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The Formal Total Synthesis of FR252921 – An Immunosuppressant

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The formal total synthesis of FR252921 is described. The key steps include the preparation of three fragments starting from 1,4-butanediol, (*R*)-malic acid, and prenol, respectively, followed by two consecutive peptide couplings of the three fragments. Other key steps involve an allene-type rearrangement or enyne isomerization to install the triene moiety, a Seebach methylation, a Julia olefination to construct the trisubstituted diene unit, and an enzymatic resolution strategy to generate the C-18 stereocenter.

Introduction

Immunosuppressive natural products such as cyclosporin A, FK506, rapamycin, deoxyspergualin, and didemnin B have proven to be useful tools for the dissection of cell signaling pathways,[1] and have also led to a significant increase in the success of organ and bone marrow transplants.[2] In 2003, three new immunosuppressive agents FR252921 (**1a**), FR252922 (**1b**), and FR256523 (**1c**), which have an unusual 19-membered lactone-dilactam structure, were isolated from the culture broth of *Pseudomonas fluorescens* no. 408813 by Fujine et al. (see Figure 1).[3]

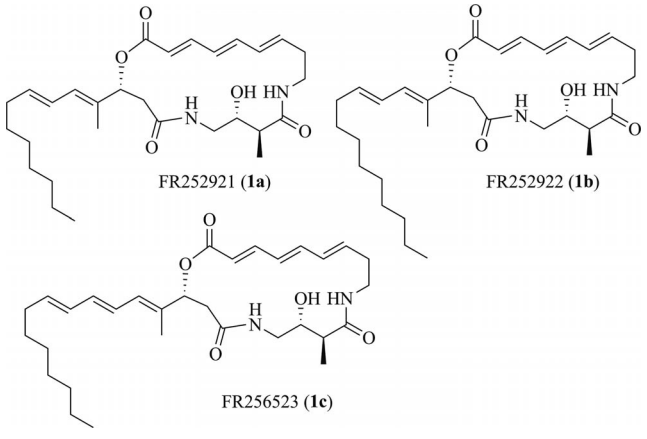

Figure 1. Structure of macrolactones FR252921 (**1a**), FR252922 (**1b**), FR256523 (**1c**).

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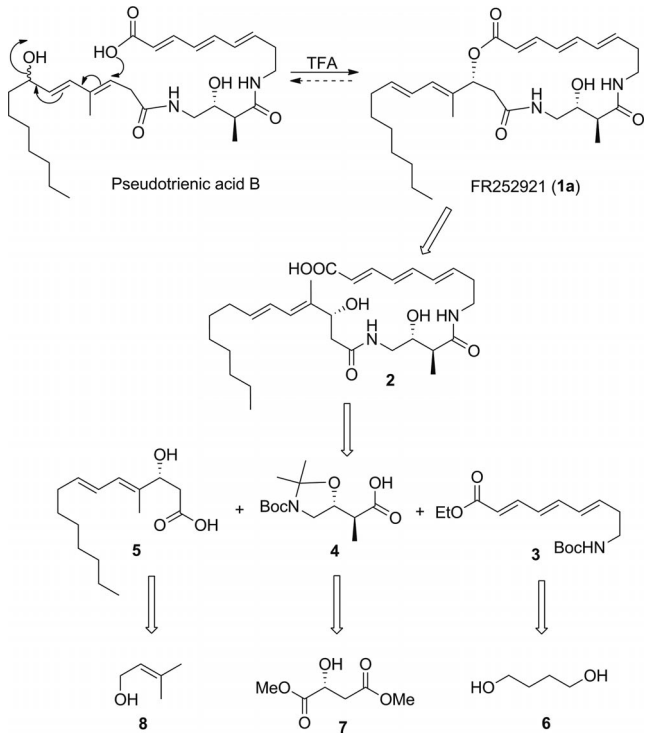
Unlike other immunosuppressants, FR252921 inhibits both lipopolysaccharide (LPS)-stimulated and *anti*-CD3 mAb-stimulated splenocyte proliferations in vitro without blocking T-cell activation.[3b] Further studies show that FR252921 decreases transcription activity regulated by an activating protein 1 (AP-1) and acts dominantly against an antigen presenting cell (APC) rather than a T-cell. To examine the possibility of FR252921 to act as a concomitant drug of FK506, a T-cell specific inhibitor was evaluated and, thus, shows a synergy with FK506 in immunosuppressive activity, both in splenic proliferation and in murine skin transplantation.[3c]

Although the overall gross structure of FR252921 was established by Fujina et al. through NMR studies, its absolute configuration was unknown for some time. In 2005, it was very exciting that the antimicrobial substance pseudotrenic acid B was isolated from the same strains by Pohanka et al., which upon treatment with TFA (trifluoroacetic acid) provided macrolactone FR252921.[4] Through this biomimetic transformation, the configurations at C-12 and C-13 were assumed as (*S*) and (*R*), respectively, but still the configuration of C-18 was unknown. In 2007, Falck et al. assigned the absolute configuration of FR252921 as (12*S*,13*R*,18*R*) through the total syntheses of all of its diastereomers.[5] The molecular architecture of macrolactone FR252921 includes the presence of an (*E*,*E*,*E*) trienic conjugated double bond, two amide bonds, and a trisubstituted conjugated (*E*,*E*) diene moiety.

Our continuing interest in the total syntheses of various biologically active natural products and the unique biological profile and challenging structural features of FR252921 prompted us to explore the synthesis of this molecule.[5,6] In planning our approach, we developed a convergent, straightforward route to provide a platform from which entry to analogues of biological interest could ultimately be realized. A detailed account of our successful endeavors towards the formal synthesis of FR252921 is presented in this paper.

Results and Discussion

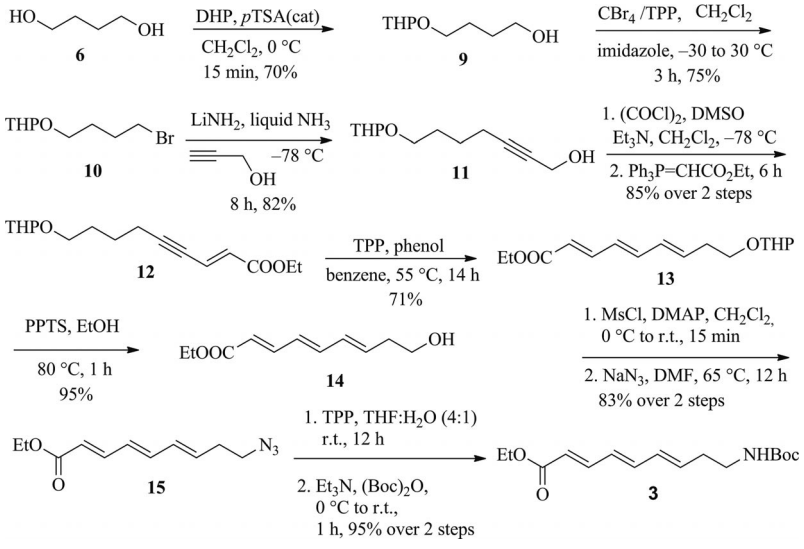
Recognizing the importance of developing a convergent synthesis for **1a**, we describe a retrosynthetic plan based on the macrocyclization of the *seco* acid **2**, as depicted in Scheme 1. Furthermore, the formation of *seco* acid **2** was envisaged to occur through two consecutive peptide couplings of the three key fragments **3**, **4**, and **5**.



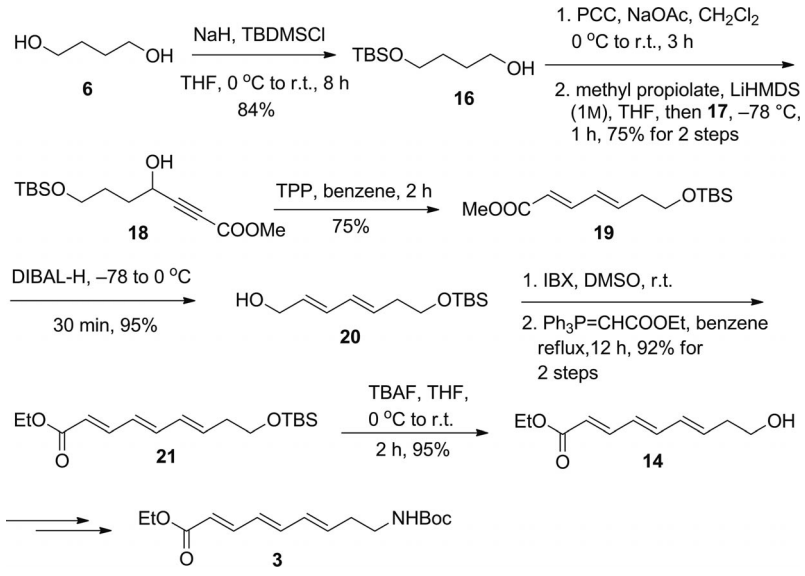
Scheme 1. Biomimetic transformation of FR252921 from pseudotrienic acid B and the retrosynthetic analysis of FR252921.

