 (53), 57 (95), 56 (21), 55 (12).

Trifluoroacetic acid (13.5 mL) was added dropwise to a solution of methyl (2*E*,4*E*,6*E*)-9-(*tert*-butoxycarbonylamino)nona-2,4,6-trienoate (1.29 g, 4.6 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) at 0 °C. After 45 min at RT, the resulting brown solution was concentrated in vacuo. The resulting trifluoroacetate ammonium salt was diluted with CH_2Cl_2 (30 mL), and was treated by a saturated aqueous solution of Na_2CO_3 (30 mL). The aqueous phase was vigorously extracted with CH_2Cl_2 (6×30 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give amine **7** (794 mg, 95 %) as a viscous brown oil. This compound was not purified but directly used in the subsequent peptide coupling step (see formation of compound **30**).

***tert*-Butyl (2-oxoethyl)carbamate (9)**: DIBAL-H (1.0 M in toluene, 26.2 mL, 26.2 mmol, 1.1 equiv) was added dropwise over 45 min via syringe pump to a solution of *N*-Boc glycine methyl ester **8** (4.5 g, 23.8 mmol, 1.0 equiv) in CH_2Cl_2 (90 mL) at −78 °C. After 1 h of stirring at −78 °C, the reaction mixture was hydrolyzed by adding a saturated aqueous solution of Rochelle's salt (6 mL) and the mixture was allowed to warm to RT. The resulting gel was filtered over Celite and the filtrate was concentrated under reduced pressure, to give the crude aldehyde **9** (2.58 g, 69 %) as a colorless oil. This extremely unstable compound was immediately used in the next step without purification.

***tert*-Butyl [(2*R*,3*R*)-2-Hydroxy-3-methylpent-4-enyl]carbamate [(*R*,*R*)-10]**: 2-Butenylmagnesium chloride (0.5 M in THF, 32.7 mL, 16.3 mmol, 1.3 equiv) was added dropwise to a stirred suspension of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride (12.3 g, 20.1 mmol, 1.6 equiv) in anhydrous Et_2O (160 mL) at 0 °C. After 2 h at 0 °C, the brown reaction mixture was cooled to −78 °C and a solution of the crude aldehyde **9** (2.0 g, 12.56 mmol, 1.0 equiv) in Et_2O (40 mL) was added dropwise via cannula. After 5 h at −78 °C, the reaction was quenched by addition of water (80 mL). The reaction mixture was stirred for 48 h at RT and then filtered over Celite. The layers were separated and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was then diluted with pentane (60 mL) and filtered to remove (4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol. After removal of pentane under reduced pressure, purification of the residue by flash chromatography on silica gel (PE/EtOAc 90:10 → 80:20) provided the desired enantioenriched homoallylic alcohol (*R*,*R*)-**10** (2.26 g, 83 %) as a colorless oil. The physical and spectral data were in accordance with those reported in the literature.[42] $R_f \approx 0.2$ (PE/EtOAc 80:20); $[\alpha]_D^{20} = -2.58$ ($c = 1.4$, $CHCl_3$) {lit.[42] $[\alpha]_D^{25} = -2.63$ ($c = 5.8$, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 5.76 (m, 1H), 5.16–5.09 (m, 2H), 5.01 (br s, 1H, NH), 3.49 (br m, 1H, H_2), 3.36 (m, 1H), 3.07 (ddd, 1H, $J = 13.6$, 8.0, 5.3 Hz), 2.47 (br s, 1H, OH), 2.24 ($sext_{app}$, 1H, $J = 7.4$ Hz), 1.45 (s, 9H), 1.06 ppm (d, 3H, $J =$ 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7$ (s), 139.9 (d), 116.6 (t), 79.5 (s), 74.2 (d), 44.2 (t), 42.4 (d), 28.4 (3q), 16.1 ppm (q); IR (neat): $\tilde{\nu} =$ 3368, 3077, 2976, 2932, 1690, 1515, 1367, 1251, 1170 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 160 (3), 159 (4), 142 (7), 131 (3), 104 (60), 86 (10), 76 (20), 75 (39), 57 (100); HRMS (ESI): *m*/*z*: calcd for $C_{11}H_{21}O_3NNa$: 238.1413; found: 238.1414 $[M+Na]^+$.

(2*S*)-2-[(5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-5-yl]propanoic acid [(*S*,*R*)-11]

***tert*-Butyl (5*R*)-5-[(1*R*)-1-methylprop-2-en-1-yl]-2,2-dimethyloxazolidine-3-carboxylate**: 2,2-Dimethoxypropane (10.5 mL, 86.11 mmol, 18 equiv) and *p*-toluenesulfonic acid monohydrate (82 mg, 0.478 mmol, 0.1 equiv) were successively added to a solution of amino alcohol (*R*,*R*)-**10** (1.03 g, 4.78 mmol, 1.0 equiv) in acetone (40 mL). After 5 min of stirring at RT, the reaction mixture was hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 95:5) furnished the title *N*,*O*-dimethyloxazolidine (1.17 g, 96 %) as a colorless oil. The physical and spectroscopic properties matched those reported in the literature.[13a] $R_f \approx 0.9$ (PE/EtOAc 80:20); $[\alpha]_D^{20} = -19.6$ ($c = 0.61$, $CHCl_3$) {lit.[13a] $[\alpha]_D^{25} = -19.08$ ($c = 2.7$, $CHCl_3$)}; ^{1}H (400 MHz, $CDCl_3$): $\delta = 5.84$ (m, 1H), 5.14–5.03 (m, 2H), 3.92 (dt_{app}, 1H, $J = 9.5$, 6.9 Hz), 3.58 (m, 1H), 3.13 (m, 1H), 2.37 ($sextuplet_{app}$, 1H, $J = 6.9$ Hz), 1.57 (s, 3H), 1.53 (s, 3H), 1.48 (s, 9H), 1.02 ppm (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.4$ and 152.0 (s), 139.8 (d), 115.1 (t), 93.5 and 93.1 (s), 80.0 and 79.4 (s), 77.1 and 76.9 (d), 48.8 and 48.7 (t), 40.4 (d), 28.5 (3q), 27.1, 26.0, 25.2 and 24.2 (2t), 14.4 ppm (q); IR (neat): $\tilde{\nu} = 2977$, 2935, 2874, 1697, 1388, 1365, 1253, 1175, 1148, 1093, 1051, 874, 769 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 255 (3), 240 (20), 200 (2), 185 (11), 184 (100), 140 (21), 100 (25), 81 (20), 72 (11), 57 (73); HRMS (CI^+, CH_4): *m*/*z*: calcd for $C_{14}H_{26}O_3N$: 256.1913; found: 256.1911 $[M+H]^+$.