Our synthesis began with the construction of aminotrienic ester fragment **3** from the commercially available starting material 1,4-butanediol (**6**), which was initially protected as mono-THP (tetrahydropyran-2-yl) ether **9** by the aid of a catalytic amount of *p*TSA (*para*-toluenesulfonic acid). Bromination of the other free hydroxy group by treatment with CBr_4/TPP (triphenylphosphine) in anhydrous CH_2Cl_2 gave bromide **10** in 52% yield over the two steps. Compound **10** was coupled with propargyl alcohol using $LiNH_2$ in liquid NH_3 to yield acetylenic alcohol **11** in 82% yield, which then underwent consecutive Swern oxidation and C-2 Wittig reactions to furnish the desired enyne ester **12** in 85% yield over the two steps. Isomerization[7] of **12** using TPP and phenol as effective cocatalysts installed the (*E*,*E*,*E*) configuration of trienic ester **13** with >95% selectivity (by ^1H and ^{13}C NMR) in 71% yield. Deprotection of the THP ether was achieved by treatment with PPTS (pyridinium *p*-toluenesulfonate) in ethanol under refluxing conditions to obtain primary alcohol **14** in 95% yield. The resulting free hydroxy group of **14** was converted into azide derivative **15**, through a mesyl protection step, in 83% yield over two steps. The Staudinger reaction[8] was employed to convert azide **15** into its amine derivative, which was then protected to give the trienic Boc (*tert*-butoxycarbonyl)-protected amino ester fragment **3** in 95% yield over two steps (see Scheme 2).

Although the synthesis of fragment **3** was efficiently achieved in 8 steps with an overall 19.5% yield, we have demonstrated an alternate route to deliver fragment **3** from the same starting material. Accordingly, **6** was monoprotected as TBS (*tert*-butyldimethylsilyl) ether **16** in 84% yield, which was then subsequently oxidized to the corresponding aldehyde **17** by PCC (pyridinium chlorochromate) oxidation. The addition of lithiated methyl propiolate to aldehyde **17** provided propargylic alcohol[9] **18** in 75% yield over the two steps. The TPP-mediated allene-type rearrangement of **18** yielded (*E*,*E*)-diene **19** in 75% yield.[10] Diene ester **19** then underwent DIBAL-H (diisobutylaluminum hydride) reduction to obtain alcohol **20** in 95% yield. Consecutive Swern oxidation and C-2 Wittig reactions were incorporated successfully to obtain trienic ester **21** in 92%



Scheme 2. Synthesis of fragment **3**.

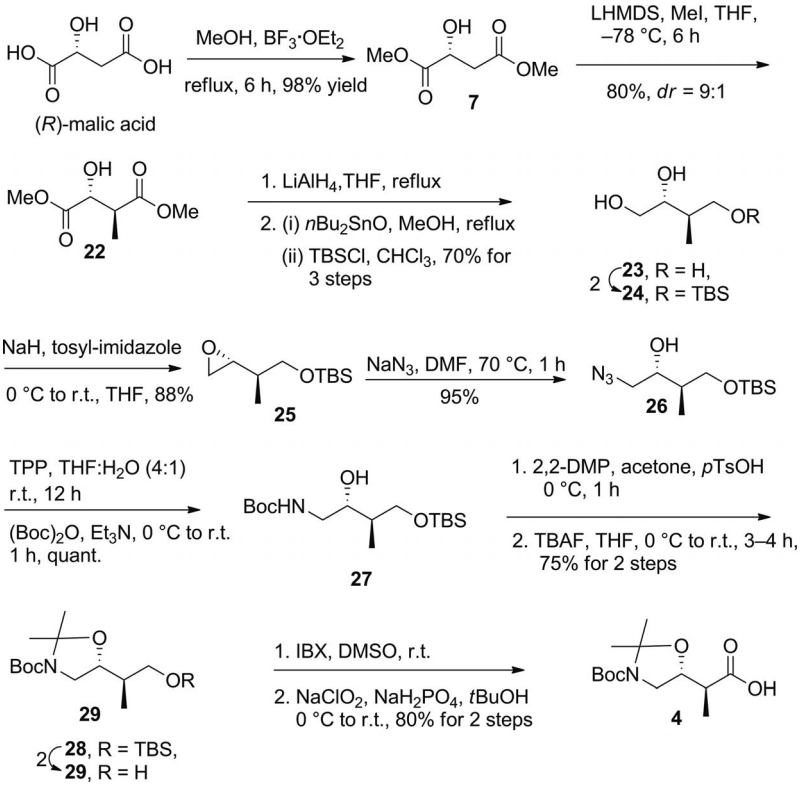


Scheme 3. Alternate route for the synthesis of fragment **3**.

yield over the two steps with excellent (*E*,*E*,*E*) selectivity (by ^{1}H and ^{13}C spectroscopy). Silyl deprotection of **21** was done by treatment with TBAF (tetra-*n*-butylammonium fluoride) at 0 °C to obtain **14** in 95% yield, which was then converted into target fragment **3** by using the same sequence of reactions as described earlier. The alternate process gave us a comparatively better yield of 31% in the same number of steps (see Scheme 3).

Next, we turned our attention towards the synthesis of carboxylic acid fragment **4**, starting from (*R*)-dimethyl malate (**7**), which was easily accessible from (*R*)-malic acid. We prepared the (2*S*,3*R*) stereoisomer by using the Seebach alkylation as the key step. (*R*)-malic acid was subjected to esterification by treatment with $BF_3{\cdot}Et_2O$ in MeOH to give dimethyl malonate in 98% yield. Accordingly, employing the procedure reported by Seebach,[11] dimethyl (*R*)-malate (**7**) was alkylated with MeI and LDA (lithium diisopropylamide) in THF (tetrahydrofuran) to give alcohol **22** along with its *syn* diastereomer (*anti*/*syn*, 8:2). We observed that using LHMDS (lithium hexamethyldisilazide) in place of LDA as the base led to a slightly improved diastereoselectivity (*anti*/*syn*, 9:1, combine yield 80%). The reduction of **22** using $LiAlH_4$ provided triol **23** in excellent yield,[12] and triol **23** was selectively protected, through a dibutyltin ketal intermediate, to give TBS ether **24** in 70% yield over the three steps.[13] In the presence of tosyl imidazole and NaH at 0 °C, the resulting diol **24** was then converted into epoxide **25** in 88% yield. The regioselective epoxide ring opening of **25** was achieved with NaN_3/DMF (*N*,*N*-dimethylformamide) at 70 °C to afford azido alcohol **26** in 95% yield. Azido alcohol **26** underwent a Staudinger reaction[8] by treatment with TPP and then was subsequently protected as its carbamate by using $(Boc)_2O$ to yield **27** in quantitative yield. It is noteworthy that the separation of the minor diastereomer was completely achieved in this step. Subsequent protection of the resulting amino alcohol as *N*,*O*-acetonide **28** was achieved, by using 2,2-DMP (2,2-dimethoxypropane) and *p*TsOH in acetone at 0 °C followed by the silyl deprotection with TBAF, to provide primary alcohol **29** (75% yield over two steps), which was then converted into carboxylic acid fragment **4** in 80% yield over two steps. IBX (2-iodoxybenzoic acid) oxidation of **29** followed by conversion of the resulting aldehyde to an acid under Pinnick conditions[14] ($NaClO_2/NaH_2PO_4$, *t*BuOH/H_2O) yielded acid fragment **4** in 8 steps and 28% overall yield (see Scheme 4).

The β-hydroxy dienic acid fragment **5**, possessing the (*R*) configuration, was synthesized by an enzymatic resolution strategy. The synthesis was initiated from commercially available prenol (**8**) as the starting material, which upon protection of the hydroxy group as its TBDPS (*tert*-butyldiphenylsilyl) ether gave protected prenol **30** in 98% yield. Allylic oxidation[15] of **30** was achieved regioselectively by using SeO_2 and *t*BuOOH in CH_2Cl_2 to obtain a mixture of the *trans* allylic alcohol and the aldehyde (3:2). Subsequent oxidation of the mixture by PCC yielded allylic aldehyde **31** as the sole product in 45% yield over the two steps. Aldehyde **31** was then converted into β-hydroxy ester **32** in 95% yield by a Reformatsky reaction,[16] which used $BrCH_2CO_2Et$ and Zn(Cu) couple in THF. Ester **32** was then protected as silyl ether **33** by treatment with TBSCl in CH_2Cl_2. Selective deprotection of the primary TBDPS ether in presence of the secondary TBS ether moiety was achieved by using NH_4F in MeOH at room temperature to give primary allylic alcohol **34** in 95% yield over the two steps. Primary allylic alcohol **34** was oxidized to its corresponding aldehyde by treatment with IBX in DMSO (dimethyl sulfoxide), and the resulting aldehyde was then used directly in the Julia olefination[17] with sulfone **35**.[18] This delivered trisubstituted dienic ester **36** in 65% yield over the two steps with a selectivity of (*E*,*E*)/(*Z*,*E*), 94:6 (by wt.-%, separated by column chromatography). Among the bases (NaHMDS, KHMDS, LiHMDS) used for this Julia olefination, KHMDS was found to be the best with regard to the yield. Silyl deprotection of **36** was done by employing



Scheme 4. Synthesis of carboxylic acid fragment **4**.

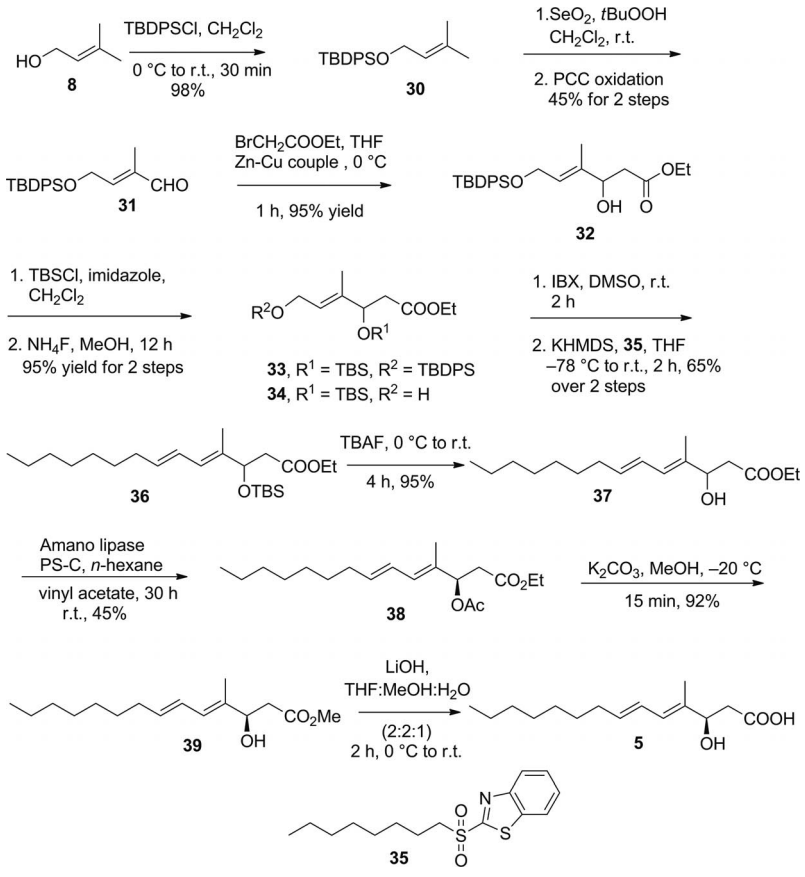
TBAF in THF at 0 °C to obtain β-hydroxy ester **37** in 95% yield. Our next step involved the resolution of β-hydroxy ester **37** through a chemical as well as enzymatic process. Although the Sharpless resolution[19] was found to be effective for resolving the alcohol, a satisfactory yield was obtained from a lipase resolution process.[20] Among the several lipases screened for this resolution, Amano lipase PS-C with the solvent hexane was found to be most effective (see Table 1). Studying 0.6 equiv. (w/w) of lipase PS-C and 6 equiv. of vinyl acetate at different temperatures showed that beyond 30 °C there was not much difference in the isolated yield of the product. Racemic β-hydroxy ester **37** was exposed to an enzymatic acylation reaction using Amano lipase PS-C in hexane in presence of vinyl acetate as the acylating agent at 25 °C for 30 h to provide enantioenriched acetate (*R*)-**38** in 45% yield and 92% *ee*.[21] After careful[22] hydrolysis of **38** by treatment with K_2CO_3 in CH_3OH, β-hydroxy ester (*R*)-**39** was formed in 92% yield. Hydrolysis of (*R*)-**39** with LiOH in THF/MeOH/H_2O (2:2:1) gave us the third and final fragment **5** in 12% overall yield (see Scheme 5).

Table 1. Lipase-mediated resolution of compound **37**.

Entry	Lipases[a]	Time [h]	% Yield[b]	% *ee*[c]
1	PS	72	22	76
2	PS-C	30	45	92
3	PPL	96	2	–
4	CRL	24	62	28
5	AK-Amano	72	19	62
6	PS-D	72	–	–
7	wheat germ	96	–	–

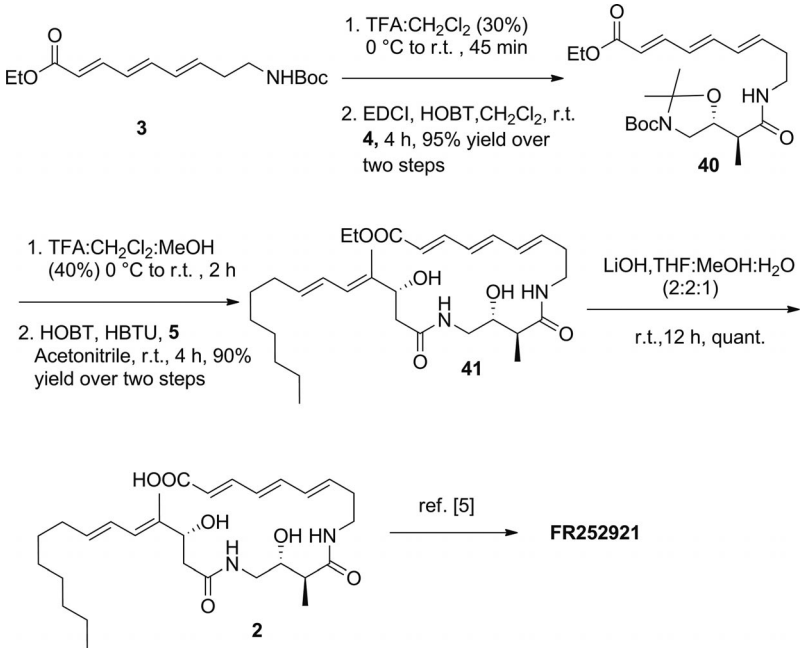
[a] *Pseudomonas cepacia* (PS) was obtained from the Amano Pharmaceutical Company, Japan; *P. cepacia* lipase was immobilized on modified ceramic particles (PS-C); *P. cepacia* lipase was immobilized on diatomite (PS-D); *Candida rugosa* lipase (CRL) and *Pseudomonas fluorescence* (AK) lipase were from the Amano Pharmaceutical Company; porcine pancreas lipase, type II (PPL) was from Sigma. [b] Isolated yield. [c] Determined by HPLC (chiral AD-H column, Daicel) employing hexane/isopropyl alcohol (85:15) as mobile phase at a flow rate of 1 mL/min and monitored by UV (254 nm).

At this stage, to assemble the core structure of **1a**, we started to connect the fragments with each other (see Scheme 6). For this purpose, the Boc group present in fragment **3** was cleaved by treatment with TFA in CH_2Cl_2 (30%), and the resulting free amine was united with carboxylic acid fragment **4** by using a suspension of *N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBT) in CH_2Cl_2 to produce peptide **40** in 95% yield over the two steps. Successful cleavage of both the *N*,*O*-acetonide and *tert*-butyloxycarbonyl protecting group was achieved with 40% TFA in CH_2Cl_2 and MeOH at room temperature, and the resulting free amino alcohol was condensed with β-hydroxy acid fragment **5** under classic peptide coupling conditions {HOBT, HBTU [*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate], NMM (*N*-methylmorpholine), CH_3CN}, to afford bis(amide) **41** in 90% yield over the two steps.