Sodium periodate (2.53 g, 11.82 mmol, 4.0 equiv) and $RuCl_3$ (31 mg, 0.148 mmol, 0.05 equiv) were successively added to a solution of *tert*-butyl (5*R*)-5-[(1*R*)-1-methylprop-2-en-1-yl]-2,2-dimethyloxazolidine-3-carboxylate (755 mg, 2.96 mmol, 1.0 equiv) in a $CCl_4/CH_3CN/H_2O$ (7:7:10, 24 mL) mixture. After 12 h of vigorous stirring at RT, CH_2Cl_2 (20 mL) and water (20 mL) were added. The resulting green heterogeneous mixture was filtered over Celite to get rid of ruthenium salts, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/CH_3COOH 100:1) furnished carboxylic acid (*S*,*R*)-**11** (635 mg, 78 %) as a brown solid. The physical and spectroscopic properties matched those reported in the literature.[13a] $R_f \approx 0.3$ (PE/EtOAc 50:50); m.p. 102 °C; $[\alpha]_D^{20} = -17.9$ ($c = 2.1$, $CHCl_3$) {lit.[13a] $[\alpha]_D^{20} = -15.2$ ($c = 2.07$, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): $\delta = 4.30$ (m, 1H), 3.65 (br m, 1H), 3.20 (m, 1H), 2.70 (m, 1H), 1.65 (s, 3H), 1.60 (m, 3H), 1.50 (s, 9H), 1.20 ppm (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers): $\delta = 179.0$ (s), 152.4 and 151.9 (s), 93.9 and 93.5 (s), 80.6 and 79.8 (s), 74.3 (d), 48.4 and 48.1 (t), 43.1 and 42.8 (d), 28.2 (3q), 27.1, 26.0, 25.2 and 24.3 (2t), 12.8 and 12.6 ppm (q); IR (neat): $\tilde{\nu} = 2977$, 2938, 2889, 1736, 1699, 1645, 1461, 1417, 1367, 1247, 1214, 1165, 1146, 1122, 1054, 872, 764, 635 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 258 (14) $[M-Me^+]$, 202 (62), 200 (10), 158 (60), 98 (11), 70 (12), 57 (100) ; HRMS (CI^+, CH_4): *m*/*z*: calcd for $C_{13}H_{24}O_3N$: 274.1654; found: 274.1649 $[M+H]^+$.

(*E*)-3-Iodo-2-methylacrylaldehyde (20): MnO_2 (33 g, 384 mmol, 20 equiv) was added in one portion at RT to a stirred solution of (*E*)-3-iodo-2-methylprop-2-en-1-ol **19**[43] (3.80 g, 19.2 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL). The resulting dark mixture was stirred vigorously for 48 h, then Celite was added and the heterogeneous mixture was filtered through a plug of Celite to remove the manganese salts. CH_2Cl_2 was removed under reduced pressure, thus affording the crude α,β-unsaturated aldehyde **20** (3.31 g, 87 %) as a brown oil which was used in the next step without further purification.

(+)-*tert*-Butyl (*E*)-(*R*)-3-hydroxy-5-iodo-4-methylpent-4-enoate (23): Solid diacetone-D-glucose (6.1 g, 23.34 mmol, 2.0 equiv) was added in one portion at RT to a solution of $[CpTiCl_3]$ (2.56 g, 11.67 mmol, 1.0 equiv) in anhydrous Et_2O (80 mL). After stirring for 5 min, freshly distilled Et_3N (4.64 mL, 33.4 mmol, 2.85 equiv) dissolved in anhydrous Et_2O (40 mL) was added via cannula to the previous solution. The resulting thick slurry was stirred at RT for 15 h, and the triethylamine salts were removed by filtration under an argon atmosphere. The yellow 0.095 M stock solution in Et_2O of chloro(cyclopentadienyl)-bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) titanate thus obtained was kept for the next reaction under an argon atmosphere in the fridge at 0 °C.

A solution of *t*BuOAc (403 μL, 2.99 mmol, 1.5 equiv) in Et_2O (5 mL) was added dropwise to a solution of freshly prepared LDA (2.99 mL, 1 M in THF/*n*-hexanes, 2.99 mmol, 1.5 equiv) in anhydrous Et_2O (40 mL) at −78 °C. After stirring for 30 min, a solution of the titanium reagent described above (42 mL, 0.095 M in Et_2O, 3.98 mmol, 2 equiv) was subsequently added via cannula dropwise over 20 min, and stirring was carried on for further 30 min. The temperature was then slowly raised to −30 °C,

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and after stirring at this temperature for 45 min the solution was finally re-cooled to −78 °C. The previously obtained crude (*E*)-3-iodo-2-methylacrylaldehyde (**20**) (390 mg, 1.99 mmol, 1.0 equiv) was azeotroped three times with toluene, then dissolved in anhydrous Et_2O (15 mL) and subsequently added dropwise within 10 min to the previous solution. After stirring at −78 °C for 1 h, the reaction was quenched by addition of a THF/H_2O solution (1:1, 60 mL) and the mixture was stirred for 1 h. The resulting white slurry was filtered through a short pad of Celite in order to remove the solid titanium salts, and the filtrate was washed with brine (80 mL). The aqueous layers were extracted with Et_2O (3×80 mL) and the combined organic phases where dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The resulting crude residue was purified by flash chromatography on silica gel (PE/EtOAc 95:5) to yield compound **23** (441 mg, 71 %) as a colorless oil. $R_f \approx 0.25$ (PE/EtOAc 95:5); $[\alpha]_D^{20} = +15.5$ (c = 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.39$ (quint$_{app}$, 1H, $J = 1.1$ Hz), 4.52 (m, 1H), 3.24 (br d, 1H, $J = 3.7$ Hz, OH), 2.54–2.43 (m, 2H), 1.83 (d, 3H, $J = 1.1$ Hz), 1.46 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$ (s), 147.7 (s), 81.8 (d), 79.1 (s), 72.5 (d), 40.8 (t), 28.1 (3q), 20.5 ppm (q); IR (neat): $\tilde{\nu} = 3401$, 2977, 2917, 1704, 1367, 1248, 1149, 1038, 1018, 954, 840 cm^{-1}.

(*E*)-1-Iodonon-1-ene (25): A solution of DIBAL-H (313 mg, 2.2 mmol, 1.1 equiv) in anhydrous THF (1 mL) was slowly added to a stirred solution of $[Cp_2ZrCl_2]$ (643 mg, 2.2 mmol, 1.1 equiv) in anhydrous THF (5 mL) at 0 °C under argon. After stirring the resulting white suspension for 30 min at 0 °C, a solution of non-1-yne **24** (248 mg, 2.0 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to RT and stirred until a homogeneous solution (ca. 45 min) was obtained, and was then cooled to −78 °C. A solution of I_2 (660 mg, 2.6 mmol, 1.3 equiv) in THF (3 mL) was added dropwise to the previous solution, and after 30 min at −78 °C, the reaction mixture was hydrolyzed with 1 M HCl (5 mL). The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic phases were successively washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), a saturated aqueous solution of $Na_2S_2O_3$ (20 mL), and brine (20 mL) followed by drying over $MgSO_4$, filtration and concentration in vacuo. Purification of the residue by flash chromatography on silica gel (100 % hexanes) provided the desired **25** (449 mg, 89 %) as a colorless oil. $R_f \approx 0.9$ (PE); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.51$ (dt, 1H, $J = 14.3$, 7.2 Hz), 5.97 (dt, 1H, $J = 14.3$, 1.4 Hz), 2.05 (m, 2H), 1.38 (m, 2H), 1.32–1.22 (m, 8H), 0.88 ppm (br t, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.8$ (d), 74.3 (s), 36.1 (t), 31.8 (t), 29.2 (t), 29.0 (t), 28.4 (t), 22.7 (t), 14.1 ppm (t); IR (neat): $\tilde{\nu} = 2954$, 2921, 2852, 1679, 1605, 1458, 1377, 1210, 1196, 944, 722, 659 cm^{-1}; MS (EI, 70 eV): m/z (%): 253 (7), 252 (68), 167 (9), 166 (36), 154 (30), 83 (60), 70 (16), 69 (100), 67 (10), 57 (19), 56 (19), 55 (60), 54 (10), 53 (10).

Tributyl[(*E*)-non-1-enyl]stannane (26): *t*BuLi (2.56 mL, 1.7 M in pentane, 4.36 mmol, 2.2 equiv) was added dropwise to a stirred solution of **25** (500 mg, 1.98 mmol, 1.0 equiv) in anhydrous Et_2O (5 mL) at −78 °C. After stirring at this temperature for 45 min, Bu_3SnCl (537 μL, 1.98 mmol, 1.0 equiv) was slowly added dropwise and the solution was allowed to warm to RT. After stirring for further 45 min, the reaction mixture was hydrolyzed with an aqueous saturated solution of NH_4Cl (15 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3×15 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by flash chromatography on silica gel (hexanes/Et_3N 99:1) provided the desired alkenyl stannane **26** (779 mg, 95 %) as a colorless oil, contaminated by unidentified stannylated impurities. $R_f \approx 0.95$ (PE); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 5.95 (dt, 1H, $J = 18.9$, 5.9 Hz), 5.86 (d, 1H, $J = 18.9$ Hz), 2.13 (q$_{app}$, 2H, $J = 7.1$ Hz), 1.54–1.45 (m, 4H), 1.36–1.26 (m, 12H), 0.92–0.86 ppm (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.9$ (d), 126.9 (d), 37.9 (t), 31.9 (t), 30.8 (2t), 29.3 (t), 29.1 (3t), 27.3 (3t), 22.7 (t), 14.1 (q), 13.7 (3q), 9.4 ppm (3t); IR (neat): $\tilde{\nu} = 2954$, 2920, 2844, 1599, 1463, 1376, 1071, 987, 960, 873, 863, 685, 659 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{21}H_{45}Sn$: 415.2536; found: 415.2734 $[M+H]^+$.

(4*E*,6*E*)-(*R*)-3-Hydroxy-4-methyltetradeca-4,6-dienoic acid [(*R*)-29]

(+)-*tert*-Butyl (4*E*,6*E*)-(*R*)-3-hydroxy-4-methyltetradeca-4,6-dienoate: $[PdCl_2(MeCN)_2]$ (13 mg, 0.049 mmol, 0.05 equiv) was added to a stirred solution of vinyl iodide (*R*)-**23** (305 mg, 0.98 μmol, 1.0 equiv) and vinyl stannane **26** (811 mg, 1.95 mmol, 2.0 equiv) in anhydrous and degassed DMF (10 mL) at RT. After 12 h of stirring at RT, the resulting dark reaction mixture was diluted with Et_2O (20 mL) and poured into a saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 95:5 → 90:10) provided the title (*E*,*E*)-diene (161 mg, 53 %) as a yellow oil. $R_f \approx 0.5$ (PE/EtOAc 90:10); $[\alpha]_D^{20} = +1.2$ (c = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.21$ (br dd, 1H, $J = 15.0$, 10.8 Hz), 6.05 (d, 1H, $J = 10.8$ Hz), 5.69 (dt, 1H, $J = 14.9$, 7.0 Hz), 4.41 (br dd, 1H, $J =$ 7.8, 4.6 Hz), 2.95 (br s, 1H, OH), 2.52–2.41 (m, 2H), 2.09 (q$_{app}$, 2H, $J =$ 7.2 Hz), 1.73 (s, 3H), 1.45 (s, 9H), 1.37 (m, 2H), 1.32–1.24 (m, 8H), 0.87 ppm (t, 3H, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.0$ (s), 135.8 (d), 135.0 (s), 125.8 (d), 125.7 (d), 81.3 (s), 73.3 (d), 41.1 (t), 33.0 (t), 31.8 (t), 29.4 (t), 29.2 (2t), 28.1 (3t), 22.7 (t), 14.1 (q), 12.5 ppm (q); IR (neat): $\tilde{\nu} = 3420$, 2923, 2855, 1719, 1457, 1368, 1250, 1150, 1063, 841, 737 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{34}O_3Na$: 333.2400; found: 333.2405 $[M+Na]^+$.

Solid NaOH (57 mg, 1.72 mmol, 5 equiv) was added in one portion to a stirred solution of *tert*-butyl (4*E*,6*E*)-(*R*)-3-hydroxy-4-methyltetradeca-4,6-dienoate (89 mg, 0.287 mmol, 1.0 equiv) in MeOH/H_2O (2:1, 6 mL) at RT. The resulting mixture was heated to 70 °C, and stirring was carried on for 2 h. The mixture was allowed to cool to RT, and then concentrated under reduced pressure to remove MeOH. EtOAc (15 mL) was added and the resulting solution was acidified with a saturated aqueous solution of NaH_2PO_4 (pH 4.5, 10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to provide the corresponding crude carboxylic acid (*R*)-**29** (72 mg, 99 %) as a viscous yellow oil which was used in the next step without further purification.

(+)-Methyl (2*E*,4*E*,6*E*)-9-[(2*S*,3*R*)-4-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylbutanamido]nona-2,4,6-trienoate [(*S*,*R*)-30]

(−)-(5*R*)-*tert*-Butyl 5-[(1*S*)-1-((3*E*,5*E*,7*E*)-8-methoxycarbonylocta-3,5,7-trienylcarbamoyl)ethyl]-2,2-dimethyloxazolidine-3-carboxylate: 1-Hydroxybenzotriazole (358 mg, 2.65 mmol, 1.2 equiv), *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (1.0 g, 2.65 mmol, 1.2 equiv) and *N*-methylmorpholine (728 μL, 6.62 mmol, 3.0 equiv) were successively added to a solution of carboxylic acid (*S*,*R*)-**11** (603 mg, 2.21 mmol, 1.0 equiv) and trienic amine **7** (480 mg, 2.65 mmol, 1.2 equiv) in anhydrous CH_3CN (50 mL) at 0 °C. The solution was allowed to warm to RT and after stirring for 6 h, the resulting brown mixture was hydrolyzed by addition of water (25 mL). The bulk of CH_3CN was removed under reduced pressure and the resulting aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), a saturated aqueous solution of NH_4Cl (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue thus obtained was purified by flash chromatography on silica gel (PE/EtOAc 50:50) which provided the desired title compound (922 mg, 96 %) as a waxy solid. $R_f \approx 0.2$ (PE/EtOAc 50:50); $[\alpha]_D^{20} = -4.5$ (c = 1.36, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (dd, 1H, $J = 15.2$, 11.2 Hz), 6.51 (dd, 1H, $J = 14.8$, 10.8 Hz), 6.30–6.15 (m, 2H + NH), 5.87 (m, 1H), 5.87 (d, 1H, $J = 15.2$ Hz), 4.09 (m, 1H), 3.75 (s, 3H), 3.64 (br s, 1H), 3.37 (m, 2H), 3.11 (t$_{app}$, 1H, $J = 9.9$ Hz), 2.37 (m, 3H, $J = 5.7$ Hz), 1.56 (br s, 3H), 1.51 (br s, 3H), 1.47 (s, 9H), 1.14 ppm (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.2$ (s), 167.5 (s), 152.2 and 151.8 (s), 144.6 (d), 140.4 (d), 136.1 (d), 131.9 (d), 128.8 (d), 120.4 (d), 94.0 and 93.5 (s), 80.4 and 79.8 (s), 75.0 (d), 51.5 (q), 49.6 and 49.5 (t), 44.2 and 44.0 (d), 38.5 (t), 33.1 (t), 28.3 (3q), 27.3, 26.2, 25.2 and 24.4 (2q), 13.4 ppm (q); IR (neat): $\tilde{\nu} = 3424$, 3338, 2978, 2938, 1693, 1658, 1616, 1542, 1392, 1367, 1253, 1140, 1007, 839 cm^{-1}; HRMS (CI$^+$, NH_3): m/z: calcd for $C_{23}H_{37}O_6N_2$: 437.2652; found: 437.2643 $[M+H]^+$.