Scheme 5. Synthesis of fragment **5**.

Saponification of the bis(amide) **41** with LiOH in THF/MeOH/H_2O (2:2:1) yielded the corresponding *seco* acid **2** quantitatively. This constitutes the formal synthesis of FR252921. The spectral and analytical data of **2** were in full agreement with those previously reported by Falck et al.[5]



Scheme 6. Formal synthesis of FR252921.

Conclusions

In summary, we have disclosed a concise, efficient, and convergent formal total synthesis of FR252921 by synthesizing and coupling three key fragments prepared from commercially available starting materials. The key features include an allene-type rearrangement or enyne isomerization to install the trienic moiety, a Seebach methylation, a Julia olefination to construct the trisubstituted dienic unit, and an enzymatic resolution strategy to generate the C-18 stereocenter. The formal synthesis consists of 12 steps in its longest linear sequence with a 10% overall yield.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectroscopic data were recorded at ambient temperature in $CDCl_3$ or CD_3OD with a 200, 300, or 500 MHz spectrometer. The coupling constant J is given in Hz. The chemical shifts are reported in ppm on scale downfield from TMS, which was used as the internal standard. The signal patterns are s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet), and br. (broad). FTIR spectra were recorded using KBr pellets and $CHCl_3$/neat (as mentioned) and are reported in wavenumbers (cm^{-1}). Optical rotations were measured with a digital polarimeter using a 1 mL cell with a 1 dm path length. For low MS and HRMS, m/z ratios are reported as values in atomic mass units. Mass spectrometric analyses were done in the ESI mode. All of the reagents were reagent grade and used without further purification, unless specified otherwise. The solvents for the reactions were distilled prior to use. THF, toluene, and diethyl ether were distilled from Na and benzophenone ketyl. MeOH was distilled from Mg and I_2, and CH_2Cl_2 was distilled from CaH_2. All air- or moisture-sensitive reactions were conducted under nitrogen or argon in flame-dried or oven-dried glassware, using magnetic stirring. Column chromatography was carried out with silica gel (60–120 mesh or 100–200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use.

4-(Tetrahydro-2*H*-pyran-2-yloxy)butan-1-ol (9): To a stirred solution of 1,4-butanediol (10.0 g, 110.9 mmol) in dry CH_2Cl_2 (300 mL) at 0 °C was added DHP (dihydropyran, 10 mL, 109.8 mmol) dropwise. After the addition was complete, a catalytic amount of *p*TSA was added, and the resulting mixture was stirred for 15 min and then checked by TLC. Then the reaction mixture was quenched with saturated Na_2CO_3 solution (50 mL) at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were washed with brine (20 mL) and dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to give the crude residue, which was purified by column chromatography on silica gel (60–120 mesh, 30% EtOAc/hexane) to afford compound **9** (13.5 g, 70%) as a colorless liquid; R_f = 0.5 (60% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3424, 2951, 2140, 1641, 1453, 1018, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (t, J = 2.9 Hz, 1 H), 3.82–3.62 (m, 2 H), 3.55 (t, J = 5.8 Hz, 2 H), 3.47–3.28 (m, 2 H), 2.66 (br. s, 1 H), 1.82–1.43 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.2, 66.8, 61.6, 30.1, 29.1, 25.7, 24.9, 18.9 ppm. MS (ESI): m/z = 197 $[M + Na]^+$.

7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-2-yn-1-ol (11): To a solution of CBr_4 (18.7 g, 56.4 mmol) in dry CH_2Cl_2 (50 mL) under nitrogen was slowly added dropwise over a period of 30 min a solution of TPP (29.6 g, 112.8 mmol) in dry CH_2Cl_2 (100 mL) at –30 °C. The mixture was stirred for an additional 30 min at –30 °C, and then a solution of alcohol **9** (10.0 g, 56.4 mmol) and imidazole (7.70 g, 112.8 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise successively to the resultant red solution. The reaction mixture was warmed to 30 °C over a period of 3 h. The solvent was concentrated to a small volume, and petroleum ether was added. The resultant precipitate was filtered, and the filtrate was concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford compound **10** (10.2 g, 75%) as a yellow liquid; R_f = 0.85 (30% EtOAc/hexane). In the next step, to liquid ammonia (150 mL) was added small finely cut pieces of lithium metal (1.76 g), and the reaction mixture was stirred for 30 min, followed by the addition of ferric nitrate (catalytic amount). The deep blue solution turned grey, indicating the formation of the lithium amide. Propargyl alcohol (4 mL, 63.0 mmol) was then added dropwise, and the reaction mixture was stirred for 2 h at liquid ammonia temperature. Then, bromo compound **10** (10.0 g, 42 mmol), which was dissolved in anhydrous THF (20 mL), was added dropwise, and the reaction mixture was stirred at liquid ammonia temperature for 8 h. Solid NH_4Cl (5 g) was added portionwise, and the ammonia was allowed to evaporate. Ether (100 mL) was added to the solid residue, and the mixture was filtered. The filtrate was concentrated, and after column chromatography on silica gel (60–120 mesh, 20% EtOAc/hexane), compound **11** (7.33 g, 82%) was obtained as a colorless liquid; R_f = 0.3 (30% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3432, 2939, 2866, 2223, 1732, 1444, 1271, 1129, 1071, 1024, 901, 572 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.56–4.54 (m, 1 H), 4.18 (br. s, 2 H), 3.85–3.69 (m, 2 H), 3.48–3.33 (m, 2 H), 2.26–2.22 (m, 2 H), 2.14 (s, 1 H), 1.86–1.42 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.5, 85.3, 78.7, 66.7, 62.0, 50.7, 30.4, 28.6, 25.2, 25.1, 19.3, 18.3 ppm. MS (ESI): m/z = 235 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ 235.1310; found 235.1311.

Ethyl (*E*)-10-(Tetrahydro-2*H*-pyran-2-yloxy)dec-2-en-5-ynoate (12): To a cold (–78 °C) solution of oxalyl chloride (3.08 mL, 35.3 mmol) in CH_2Cl_2 (50 mL) was added DMSO (3.01 mL, 42.5 mmol). After stirring for 10 min at –78 °C, a solution of propargylic alcohol **11** (5.0 g, 23.6 mmol) was added dropwise to the reaction mixture. The solution was stirred for 15 min at the same temperature, and then Et_3N (19.7 mL, 141.6 mmol) was added dropwise. The reaction mixture was stirred at that same temperature for 45 min and then poured into an aqueous saturated NH_4Cl solution (20 mL). The organic phase was separated and washed with aqueous saturated $NaHCO_3$ solution (20 mL). The organic phase was dried, filtered, and concentrated in vacuo to give the crude aldehyde, which was used in the C-2 Wittig reaction without any further purification. The C-2 Wittig ylide (13.1 g, 37.7 mmol) was added to a solution of the crude aldehyde in CH_2Cl_2 (100 mL), and the reaction was allowed to continue for 6 h at room temperature. After the completion of the reaction, checked by TLC, column chromatography on silica gel (60–120 mesh, 5% EtOAc/hexane) gave ester compound **12** (5.6 g, 85% over two steps) as a colorless liquid; R_f = 0.8 (20% EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 3421, 2942, 2869, 2214, 1716, 1619, 1448, 1300, 1267, 1156, 1033, 956, 867, 812 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (dd, J = 16.1, 2.1 Hz, 1 H), 6.10 (d, J = 16.1 Hz, 1 H), 4.54 (m, 2 H), 4.17 (q, J = 7.3 Hz, 2 H), 3.82–3.70 (m, 2 H), 3.48–3.34 (m, 2 H), 2.42 (t, J = 5.1 Hz, 2 H), 1.85–1.50 (m, 10 H), 1.29 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 129.3, 125.9, 100.3, 98.7, 78.0, 66.7, 62.2, 60.5, 30.6, 28.8, 25.4, 25.1, 24.6, 19.5, 14.1 ppm. MS (ESI): m/z = 303 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1572; found 303.1568.