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p-Toluenesulfonic acid (132 mg, 0.695 mmol, 0.5 equiv) was added in one portion to a stirred solution of the previously obtained *N*,*O*-dimethyloxazolidine (609 mg, 1.39 mmol, 1.0 equiv) in MeOH (10 mL). After stirring for 4 h at RT, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and the resulting aqueous layer was extracted with Et_2O (3×15 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), a saturated aqueous solution of NH_4Cl (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 98:2) which provided the desired *N*-Boc protected amino alcohol (*S*,*R*)-**30** (451 mg, 82%) as a yellow foam. R_f ≈0.25 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D^{20}$ = +11.3 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29 (dd, 1H, *J*=15.2, 11.2 Hz), 6.52 (dd, 1H, *J*=14.9, 10.8 Hz), 6.40 (br m, 1H, NH), 6.25 (dd, 1H, *J*=15.1, 11.2 Hz), 6.21 (dd, 1H, *J*=15.3, 10.8 Hz), 5.87 (d, 1H, *J*=15.2 Hz), 5.86 (m, 1H), 5.0 (br m, 1H, NH), 4.16 (m, 1H), 3.75 (s, 3H), 3.64 (br m, 1H, OH), 3.42–3.28 (m, 3H), 3.08 (m, 1H), 2.42–2.28 (m, 3H), 1.44 (s, 9H), 1.25 ppm (d, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.6 (s), 167.5 (s), 156.8 (s), 144.7 (d), 140.5 (d), 135.9 (d), 133.0 (d), 128.7 (d), 120.2 (d), 79.6 (s), 73.5 (d), 51.5 (q), 45.0 (t), 43.2 (d), 38.5 (t), 33.0 (t), 28.3 (3q), 15.5 ppm (q); IR (neat): $\tilde{\nu}$=3307, 2978, 2932, 1714, 1662, 1639, 1620, 1534, 1247, 1233, 1171, 1137, 1002, 729 cm^{-1}; HRMS (CI$^+$, NH_3): *m*/*z*: calcd for $C_{20}H_{33}O_6N_2$: 397.2339; found: 397.2343 $[M+H]^+$.

(+)-Methyl (2*E*,4*E*,6*E*)-9-{(2*S*,3*R*)-4-[(4*E*,6*E*)-(*R*)-3-hydroxy-4-methyltetradeca-4,6-dienoylamino]2-methylbutyrylamino}nona-2,4,6-trienoate (46): Trifluoracetic acid (1 mL) was added dropwise to a stirred solution of carbamate (*S*,*R*)-**30** (133 mg, 0.335 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (4 mL) at 0°C. The resulting brown mixture was allowed to warm to RT, and after 45 min of stirring the solution was concentrated in vacuo. The ammomium trifluoroacetate thus obtained was used in the next step without further purification.

1-Hydroxybenzotriazole (50 mg, 0.368 mmol, 1.1 equiv), *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (140 mg, 0.368 mmol, 1.1 equiv) and *N*-methylmorpholine (110 μL, 1.01 mmol, 3.0 equiv) were successively added to a solution of the ammonium trifluoroacetate previously obtained (0.335 mmol, 1.0 equiv) and carboxylic acid (*R*)-**29** (85 mg, 0.335 mmol, 1.0 equiv) in anhydrous CH_3CN (15 mL) at 0°C. The mixture was allowed to reach RT, and after 6 h of stirring, the resulting brown mixture was hydrolyzed by adding water (5 mL). CH_3CN was evaporated under reduced pressure and EtOAc (15 mL) was added. After decantation, the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), a saturated aqueous solution of NH_4Cl (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue thus obtained was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) which provided the desired diamide **46** (138 mg, 78% over 2 steps) as a yellow foam. R_f ≈0.15 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{20}$ = 11.2 (*c* = 1.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26 (dd, 1H, *J*=15.2, 11.3 Hz), 6.93 (br m, 1H, NH), 6.65 (br t, 1H, *J*=5.7 Hz, NH), 6.49 (dd, 1H, *J*=14.8, 10.7 Hz), 6.21 (dd, 1H, *J*=14.8, 11.3 Hz), 6.21–6.12 (m, 2H), 6.04 (d, 1H, *J*=11.1 Hz), 5.85 (d, 1H, *J*=15.2 Hz), 5.84 (m, 1H), 5.68 (dt, 1H, *J*=14.9, 7.0 Hz), 4.67 (m, 1H, OH), 4.41 (br d, 1H, *J*=7.0 Hz), 3.95 (br s, 1H, OH), 3.72 (s, 3H), 3.71 (m, 1H), 3.59 (ddd, 1H, *J*=11.3, 7.2, 4.1 Hz), 3.30 (m, 2H), 3.01 (ddd, 1H, *J*=12.6, 7.6, 4.7 Hz), 2.48–2.26 (m, 5H), 2.07 (q_{app}, 2H, *J*=7.1 Hz), 1.71 (s, 3H), 1.34 (m, 2H), 1.31–1.21 (m, 8H), 1.19 (d, 3H, *J*=7.0 Hz), 0.86 ppm (t, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.7 (s), 172.9 (s), 167.6 (s), 144.7 (d), 140.4 (d), 136.0 (d), 135.8 (d), 135.4 (s), 132.0 (d), 128.9 (d), 125.6 (d), 125.5 (d), 120.4 (d), 73.7 (d), 72.9 (d), 51.5 (q), 44.1 (t), 43.7 (d), 41.7 (t), 38.6 (t), 33.0 (2t), 31.9 (t), 29.4 (t), 29.2 (2t), 22.7 (t), 15.5 (q), 14.1 (q), 12.6 ppm (t); IR (neat): $\tilde{\nu}$=3305, 2923, 2854, 1717, 1641, 1618, 1546, 1434, 1262, 1234, 1137, 1006, 966 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{30}H_{48}O_6N_2Na$: 555.3405; found: 555.3409 $[M+Na]^+$.

(+)-(2*E*,4*E*,6*E*)-9-{(2*S*,3*R*)-4-[(4*E*,6*E*)-(*R*)-3-Hydroxy-4-methyltetradeca-4,6-dienoylamino]-2-methylbutyrylamino}nona-2,4,6-trienoic acid (47): Solid LiOH (46 mg, 1.92 mmol, 20 equiv) was added in one portion to a stirred solution of trienic ester **46** (51.1 mg, 0.096 mmol, 1.0 equiv) in THF/MeOH/H_2O (2:2:1, 12.5 mL) at 0°C and the resulting yellow mixture was then allowed to reach RT. After stirring for 12 h, the mixture was concentrated under reduced pressure to remove THF and MeOH, diluted with EtOAc (15 mL) and acidified with a saturated aqueous solution of NaH_2PO_4 (pH 4.5, 10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to provide the corresponding crude carboxylic acid **47** (49.1 mg, 99%) as a white solid with a satisfying level of purity. R_f ≈0.15 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{20}$ + 8.8 (*c* 1.38, MeOH) {lit.[3] $[\alpha]_D^{20}$ = +7.7 (*c* = 1.2, MeOH)}; ^{1}H NMR (400 MHz, CD_3OD): δ=7.94 (br t, 1H, *J*=5.8 Hz, NH), 7.89 (br t, 1H, *J*=5.8 Hz, NH), 7.29 (dd, 1H, *J*=15.2, 11.2 Hz), 6.60 (dd, 1H, *J*=14.9, 10.6 Hz), 6.32 (dd, 1H, *J*=14.9, 11.2 Hz), 6.31–6.22 (m, 2H), 6.04 (d, 1H, *J*=10.8 Hz), 5.95 (dt, 1H, *J*=15.1, 7.2 Hz), 5.84 (d, 1H, *J*=15.2 Hz), 5.68 (dt, 1H, *J*=14.9, 7.0 Hz), 4.43 (dd, 1H, *J*=8.5, 4.8 Hz), 3.71 (m, 1H), 3.42 (dd, 1H, *J*=13.8, 4.0 Hz), 3.32–3.25 (m, 2H), 3.15 (dd, 1H, *J*=13.8, 7.0 Hz), 2.49–2.33 (m, 5H), 2.11 (q_{app}, 2H, *J*=7.0 Hz), 1.75 (s, 3H), 1.39 (m, 2H), 1.34–1.25 (m, 8H), 1.12 (d, 3H, *J*=7.0 Hz), 0.90 ppm (t, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ=177.5 (s), 174.3 (s), 170.6 (s), 146.6 (d), 142.2 (d), 137.7 (d), 137.3 (s), 136.2 (d), 133.1 (d), 129.8 (d), 127.3 (d), 126.8 (d), 121.6 (d), 75.1 (d), 73.3 (d), 45.4 (d), 44.5 (t), 43.2 (t), 39.7 (t), 34.0 (t), 33.9 (t), 33.6 (t), 30.6 (t), 30.3 (2t), 23.7 (t), 15.2 (q), 14.5 (q), 12.4 ppm (t); IR (neat): $\tilde{\nu}$=3306, 2922, 2853, 1685, 1617, 1551, 1458, 1435, 1364, 1238, 1141, 1006, 965, 886, 675 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{46}O_6N_2Na$: 541.3248; found: 541.3257 $[M+Na]^+$.

(−)-(13*E*,15*E*,17*E*)-(2*R*,7*R*,8*S*)-7-Hydroxy-8-methyl-2-[(1*E*,3*E*)-1-methylundeca-1,3-dienyl]-1-oxa-5,10-diazacyclononadeca-13,15,17-triene-4,9,19-trione [FR252921 (2b)]: A solution of *seco*-acid **47** (42 mg, 0.081 mmol, 1.0 equiv) in THF (10 mL) was added via syringe pump over 20 h to a solution of 2-methyl-6-nitrobenzoic anhydride (84 mg, 0.243 mmol, 3.0 equiv) and 4-DMAP (33 mg, 0.292 mmol, 3.6 equiv) in THF (130 mL). After 96 h of stirring at RT, the reaction mixture was hydrolyzed by adding water (25 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×20 mL). The combine organic layers were washed with brine (50 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH 20:1 to 95:5) furnished 14.8 mg of a yellow oil containing multiple products according to ^{1}H NMR analysis. The residue was re-purified by preparative TLC (SiO_2, $CHCl_3$/MeOH 92:8) which yielded 1.9 mg of FR252921 (**2b**) contaminated by an unidentified impurity. Further purification by analytic HPLC using a Kromasil 100 C18 5μm (Bios Analytique, Higgins Analytical) column, (CH_3CN/H_2O 50:50 → 80:20) allowed to obtain FR252921 (**2b**) as a white solid (≈1 mg) in pure form. R_f ≈0.55 ($CHCl_3$/MeOH 10:1); $[\alpha]_D^{20}$ has been measured but is not reliable on such a small quantity (m_{sample} < 1 mg). Its sign was (−). {lit.[2] $[\alpha]_D^{20}$ = −222 (*c*=0.2, DMSO)}; ^{1}H NMR (500 MHz, DMSO): δ=7.93 (br t, 1H, *J*=4.6 Hz, NH), 7.72 (br t, 1H, *J*=6.0 Hz, NH), 7.31 (dd, 1H, *J*=15.3, 11.3 Hz), 6.95 (dd, 1H, *J*=14.6, 11.7 Hz), 6.41 (dd, 1H, *J*=14.7, 11.3 Hz), 6.27–6.20 (m, 2H), 5.97 (br d, 1H, *J*=10.8 Hz), 5.80 (m, 1H), 5.79 (d, 1H, *J*=15.3 Hz), 5.69 (dt, 1H, *J*=15.0, 7.1 Hz), 5.23 (dd, 1H, *J*=11.1, 3.1 Hz), 5.00 (br s, 1H, OH), 3.60 (m, 1H), 3.50–3.28 (m, 1H), 3.28–3.23 (m, 1H), 3.11–3.04 (m, 1H), 2.82 (ddd, 1H, *J*=13.2, 8.5, 4.3 Hz), 2.69 (dd, 1H, *J*=13.9, 11.3 Hz), 2.49–2.41 (m, 1H), 2.38 (dd, 1H, *J*=14.0, 3.4 Hz), 2.35–2.24 (m, 2H), 2.08 (br q_{app}, 2H, *J*=7.0 Hz), 1.71 (s, 3H), 1.36 (m, 2H), 1.33–1.20 (m, 8H), 0.94 (d, 3H, *J*=7.2 Hz), 0.87 ppm (t, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, DMSO): δ=173.6 (s), 169.0 (s), 164.9 (s), 144.9 (d), 136.7 (d), 135.2 (d), 135.1 (d), 133.1 (s), 130.0 (d), 129.8 (d), 125.7 (d), 125.1 (d), 120.4 (d), 75.6 (d), 71.5 (d), 44.5 (d), 42.6 (t), 39.9 (t), 38.4 (t), 32.3 (t), 31.2 (t), 28.8 (t), 28.6 (t), 28.5 (2t), 22.1 (t), 13.9 (q), 12.8 (q), 12.3 ppm (q); HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{45}N_2O_5$: 501.3328; found: 501.3317 $[M+H]^+$.

(*E*)-4-Tributylstannylpent-3-en-1-ol (49): *n*BuLi (2.5 M in THF, 30.5 mL, 76.1 mmol, 8.0 equiv) was added dropwise to a suspension of CuCN (3.41 g, 38.1 mmol, 4.0 equiv) in THF (100 mL) at −78°C. The solution was warmed to −65°C and was stirred 10 min at this temperature to give

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a homogeneous, colorless solution. The reaction mixture was cooled down to −78 °C and tri-*n*-butyltin hydride (20.5 mL, 76.1 mmol, 8.0 equiv) was added dropwise (the solution becomes yellow). After 10 min at −78 °C, methanol (56.5 mL, 150 equiv) was added. The solution was warmed to −40 °C (the mixture becomes red) and pent-3-yn-1-ol (**48**) (877 μL, 9.51 mmol, 1.0 equiv) was added dropwise. After 15 h of stirring at −40 °C, the reaction mixture was hydrolyzed by adding a saturated aqueous solution of NH_4Cl containing 10% of aqueous ammoniac (200 mL). The cold bath was removed and a vigorous stirring was maintained for 30 min. The mixture was then filtered over Celite, and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentane/EtOAc 100:0 → 85:15) furnished vinyl stannane **49** (2.37 g, 67%) and its regioisomer **50** (264 mg, 7%) both as a colorless oil. The physical and spectra data for **49** were in accordance with those reported in the literature.[44] $R_f \approx 0.6$ (PE/EtOAc 85:15); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.51$ (br tq, 1H, $J = 7.0$, 1.8 Hz), 3.65 (q, 2H, $J = 6.4$ Hz), 2.42 (br q, 2H, $J = 6.5$ Hz), 2.31 (br d, 3H, $J = 1.2$ Hz), 1.52–1.43 (m, 6H + OH), 1.30 (sext$_{app}$, 6H, $J = 7.3$ Hz), 0.88 ppm (t, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.4$ (s), 135.7 (d), 62.2 (t), 31.7 (t), 29.2 (3t), 27.4 (3t), 19.3 (q), 13.7 (3q), 7.5 ppm (3t); IR (neat): $\tilde{\nu} = 3317$, 2955, 2922, 2871, 2852, 1611, 1462, 1376, 1043, 1020, 874, 863, 686, 660 cm^{-1}.