Ethyl (2*E*,4*E*,6*E*)-9-(Tetrahydro-2*H*-pyran-2-yloxy)nona-2,4,6-trienoate (13): To the solution of ester **12** (5.0 g, 17.8 mmol) in benzene (17.8 mL) were added TPP (4.7 g, 17.8 mmol) and phenol (1.7 g, 17.8 mmol). The resulting mixture was warmed to 55 °C and stirred for 12–14 h, and then the solution was cooled to ambient temperature and then diluted with diethyl ether (50 mL) and NaOH (1 N solution, 10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (5 mL) and brine solution (5 mL), dried, and concentrated under reduced pressure. Purified of the residue by flash chromatography on silica gel (60–120 mesh, 5% EtOAc/hexane) afforded triene ester compound **13** (3.55 g, 71%) as a colorless liquid; R_f = 0.8 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3423, 2941, 2870, 1710, 1617, 1444, 1300, 1262, 1133, 1071, 1032, 977, 869, 755, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23 (dd, J = 15.8, 11.3 Hz, 1 H), 6.50 (dd, J = 14.3, 10.5 Hz, 1 H), 6.28–6.14 (m, 2 H), 5.98–5.89 (m, 1 H), 5.79 (d, J = 15.8 Hz, 1 H), 4.56 (m, 1 H), 4.16 (q, J = 6.7 Hz, 2 H), 3.89–3.70 (m, 2 H), 3.48–3.38 (m, 2 H), 2.41 (q, J = 6.7 Hz, 2 H), 1.85–1.49 (m, 6 H), 1.29 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 144.5, 140.7, 136.2, 131.4, 128.3, 120.3, 98.7, 66.4, 62.2, 60.1, 33.3, 30.6, 25.3, 19.5, 14.2 ppm. MS (ESI): m/z = 303 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1572; found 303.1583.

Ethyl (2*E*,4*E*,6*E*)-9-Hydroxynona-2,4,6-trienoate (14): To a solution of compound **13** (5.0 g, 17.8 mmol) in EtOH (30 mL) was added PPTS (catalytic amount), and the resulting mixture was heated to reflux for 1–2 h. After completion of the reaction (checked by TLC), the mixture was cooled to room temperature, and a saturated $NaHCO_3$ solution (10 mL) was added. The EtOH was removed with a rotary evaporator, and the residue was diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water and then brine solution, dried, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (60–120 mesh, 20% EtOAc/hexane) afforded compound **14** (3.30 g, 95%) as a colorless liquid; R_f = 0.2 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3423, 2936, 1708, 1620, 1370, 1267, 1184, 1141, 1047, 871, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (dd, J = 14.8, 10.8 Hz, 1 H), 6.49 (dd, J = 15.8, 10.8 Hz, 1 H), 6.25–6.18 (m, 2 H), 5.90–5.80 (m, 1 H), 5.80 (d, J = 14.8 Hz, 1 H), 4.17 (q, J = 6.9 Hz, 2 H), 3.68 (t, J = 5.9 Hz, 2 H), 2.39 (q, J = 6.9 Hz, 2 H), 1.45 (br. s, 1 H), 1.29 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 144.4, 140.5, 135.9, 131.5, 128.0, 120.0, 61.1, 59.9, 35.9, 13.9 ppm. MS (ESI): m/z = 219 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{11}H_{16}O_3Na$ $[M + Na]^+$ 219.0997; found 219.0993.

Ethyl (2*E*,4*E*,6*E*)-9-Azidonona-2,4,6-trienoate (15): To a solution of compound **14** (3.0 g, 15.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (4.3 mL, 30.6 mmol), and the resulting mixture was stirred for 10 min. Then, MsCl (1.8 mL, 22.9 mmol) and DMAP [4-(dimethylamino)pyridine, catalytic amount] were added to the reaction mixture, which was then stirred for 30 min. After completion, the reaction was quenched with water (5 mL), and the resulting solution was diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water and brine solution, dried, and concentrated under reduced pressure. Purification of the residue by flash chromatography afforded the crude mesylated compound. To this mesylated compound in dry DMF (10 mL) was added NaN_3 (3.0 g, 46.0 mmol), and the reaction mixture was stirred at 60–70 °C for 12 h. The reaction was checked by TLC, cooled, and then diluted with EtOAc (20 mL). The organic layer was washed with water (5 mL) and brine solution (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (60–120 mesh, 5% EtOAc/hexane) afforded compound **15** (2.80 g, 83% over two steps) as a yellow liquid; R_f = 0.8 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3450, 2982, 2932, 2097, 1707, 1618, 1455, 1301, 1260, 1135, 1005, 767 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23 (dd, J = 15.4, 11.0 Hz, 1 H), 6.49 (dd, J = 14.7, 10.3 Hz, 1 H), 6.30–6.15 (m, 2 H), 5.87 (dt, J = 15.4, 7.3 Hz, 1 H), 5.83 (d, J = 15.4 Hz, 1 H), 4.16 (q, J = 7.3 Hz, 2 H), 3.34 (t, J = 7.3 Hz, 2 H), 2.41 (m, 2 H), 1.30 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 144.1, 139.8, 134.3, 132.2, 129.0, 120.8, 60.0, 50.2, 27.6, 14.1 ppm. MS (ESI): m/z = 244 $[M + Na]^+$, 222 $[M + H]^+$. HRMS (ESI): calcd. for $C_{11}H_{15}N_3O_2Na$ $[M + Na]^+$ 244.1061; found 244.1062.

4-(*tert*-Butyldimethylsilyloxy)butan-1-ol (16): To a stirred suspension of NaH (60% w/v dispersion in mineral oil, 3.91 g, 97.7 mmol) in dry THF (60 mL) was added dropwise a solution of 1,4-butanediol (**6**, 8.0 g, 88.8 mmol) in anhydrous THF (100 mL) at 0 °C. The stirring was continued for 1 h at room temperature. After 1 h, TBSCl (13.4 g, 88.8 mmol) was added slowly at room temperature. The reaction was completed within 8 h. Then, the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude residue, which was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford compound **16** (15.2 g, 84%) as a colorless liquid; R_f = 0.5 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3368, 2932, 2859, 1468, 1388, 1254, 1188, 1101, 1063, 837, 776, 662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.68–3.58 (m, 4 H), 2.88 (br. s, 1 H), 1.64–1.57 (m, 4 H), 0.87 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.1, 62.0, 29.5, 29.4, 25.7, 18.1, –5.5 ppm. MS (ESI): m/z = 205 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{10}H_{24}O_2Si$ $[M + H]^+$ 205.1623; found 205.1634.

Methyl 7-(*tert*-Butyldimethylsilyloxy)-4-hydroxyhept-2-ynoate (18): To a stirred solution of Celite (47.0 g) in CH_2Cl_2 (200 mL) at 0 °C was added PCC (31.6 g, 147.0 mmol). After 10 min, alcohol **16** (15.0 g, 73.5 mmol) and NaOAc (12.0 g, 147.0 mmol) were added successively to the reaction at the same temperature, and the mixture was stirred for 2 h at 0 °C. After completion of the reaction, the reaction mass was filtered, and the filtrate was concentrated in vacuo to give crude aldehyde **17**, which was used in the next step without any further purification. To a stirred solution of methyl propiolate (5.03 g, 59.9 mmol) in THF (150 mL) at –78 °C was slowly added LiHMDS (1.0 M solution in hexane, 80 mL, 80.0 mmol), and the resulting mixture was stirred at –78 °C for 1 h. Then, aldehyde **17** (10.13 g, 49.9 mmol) in THF (150 mL) was added dropwise to the reaction mixture at –78 °C, and the stirring was continued for 30 min. The reaction mixture was quenched with aqueous saturated NH_4Cl solution (20 mL), and the resulting solution was warmed to room temperature. The mixture was diluted with water (10 mL), and the solution was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 5→10% EtOAc in hexane) to give alkynol **18** (15.7 g, 75% yield for two steps) as a colorless oil; R_f = 0.5 (10% EtOAc/hexane). IR (neat, KBr): $\tilde{\nu}$ = 3424, 2954, 2928, 2056, 2236, 1718, 1436, 1253, 1097, 836, 776, 752, 664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.56–4.44 (m, 1 H), 3.75 (s, 3 H), 3.73–3.59 (m, 2 H), 1.92–1.65 (m, 4 H), 0.89 (s, 9 H), 0.07 (d, J = 1.5 Hz 6 H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 153.9, 88.4, 76.0, 63.1, 61.6, 52.7, 34.7, 28.2, 25.8, 18.2, –5.5 ppm. MS (ESI): *m*/*z* = 309 $[M + Na]^+$.