(*E*)-4-Iodopent-3-en-1-ol (51): I_2 (1.73 g, 6.79 mmol, 1.5 equiv) was added in one portion to a solution of vinyl stannane **49** (1.7 g, 4.53 mmol, 1.0 equiv) in Et_2O (100 mL) at 0 °C. After 30 min at 0 °C and 2 h at RT, the reaction mixture was hydrolyzed by adding a 1 M aqueous solution of KF (10 mL) and acetone (10 mL). The mixture was vigorously stirred for 2 h at RT, then filtered over Celite. The aqueous phase was extracted with AcOEt (3×50 mL) and the combined organic layers were successively washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL), brine (50 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentane/Et_2O 100:0 → 50:50) furnished the vinyl iodide **51** (899 mg, 94%) as a yellow oil. The physical and spectral properties of compound **51** were in accordance with those described in the literature.[45] $R_f \approx 0.25$ (PE/EtOAc 85:15); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.19$ (tq, 1H, $J = 7.5$, 1.5 Hz), 3.65 (t, 2H, $J = 6.4$ Hz), 2.41 (br q, 3H, $J = 1.3$ Hz), 2.31 (q$_{app}$, 2H, $J = 6.6$ Hz), 1.90 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.1$ (d), 96.2 (s), 61.4 (t), 34.0 (t), 27.8 (q); HRMS (CI$^+$, CH_4): *m*/*z*: calcd for C_5H_9OI: 211.9698; found: 211.9695 $[M+H]^+$.

(*E*)-4-Iodopent-3-enoic acid (52): *Preparation of Jones reagent $CrO_3{\cdot}H_2SO_4$*: Sulfuric acid (500 μL, 11 mmol, 2 equiv) was added dropwise to CrO_3 (570 mg, 5.5 mmol, 1 equiv) at 0 °C. At the end of the addition, water (2 mL) was added and the mixture was allowed to warm to RT.

A solution of freshly prepared Jones reagent (650 μL, 3.0 equiv) was added dropwise to a solution of alcohol **51** (100 mg, 0.472 mmol, 1.0 equiv) in acetone at 0 °C. After 30 min of stirring at this temperature, methanol (1.5 mL) was slowly added at 0 °C. The reaction mixture was filtered over Celite to remove the chromium salts and the filtrate was concentrated under reduced pressure. Water (10 mL) and EtOAc (10 mL) were added, and the aqueous phase was extracted with AcOEt (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 90:10) furnished carboxylic acid **52** (98 mg, 92%) as a yellow oil which recrystallized upon standing in the fridge at −20 °C. $R_f \approx 0.15$ (PE/EtOAc 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.26$ (br s, 1H, COOH), 6.31 (tq, 1H, $J = 7.2$ Hz and $J = 1.5$ Hz), 3.10 (dq, 2H, $J = 7.5$, 0.9 Hz), 2.40 ppm (br d, 3H, $J = 1.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.6$ (s), 131.1 (d), 97.5 (s), 35.3 (t), 27.8 ppm (q); IR (neat): $\tilde{\nu} =$ 2916, 2847, 1705, 1639, 1617, 1422, 1377, 1293, 1217, 1169, 1085, 1057, 821 cm^{-1}; HRMS (CI$^+$, CH_4): *m*/*z*: calcd for $C_5H_7O_2I$: 225.9491; found: 225.9491 $[M]^+$.

Dec-1-yn-3-ol (54): A solution of octanal **53** (3.9 mL, 25 mmol, 2.0 equiv) in THF (10 mL) was added dropwise to a solution of ethynylmagnesium bromide (0.5 M in THF, 3.9 mL, 25 mmol, 1.0 equiv) in THF (50 mL) at 0 °C. After 12 h of stirring at RT, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (30 mL) cooled down to 0 °C. The aqueous phase was extracted with ether (3×30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 95:5 → 90:10) furnished propargylic alcohol **54** (3.11 g, 81%) as a colorless oil. $R_f \approx 0.5$ (PE/EtOAc 85:15); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.37$ (td, 1H, $J = 6.7$, 2.1 Hz), 2.46 (d, 1H, $J = 2.1$ Hz), 1.88 (br s, 1H, OH), 1.71 (m, 2H), 1.45 (m, 2H), 1.36–1.22 (m, 8H), 0.88 ppm (br t, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 85.0$ (s), 72.8 (s), 62.3 (d), 37.7 (t), 31.8, 29.2 and 25.0 (4t), 22.7 (t), 14.1 ppm (q); IR (neat): $\tilde{\nu} = 3311$, 2922, 2855, 1464, 1378, 1118, 1045, 1021, 651, 625 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 125 (1), 121 (5), 107 (16), 97 (16), 95 (8), 94 (9), 93 (25), 91 (8), 84 (9), 83 (33), 81 (17), 80 (15), 79 (46), 77 (10), 70 (57), 69 (19), 68 (14), 67 (16), 57 (100), 56 (26), 55 (80), 53 (10).

1-Bromodec-1-yn-3-ol (55): *N*-Bromosuccinimide (1.28 g, 7.21 mmol, 1.1 equiv) and silver nitrate (111 mg, 0.656 mmol, 0.1 equiv) were successively added to a solution of alkyne **54** (1.01 g, 6.56 mmol, 1.0 equiv) in acetone (20 mL) at RT. After 12 h of stirring in the dark, the reaction mixture was filtrated over Celite. The Celite was successively washed with water and acetone (3×30 mL) and the bulk of acetone was evaporated under reduced pressure. Ethyl acetate (50 mL) was then added and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (PE/EtOAc 95:5 → 90:10) furnished the bromoalkyne **55** (1.43 g, 93%) as a colorless oil. $R_f \approx 0.6$ (PE/EOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.37$ (br t, 1H, $J = 6.3$ Hz), 2.17 (br s, 1H, OH), 1.69 (m, 2H), 1.42 (m, 2H), 1.35–1.20 (m, 8H), 0.88 ppm (br t, 3H, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 81.2$ (s), 63.5 (d), 45.0 (s), 37.6 (t), 31.8 (t), 29.2 (2t), 25.0 (t), 22.6 (t), 14.1 ppm (q); IR (neat): $\tilde{\nu} = 3303$, 2921, 2854, 1707, 1458, 1377, 1046, 1019, 909, 725 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 233 (1) $[M]^+$, 177 (2), 175 (2), 163 (3), 161 (4), 150 (12), 148 (14), 136 (8), 135 (100), 133 (99), 107 (10), 105 (8), 97 (32), 95 (11), 93 (15), 91 (8), 83 (19), 82 (14), 81 (12), 79 (18), 69 (21), 67 (16), 57 (45), 55 (35).

(*E*)-1-Tributylstannyldec-1-en-3-ol (56): $[PdCl_2(PPh_3)_2]$ (139 mg, 0.198 mmol, 0.05 equiv) and tri-*n*-butyltin hydride (4.25 mL, 15.81 mmol, 4.0 equiv) in THF (20 mL) were successively added to a solution of bromoacetylene **55** (921 mg, 3.95 mmol, 1.0 equiv) in THF (100 mL) at 0 °C. After 4 h of stirring at this temperature, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentane/EtOAc 100:0 → 96:45) provided the vinyl stannane **56** (1.23 g, 70%) as a colorless oil. $R_f \approx 0.5$ (PE/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.12$ (dd, 1H, $J = 19.1$, 0.8 Hz), 5.99 (dd, 1H, $J = 19.2$, 5.5 Hz), 4.06 (m, 1H), 1.57–1.45 (m, 8H), 1.36–1.23 (m, 14H + OH), 0.92–0.85 (m, 11H), 0.89 ppm (t, 9H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.1$ (d), 127.6 (d), 75.7 (d), 37.0 (t), 31.8 (t), 29.6 (t), 29.3 (t), 29.1 (3t), 27.3 (3q), 25.4 (t), 22.7 (t), 14.1 (q), 13.7 (3q), 9.5 ppm (3t); IR (neat): $\tilde{\nu} = 3321$, 2955, 2921, 1601, 1463, 1377, 1071, 1045, 989, 908, 735 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{46}ONaSn$: 469.2467; found: 469.2461 $[M+Na]^+$.

(+)-Methyl (2*E*,4*E*,6*E*)-9-[(2*S*,3*R*)-3-hydroxy-4-((*E*)-4-iodopent-3-enamido)-2-methylbutanamido]nona-2,4,6-trienoate (57): Trifluoracetic acid (2 mL) was added dropwise to a stirred solution of carbamate (*S*,*R*)-**30** (123 mg, 0.310 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (8 mL) at 0 °C. The resulting brown mixture was allowed to warm to RT, and after 45 min of stirring, the solution was concentrated in vacuo. The ammonium trifluoroacetate thus obtained was diluted with $CHCl_3$ (10 mL), treated by a saturated aqueous solution of Na_2CO_3 (10 mL) and the aqueous layer was vigorously extracted with $CHCl_3$ (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the corresponding free amine (91 mg, 100%) as a viscous brown oil, which was used in the next step without further purification.

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1-Hydroxybenzotriazole (46 mg, 0.338 mmol, 1.1 equiv), *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (128 mg, 0.338 mmol, 1.1 equiv) and *N*-methylmorpholine (101 μL, 0.921 mmol, 3.0 equiv) were successively added to a solution of the previously obtained amine (91 mg, 0.307 mmol, 1.0 equiv) and carboxylic acid **52** (70 mg, 0.307 mmol, 1.0 equiv) in CH_3CN (15 mL) at 0 °C. After 6 h of stirring at RT, the resulting brown mixture was hydrolyzed by adding water (5 mL). The bulk of CH_3CN was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), a saturated aqueous solution of NH_4Cl (15 mL), brine (15 mL) then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH 98:2) furnished diamide **57** (121 mg, 79%) as a colorless oil. $R_f \approx 0.2$ (CH_2Cl_2/MeOH 98:2); $[\alpha]_D^{20} = +6.93$ (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (dd, 1H, $J = 15.3$, 11.3 Hz), 6.78 (br m, 1H, NH), 6.57 (br m, 1H, NH), 6.52 (dd, 1H, $J = 14.9$, 10.8 Hz), 6.31 (br t, 1H, $J = 7.5$ Hz), 6.25 (dd, 1H, $J = 14.9$, 11.3 Hz), 6.20 (dd, 1H, $J = 15.4$, 10.8 Hz), 5.87 (d, 1H, $J = 15.3$ Hz), 5.87 (m, 1H), 4.61 (m, 1H), 3.74 (s, 3H), 3.66 (br m, 1H, OH), 3.51 (ddd, 1H, $J = 11.5$, 6.6, 4.2 Hz), 3.34 (m, 2H), 3.12 (ddd, 1H, $J = 12.5$, 7.5, 4.9 Hz), 2.97 (d, 2H, $J = 7.5$ Hz), 2.40 (s, 3H), 2.40–2.31 (m, 3H), 1.24 ppm (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.8$ (s), 170.2 (s), 167.5 (s), 144.7 (d), 140.4 (d), 135.7 (d), 132.8 (d), 132.1 (d), 128.9 (d), 120.3 (d), 97.8 (s), 73.2 (d), 51.6 (q), 44.4 (t), 43.2 (d), 38.5 (t), 37.7 (t), 33.0 (t), 27.9 (q), 15.7 ppm (q); IR (neat): $\tilde{\nu} = 3293$, 2930, 1711, 1639, 1616, 1541, 1433, 1263, 1233, 1136, 1004, 732, 618 cm^{-1}; HRMS (CI$^+$, NH_3): *m*/*z*: calcd for $C_{20}H_{30}O_5N_2I$: 505.1199; found: 505.1195 $[M+H]^+$.

(+)-Methyl (2*E*,4*E*,6*E*)-9-{(2*S*,3*R*)-3-hydroxy-4-[(3*E*,5*E*)-7-hydroxy-4-methyltetradeca-3,5-dienamido]-2-methylbutanamido}nona-2,4,6-trienoate (58): $[PdCl_2(MeCN)_2]$ (5 mg, 0.02 mmol, 0.05 equiv) was added to a solution of vinyl iodide **57** (205 mg, 0.406 mmol, 1.0 equiv) and vinyl stannane **56** (270 mg, 0.609 mmol, 1.2 equiv) in DMF (10 mL) degassed with argon. After 12 h of stirring at RT and in the dark, the reaction mixture was diluted with Et_2O (50 mL) and then poured into a saturated aqueous solution of NH_4Cl (30 m). The aqueous phase was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was first filtered over a plug of silica gel (3 cm) on top of which was added solid KF beforehand to remove stannylated impurities, and then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 98:2) to give **58** (111 mg, 51%) as a viscous yellow oil which recrystallized upon standing in the fridge at −78 °C. $R_f \approx 0.1$ (CH_2Cl_2/MeOH 98:2); $[\alpha]_D^{20} = +7.37$ (*c* = 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (dd, 1H, $J = 15.2$, 11.2 Hz), 6.45 (dd, 1H, $J = 14.7$, 10.7 Hz), 6.29 (m, 1H, NH), 6.20 (d, 1H, $J = 15.7$ Hz), 6.20–6.04 (m, 2H + NH), 5.81 (m, 1H), 5.80 (d, 1H, $J = 15.2$ Hz), 5.62 (dd, 1H, $J = 15.6$, 6.8 Hz), 5.53 (br t, 1H, $J = 7.6$ Hz), 4.33 (d, 1H, $J = 5.9$ Hz, OH), 4.09 (m, 1H), 3.68 (s, 3H), 3.55 (br m, 1H), 3.45 (m, 1H), 3.29 (m, 2H), 3.03 (m, 3H), 2.31 (q_{app}, 2H, $J = 6.8$ Hz), 2.22 (m, 1H), 1.70 (s, 3H), 1.55–1.40 (m, 2H), 1.30–1.15 (m, 10H + OH), 1.18 (d, 3H, $J = 7.6$ Hz), 0.81 ppm (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.6$ (s), 172.0 (s), 167.6 (s), 144.7 (d), 140.4 (d), 137.6 (s), 135.7 (d), 133.9 (d), 132.2 (d), 132.0 (d), 128.9 (d), 123.2 (d), 120.4 (d), 73.5 (d), 72.9 (d), 51.6 (q), 44.4 (t), 43.2 (d), 38.5 (t), 37.5 (t), 36.2 (t), 33.0 (t), 31.8 (t), 29.6 (t), 29.3 (t), 25.5 (t), 22.7 (t), 15.7 (q), 14.1 (q), 12.8 ppm (q); IR (neat): $\tilde{\nu} = 3308$, 2956, 2927, 2856, 1720, 1646, 1619, 1546, 1459, 1435, 1271, 1137, 1074, 1007, 739 cm^{-1}; HRMS (CI$^+$, NH_3): *m*/*z*: calcd for $C_{30}H_{49}O_6N_2$: 533.3591; found: 533.3597 $[M+H]^+$.