Methyl (2*E*,4*E*)-7-(*tert*-Butyldimethylsilyloxy)hepta-2,4-dienoate (19): A mixture of alkynol **18** (4.0 g, 13.9 mmol) and TPP (4.48 g, 16.7 mmol) in benzene (30 mL) was stirred at room temperature. After completion of the reaction (2 h, monitored by TLC), the solvent was removed under vacuum, and the crude mixture was purified by column chromatography (silica gel, 2→5% EtOAc in hexane) to give conjugated diene ester **19** (2.80 g, 75%) as a colorless liquid; R_f = 0.8 (10% EtOAc/hexane). IR (neat, KBr): $\tilde{\nu}$ = 3448, 2954, 2930, 2857, 1728, 1654, 1467, 1437, 1359, 1256, 1173, 1097, 836, 777, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 14.8, 10.5 Hz, 1 H), 6.19 (dd, *J* = 14.8, 10.5 Hz, 1 H), 6.13–6.07 (m, 1 H), 5.76 (d, *J* = 15.8 Hz 1 H), 3.72 (s, 3 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 2.35 (q, *J* = 6.3 Hz, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 145.0, 140.9, 129.9, 119.1, 62.0, 51.3, 36.4, 25.8, 18.2, –5.4 ppm. MS (ESI): *m*/*z* = 293 $[M + Na]^+$.

(2*E*,4*E*)-7-(*tert*-Butyldimethylsilyloxy)hepta-2,4-dien-1-ol (20): To conjugated diene ester **19** (4.0 g, 14.8 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAL-H (25% solution in toluene, 26 mL, 46.3 mmol) at –78 °C, and the mixture was stirred for 30 min at the same temperature. Then, the reaction mixture was quenched by adding a saturated potassium sodium tartrate solution (10 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and filtered. The solvents were evaporated, and the resulting crude product was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford compound **20** (3.40 g, 95%) as a colorless liquid; R_f = 0.4 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3358, 3020, 2954, 2930, 2858, 1717, 1467, 1384, 1254, 1099, 989, 936, 837, 777, 663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.21–6.01 (m, 2 H), 5.74–5.60 (m, 2 H), 4.12 (d, *J* = 6.0 Hz, 2 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 2.27 (q, *J* = 6.8 Hz, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.6, 131.3, 131.2, 130.0, 63.2, 62.8, 36.2, 29.6, 25.9, –5.3 ppm. MS (ESI): *m*/*z* = 265 $[M + Na]^+$.

Ethyl (2*E*,4*E*,6*E*)-9-(*tert*-Butyldimethylsilyloxy)nona-2,4,6-trienoate (21): To a stirred solution of IBX (3.80 g, 13.4 mmol) in dry DMSO (9 mL) under nitrogen was added alcohol **20** (2.17 g, 8.96 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred for 2 h and then diluted with an excess amount of ether (50 mL), and the resulting mixture was filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL), and then brine solution (10 mL). The organic layer was dried with Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (5% ethyl acetate in hexane) to give the aldehyde, which was then dissolved in benzene. To this stirring and refluxing solution was added the C-2 Wittig ylide (5.53 g, 16.0 mmol) portionwise to obtain the crude trienic ester. The resulting crude product was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford compound **21** (2.55 g, 92% for two steps) as a colorless liquid; R_f = 0.5 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3448, 2954, 2931, 2897, 2858, 1719, 1650, 1467, 1388, 1366, 1256, 1203, 1176, 1099, 1042, 835 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 15.8, 12.1 Hz, 1 H), 6.98 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.52 (dd, *J* = 15.1, 10.6 Hz, 1 H), 6.19 (ddd, *J* = 15.1, 11.3, 10.5 Hz, 1 H), 5.97–5.79 (m, 2 H), 4.18 (q, *J* = 6.8 Hz, 2 H), 3.65 (dt, *J* = 14.3, 6.8 Hz, 2 H), 2.39–2.23 (m, 2 H), 1.28 (t, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 144.5, 140.7, 136.3, 131.4, 128.1, 121.3, 62.3, 60.0, 31.0, 25.8, 18.1, 14.2, –5.4 ppm. MS (ESI): *m*/*z* = 310 $[M + Na]^+$.

Ethyl (2*E*,4*E*,6*E*)-9-(*tert*-Butoxycarbonylamino)nona-2,4,6-trienoate (3): TPP (2.80 g, 10.8 mmol) was added to a solution of compound **15** (2.0 g, 9.0 mmol) in THF/H_2O (4:1, 25 mL) at room temperature. After 20 h, the reaction mixture was quenched with HCl (1 N solution, pH = 1–2), and the resulting solution was washed with toluene and then basified with NaOH (10% solution, 5 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried with Na_2SO_4 and then concentrated to give the crude amine. To the crude amine in THF (20 mL) were added Et_3N (2.5 mL, 18 mmol) and $(Boc)_2O$ (3.1 mL, 13.5 mmol) successively at 0 °C, and the reaction mixture was allowed to come to room temperature for 2–3 h. After completion of the reaction, EtOAc (20 mL) was added to dilute the mixture. The organic layer was washed with water (5 mL) and brine solution (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (60–120 mesh, 20% EtOAc/hexane) afforded fragment **3** (2.50 g, 95% over two steps) as a yellow liquid; R_f = 0.5 (30% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3371, 2978, 2932, 1709, 1618, 1518, 1452, 1367, 1254, 1173, 1140, 1038, 1004, 865, 779 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 15.3, 11.5 Hz, 1 H), 6.48 (dd, *J* = 14.7, 10.8 Hz, 1 H), 6.26–6.13 (m, 2 H), 5.83 (d, *J* = 15.3 Hz, 1 H), 5.79 (m, 1 H), 4.51 (br. s, 1 H, NH), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.21 (m, 2 H), 2.34 (m, 2 H), 1.42 (s, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 155.8, 144.3, 140.2, 135.9, 131.8, 128.6, 120.6, 79.2, 60.2, 39.6, 33.5, 28.3, 14.2 ppm. MS (ESI): *m*/*z* = 318 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{25}NO_4Na$ $[M + Na]^+$ 318.1618; found 318.1613.

Dimethyl (2*R*,3*S*)-2-Hydroxy-3-methylsuccinate (22): To a stirred solution of dimethyl malate (**7**, 4.0 g, 24.7 mmol) in dry THF (40 mL) at –78 °C was slowly added LHMDS (1 M solution in THF, 54.3 mL, 54.3 mmol), and the reaction mixture was stirred for 1 h at the same temperature. Methyl iodide (2.31 mL, 37.0 mmol) in THF (7 mL) was added slowly, and the mixture was stirred at –78 °C for 3 h. Then, the temperature was gradually increased to 0 °C over 20 h. After completion of the reaction, the reaction mixture was quenched with aqueous NH_4Cl solution (10 mL). Later, the mixture was acidified with dilute HCl, and the THF was evaporated. The resulting solution was extracted with EtOAc (2 × 60 mL), and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 10:90) to afford a diastereomeric mixture (9:1) of compound **22** (3.75 g, 80%) as a yellow oil; R_f = 0.4 (50% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3487, 2955, 1740, 1440, 1213, 1104, 1007, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (t, *J* = 4.5 Hz, 1 H), 3.78 (s, 3 H), 3.67 (s, 3 H), 3.07 (br. d, *J* = 6.0 Hz, 1 H), 3.01–2.93 (m, 1 H), 1.26 (d, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 173.0, 72.1, 52.1, 51.5, 42.9, 12.5 ppm. MS (ESI): *m*/*z* = 177 $[M + H]^+$.