(+)-(2*E*,4*E*,6*E*)-9-{(2*S*,3*R*)-3-Hydroxy-4-[(3*E*,5*E*)-7-hydroxy-4-methyltetradeca-3,5-dienamido]-2-methylbutanamido}nona-2,4,6-trienoic acid [pseudotrienic acid B (1b)]: LiOH (6 mg, 0.263 mmol, 20 equiv) was added in one portion to a solution of methyl ester **58** (7 mg, 0.013 mmol, 1.0 equiv) in THF/MeOH/H_2O (2:2:1, 2 mL) at 0 °C. After 12 h of stirring at RT, the reaction mixture was concentrated under reduced pressure to remove THF and MeOH. The resulting solution was diluted with EtOAc (3 mL) and acidified by adding a saturated aqueous solution of NaH_2PO_4 (pH 4.5, 3 mL). The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by preparative TLC (SiO_2, CH_2Cl_2/MeOH 90:10) provided pseudotrienic acid B (**1b**) (5 mg, 75%) as a colorless oil. The physical and spectral properties of **1b** were in agreement with those reported in the literature.[1] $R_f \approx 0.1$ (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{20} = +4.8$ (*c* = 0.17, MeOH) {lit.[1] $[\alpha]_D^{20} +1.9$ (*c* = 0.4, $CHCl_3$)}; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.28$ (dd, 1H, $J = 15.8$, 11.6 Hz), 6.60 (dd, 1H, $J = 14.8$, 10.5 Hz), 6.32 (dd, 1H, $J = 14.4$, 11.6 Hz), 6.27 (dd, 1H, $J = 15.3$, 8.8 Hz), 6.26 (d, 1H, $J = 15.3$ Hz), 5.95 (br dt, 1H, $J = 14.8$, 7.4 Hz), 5.86 (d, 1H, $J = 14.4$ Hz), 5.65 (dd, 1H, $J = 15.3$, 6.5 Hz), 5.63 (br t, 1H, $J = 7.9$ Hz), 4.08 (q_{app}, 1H, $J = 7.0$ Hz), 3.71 (br dt, 1H, $J = 7.4$, 4.6 Hz), 3.41 (dd, 1H, $J = 14.4$, 3.3 Hz), 3.29 (m, 2H), 3.16 (br dd, 1H, $J = 14.4$, 6.0 Hz), 3.13 (d, 2H, $J = 7.4$ Hz), 2.43–2.30 (m, 3H, $J = 7.0$ Hz), 1.80 (m, 3H), 1.60–1.45 (m, 2H), 1.39–1.25 (m, 10H), 1.14 (d, 3H, $J = 7.4$ Hz), 0.91 ppm (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 177.2$ (s), 174.1 (s), 170.5 (s), 146.0 (d), 141.7 (d), 137.3 (s), 137.2 (d), 135.0 (d), 132.8 (d), 132.1 (d), 129.5 (d), 124.8 (d), 121.6 (d), 73.4 (d), 73.0 (d), 45.4 (d), 44.3 (t), 39.3 (t), 38.3 (t), 36.2 (t), 33.6 (t), 32.7 (t), 30.5 (t), 30.4 (t), 26.3 (t), 23.4 (t), 14.8 (q), 14.1 (q), 12.6 ppm (q); IR (neat): $\tilde{\nu} = 3296$, 2926, 2856, 1741, 1640, 1548, 1390, 1350, 1233, 1139, 1112, 1006, 702 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{46}O_6N_2Na$: 541.3248; found: 541.3241 $[M+Na]^+$.

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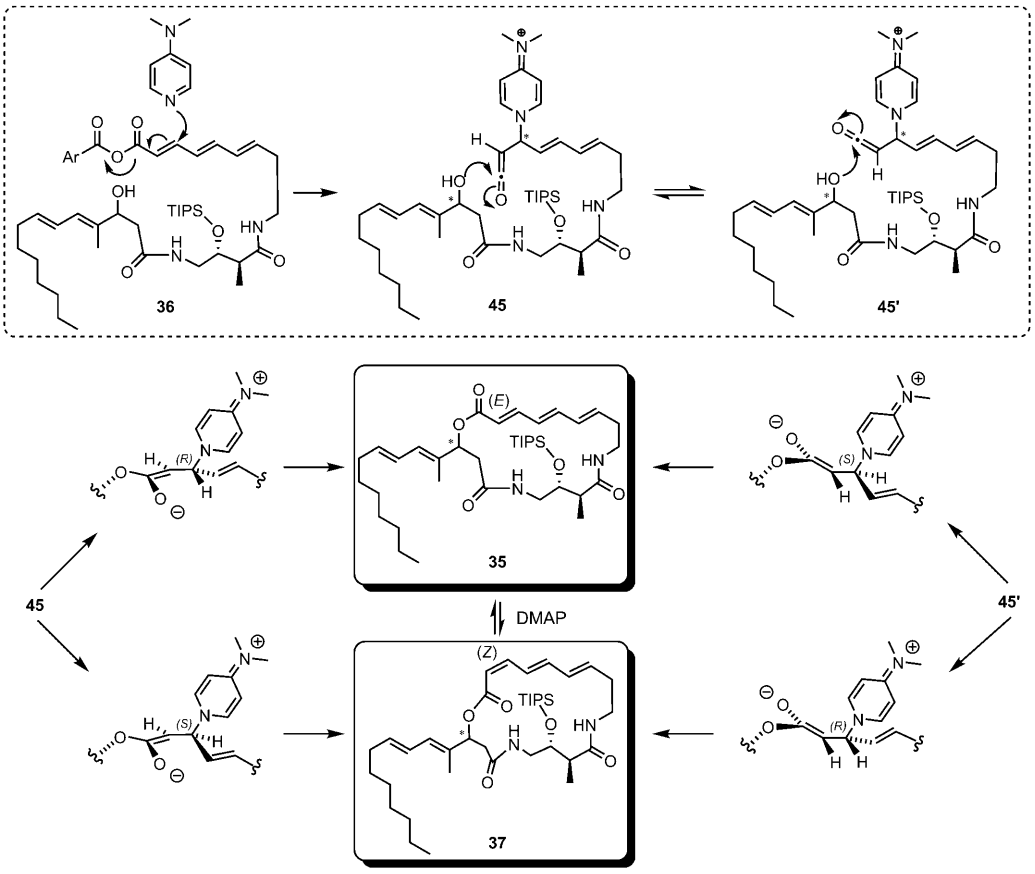

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lates, which after elimination of 4-DMAP would give rise to the formation of either the desired (2*E*,4*E*,6*E*) trienic lactone **35** or lactone **37** possessing the (2*Z*,4*E*,6*E*)-configuration. Similarly, conformer **45′** could also provide access to both isomeric lactones **35** and **37**. The transition state energy of this elimination would determine the double bond stereochemistry in a kinetically controlled process. Alternatively, 4-DMAP could catalyze the interconversion of the (*E*) and (*Z*)-isomers **35** and **37** via the same enolate intermediates, in which case a thermodynamic argument would prevail.

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