(2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methylbutane-1,2-diol (24): To a suspension of $LiAlH_4$ (5.38 g, 141.7 mmol) in THF (100 mL) was slowly added a solution of the diastereomeric mixture (9:1) of methylated dimethyl (*R*)-malate **22** (6.24 g, 35.4 mmol) in THF (50 mL). The mixture was heated at reflux for 2 h and then cooled to room temperature. Water (5.54 mL) and NaOH (15% aqueous solution, 5.54 mL) were added at 0 °C, sequentially and slowly with care. The mixture was filtered through Celite, which was washed with Et_2O (300 mL). The filtrate was concentrated in vacuo to give a diastereomeric mixture (9:1) of triol **23** (3.47 g). A solution of the

crude triol in MeOH (150 mL) was treated with nBu$_2$SnO (7.211 g, 28.97 mmol). The mixture was heated at reflux overnight to give a clear solution. The solution was concentrated under high vacuum to give a white solid. A solution of the solid in $CHCl_3$ (150 mL) was treated with TBSCl (5.25 g, 34.7 mmol) for 20 min. Acetonitrile (150 mL) was then added, and the solution was concentrated to about 50 mL. Hexane (150 mL) was added, and the mixture was extracted with CH_3CN (3 × 100 mL). The combined acetonitrile extracts were concentrated. Flash chromatography (hexane/EtOAc, 2:1) gave a diastereomeric mixture (9:1) of 1,2-diol **24** (5.80 g, 70% yield from the dimethyl ester) as a colorless liquid; R_f = 0.6 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3384, 2959, 2928, 2866, 1650, 1462, 1254, 1075, 1026, 837, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (br. s, 1 H), 3.71 (dd, J = 10.0, 4.1 Hz, 1 H), 3.67–3.48 (m, 4 H), 2.47 (br. s, 1 H), 1.88–1.74 (m, 1 H), 0.91 (s, 9 H), 0.86 (d, J = 7.0 Hz, 3 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.6, 76.3, 64.7, 64.6, 37.1, 37.0, 26.9, 25.7, 25.6, 13.6, 13.4, –5.4, –5.7 ppm. MS (ESI): m/z = 353 [M + Sn + H]$^+$.

***tert*-Butyldimethyl{(*R*)-2-[(*R*)-oxiran-2-yl]propoxy}silane (25):** To a solution of the diastereomeric mixture (9:1) of 1,2-diol **24** (8.0 g, 34.2 mmol) in THF (200 mL) at 0 °C was added NaH (60% in mineral oil, 0.90 g, 37.6 mmol). The mixture was stirred at 0 °C for 20 min. Then 1-(*p*-tolylsulfonyl)imidazole (8.45 g, 37.6 mmol) was added slowly with caution. Then, the cooling bath was removed, and the mixture was stirred at room temperature for 14 h. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with water (10 mL) and brine solution (5 mL), dried with $MgSO_4$, and concentrated. Column chromatography (hexane/EtOAc, 20:1) gave a diastereomeric mixture (9:1) of epoxide **25** (6.50 g, 88%); R_f = 0.6 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2956, 2929, 2857, 1466, 1254, 1096, 1035, 838, 776, 667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (d, J = 5.3 Hz, 2 H), 2.83–2.74 (m, 1 H), 2.71–2.66 (m, 1 H), 2.46 (ddd, J = 8.3, 5.3, 3.0 Hz, 1 H), 1.54–1.40 (m, 1 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.04 (d, J = 1.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.1, 53.7, 45.5, 38.6, 29.6, 25.7, 12.5, –5.6 ppm. MS (ESI): m/z = 217 [M + H]$^+$.

(2*R*,3*R*)-1-Azido-4-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-ol (26): To a solution of the diastereomeric mixture (9:1) of epoxide **25** (1.40 g, 6.48 mmol) in MeOH/H_2O (8:2, 30 mL) were added NaN_3 (1.40 g, 21.5 mmol) and NH_4Cl (0.58 g, 10.7 mmol). The mixture was stirred at 80 °C for 2 h. After the completion of the reaction, the mixture was cooled to room temperature. The MeOH was removed in vacuo, and the residue was diluted with EtOAc (20 mL). Then, the reaction mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with water (5 mL) and brine solution (5 mL), dried with $MgSO_4$, and concentrated. Column chromatography (hexane/EtOAc, 10:1) gave a diastereomeric mixture (9:1) of azide **26** (1.59 g, 95% yield); R_f = 0.4 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3448, 2921, 2851, 2101, 1732, 1399, 1088, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (dd, J = 10.0, 4.0 Hz, 1 H), 3.70–3.64 (m, 1 H), 3.59 (dd, J = 9.8, 7.5 Hz, 1 H), 3.41–3.32 (m, 1 H), 3.26–3.18 (m, 1 H), 1.91–1.83 (m, 1 H), 0.91 (s, 9 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.8, 67.7, 55.0, 37.4, 37.2, 25.7, 13.2, –5.7, –5.8 ppm. MS (ESI): m/z = 282 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{11}H_{25}O_2N_3S_iNa$ [M + Na]$^+$ 282.1613; found 282.1607.

***tert*-Butyl (2*R*,3*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethylbutylcarbamate (27):** TPP (0.60 g, 2.31 mmol) was added to a solution of compound **26** (0.50 g, 1.93 mmol) in THF/H_2O (4:1, 5 mL) at room temperature. After 20 h, the reaction was quenched with HCl (1 N solution, pH = 1–2), and the resulting solution was washed with toluene and basified with NaOH (10% solution, 5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried with Na_2SO_4 and then concentrated to give the crude amine. To the crude amine in THF (5 mL) were added successively Et_3N (0.538 mL, 3.86 mmol) and $(Boc)_2O$ (0.76 mL, 3.47 mmol) at 0 °C, and the mixture was allowed to come to room temperature over 2–3 h. After completion of the reaction, the mixture was diluted with EtOAc (20 mL). The organic layer was washed with water (5 mL) and brine solution (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (60–120 mesh, 20% EtOAc/hexane) afforded compound **27** (0.76 g, quantitative as combined yield for two steps) as a yellow liquid; R_f = 0.5 (20% EtOAc/hexane). $[a]_D^{24}$ = –13.9 (c = 2.52, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3448, 2957, 2930, 2859, 1693, 1513, 1366, 1253, 1171, 1094, 839, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.98 (br. s, 1 H), 4.03 (br. s, 1 H), 3.75 (dd, J = 10.6, 4.5 Hz, 1 H), 3.61–3.51 (m, 2 H), 3.38–3.31 (m, 1 H), 3.10–3.02 (m, 1 H), 1.81–1.70 (m, 1 H), 1.44 (s, 9 H), 0.90 (s, 9 H), 0.84 (d, J = 7.5 Hz, 3 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 79.0, 75.8, 68.3, 44.5, 37.6, 28.3, 25.7, 18.0, 13.0, –5.7 ppm. MS (ESI): m/z = 356 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{35}O_4NS_iNa$ [M + Na]$^+$ 356.2233; found 356.2227.

***tert*-Butyl (*R*)-5-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-yl]-2,2-dimethyloxazolidine-3-carboxylate (28):** To a stirred solution of compound **27** (0.87 g, 2.60 mmol) in CH_2Cl_2/Et_2O (9:1, 20 mL) were added successively 2,2-dimethoxypropane (1.9 mL, 15.63 mmol) and CSA (camphorsulfonic acid, catalytic amount) at room temperature. The reaction mixture was stirred for 1 h at the same temperature and then checked by TLC. After the completion of the reaction, the mixture was quenched with saturated $NaHCO_3$ solution (5 mL), and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried with Na_2SO_4 and then concentrated under reduced pressure. Purification of the residue by flash chromatography (4% EtOAc/hexane) afforded compound **28** (0.77 g, 80%) as a colorless liquid; R_f = 0.6 (10% EtOAc/hexane). $[a]_D^{24}$ = –6.7 (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3451, 2958, 2932, 2892, 2860, 1702, 1467, 1392, 1255, 1175, 1097, 1049, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.96–3.88 (m, 1 H), 3.66–3.46 (m, 3 H), 3.07 (t, J = 9.4 Hz, 1 H), 1.77 (m, 1 H), 1.52–1.45 (m, 15 H), 0.93–0.89 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 152.0, 93.0, 92.7, 79.8, 79.1, 74.9, 74.4, 64.5, 48.9, 39.0, 38.6, 28.5, 27.1, 26.1, 25.9, 25.1, 24.1, 18.2, 12.3, 12.1, –5.5 ppm. MS (ESI): m/z = 396 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{19}H_{39}O_4NS_iNa$ [M + Na]$^+$ 396.2546; found 396.2548.

***tert*-Butyl (*R*)-5-[(*R*)-1-Hydroxypropan-2-yl]-2,2-dimethyloxazolidine-3-carboxylate (29):** To an ice cooled solution of silyl ether **28** (0.94 g, 2.53 mmol) in dry THF (10 mL) was added TBAF (2.60 mL, 1 M solution in THF, 2.60 mmol). After 15 min of stirring, the reaction mixture was warmed to room temperature and then stirred for another 2 h. After completion the reaction, the mixture was cooled and then quenched with an ammonium chloride solution (5 mL). The resulting solution was extracted with EtOAc (3 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to give alcohol **29** (0.62 g, 95%) as a colorless oil; R_f = 0.5 (20% EtOAc/hexane). $[a]_D^{24}$ = –16.8 (c = 1.15, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3459, 2975, 2931, 1695, 1467, 1399, 1255, 1096, 1045, 871, 766 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (q, J = 9.5 Hz, 1 H), 3.79–3.49 (m, 3 H), 3.18–3.03 (m, 1 H), 2.37 (br. s, 1 H), 1.92–1.77 (m, 1 H), 1.61–1.37 (m, 15 H), 0.87 (d, J = 6.6 Hz,

3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 151.8, 93.7, 93.4, 80.1, 79.5, 77.8, 66.6, 49.9, 39.0, 28.3, 27.1, 26.0, 25.0, 24.2, 12.7 ppm. MS (ESI): *m*/*z* = 282 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{25}O_4NNa$ [M + Na]$^+$ 282.1681; found 282.1679.

(*S*)-2-[(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-5-yl]-propanoic Acid (4): To a stirred solution of IBX (0.88 g, 3.08 mmol) in anhydrous DMSO (4 mL) under nitrogen was added alcohol **29** (0.50 g, 1.93 mmol) in dry CH_2Cl_2 (12 mL) at room temperature. The reaction mixture was stirred for 2 h and then diluted with an excess amount of ether (20 mL). The resulting mixture was filtered through Celite, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (5 mL), water (5 mL), and then brine solution (5 mL). The organic layer was dried with Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was used for next step without any further purification. To a solution of the aldehyde (0.44 g, 1.73 mmol) in *tert*-butyl alcohol (10 mL) was added 2-methyl-2-butene (2 M solution in THF, 1.08 mL, 2.16 mmol) at room temperature. Sodium dihydrogenphosphate (0.88 g, 5.67 mmol) and sodium chlorite (255 g, 2.83 mmol) were dissolved in water (5 mL) to make a clear solution, which was subsequently added to the above-mentioned reaction mixture at 0 °C. The reaction mixture was allowed to stir for an additional 3 h at room temperature and then was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 3:7) to afford acid fragment **4** (0.38 g, 80%) as a colorless oil; R_f = 0.3 (30% EtOAc/hexane). $[\alpha]_D^{24}$ = –19.3 (*c* = 0.93, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3452, 2977, 2927, 1699, 1508, 1460, 1392, 1252, 1172, 1103, 1048, 870, 640 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.28 (m, 1 H), 3.79–3.58 (m, 1 H), 3.20–3.12 (m, 1 H), 2.69–2.63 (m, 1 H), 1.54–1.46 (m, 15 H), 1.19 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 152.4, 151.8, 93.8, 93.5, 80.5, 79.7, 74.3, 48.4, 48.1, 43.0, 42.8, 28.3, 27.0, 26.0, 25.1, 24.2, 12.8, 12.6 ppm. MS (ESI): *m*/*z* = 296 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{23}O_5NNa$ [M + Na]$^+$ 296.1473; found 296.1463.

***tert*-Butyl(3-methylbut-2-enyloxy)diphenylsilane (30):** To a stirred solution of prenol (**8**, 10.0 g, 116.3 mmol) in dry CH_2Cl_2 (300 mL) were added imidazole (11.8 g, 174.4 mmol) and TBDPSCl (35.0 g, 127.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (100 mL), and the resulting solution was washed with water (20 mL) and brine (20 mL) and then dried with anhydrous Na_2SO_4. Removal of solvent in vacuo and purification by silica gel column chromatography (5% ethyl acetate in hexane) afforded **30** (37.0 g, 98% yield) as a colorless liquid; R_f = 0.5 (5% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3449, 3067, 2959, 2932, 2858, 1893, 1673, 1474, 1429, 1193, 1111, 822, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 4 H), 7.37–7.30 (m, 6 H), 5.36–5.30 (m, 1 H), 4.13 (d, *J* = 6.8 Hz, 2 H), 1.68 (s, 3 H), 1.45 (s, 3 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6, 134.0, 133.6, 129.4, 127.5, 124.2, 61.0, 26.8, 25.6, 19.1, 17.8 ppm. MS (ESI): *m*/*z* = 347 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{28}OSiNa$ [M + Na]$^+$ 347.1807; found 347.1800.

(*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylbut-2-enal (31): A 70% solution of TBHP (tert-butyl hydroperoxide, 53.6 mL, 391.2 mmol, 3.6 equiv.) was added to SeO_2 (0.63 g, 5.70 mmol, 0.15 equiv.) in CH_2Cl_2 (40 mL) at 0 °C. After stirring for some time, compound **30** (35.3 g, 108.6 mmol) in CH_2Cl_2 (150 mL) was added dropwise at the same temperature, and the reaction was left for 7 h at 25 °C. After the completion of the reaction (checked by TLC), the CH_2Cl_2 was evaporated, and the residue was diluted with diethyl ether (150 mL). Then, the solution was washed with KOH (10% solution, 30 mL) portionwise and with brine solution (1 × 20 mL) and then dried with anhydrous Na_2SO_4. Removal of solvent was done in vacuo to afford a crude mixture (alcohol/aldehyde, 1:4), which without any further purification underwent PCC oxidation in the next step. To a stirred solution of Celite (14.5 g) in CH_2Cl_2 (90 mL) at 0 °C was added PCC (9.60 g, 45.0 mmol). After 10 min, the crude mixture of the alcohol and aldehyde was added at the same temperature, and the reaction mixture was stirred for 2 h at 0 °C. After the reaction was completed, the reaction mass was filtered, and the filtrate was concentrated in vacuo to get the crude aldehyde. Purification by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) afforded compound **31** (16.6 g, 45% for two steps) as a colorless liquid; R_f = 0.5 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3457, 3067, 2933, 2858, 1733, 1467, 1380, 1267, 1162, 1110, 1060, 823 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 7.64 (d, *J* = 7.0 Hz, 4 H), 7.38 (m, 6 H), 6.52 (t, *J* = 5.0 Hz, 1 H), 4.47 (d, *J* = 5.0 Hz, 2 H), 1.55 (s, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 152.4, 137.7, 135.4, 132.9, 129.8, 127.7, 61.1, 26.6, 19.0, 9.2 ppm. MS (ESI): *m*/*z* = 361 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{26}O_2SiNa$ [M + Na]$^+$ 361.1600; found 361.1584.

Ethyl (*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-4-methylhex-4-enoate (32): To a stirred solution of **31** (15.0 g, 44.2 mmol) in anhydrous THF (150 mL) was added ethyl bromoacetate (10.2 mL, 110.5 mmol), and the reaction mixture was cooled to –10 °C. After that, the Zn–Cu couple (20.0 g) was added portionwise at the same temperature, and the reaction was stirred for an additional 1 h. The metallic Zn–Cu couple was removed by filtration and washed with dry petroleum ether (50 mL). The solvent was removed until the solution became turbid. At this stage, water (20 mL) was added to the reaction mixture. The white precipitate of zinc hydroxide, thus formed, was removed by filtration and washed with ethyl acetate (4 × 50 mL). The organic layer was separated and dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography (10% ethyl acetate in hexane) afforded **32** (17.8 g, 95% yield) as a colorless liquid; R_f = 0.2 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3457, 3069, 2933, 2858, 1734, 1468, 1380, 1267, 1161, 1110, 1061, 941, 823, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.5 Hz, 4 H), 7.39–7.32 (m, 6 H), 5.64 (t, *J* = 6.0 Hz, 1 H), 4.34 (m, 1 H), 4.20 (d, *J* = 6.0 Hz, 2 H), 4.14 (q, *J* = 6.8 Hz, 2 H), 2.66 (br. s, 1 H), 2.43 (dd, *J* = 6.8, 3.0 Hz, 2 H), 1.44 (s, 3 H), 1.27 (t, *J* = 6.8 Hz, 3 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 135.5, 129.7, 129.5, 127.7, 127.6, 125.9, 70.5, 62.3, 60.8, 37.6, 26.7, 19.1, 14.1, 13.3 ppm. MS (ESI): *m*/*z* = 449 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{34}O_4SiNa$ [M + Na]$^+$ 449.2124; found 449.2107.

Ethyl (*E*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-ethylhexenoate (33): To an ice cooled solution of **32** (6.0 g, 14.1 mmol) in CH_2Cl_2 (40 mL), was added imidazole (1.50 g, 22.5 mmol) followed by TBDMSCl (2.50 g, 16.9 mmol). The reaction mixture was stirred for 4 h and then was quenched with NH_4Cl solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The crude mixture was purified by silica gel column chromatography (5% ethyl acetate/hexane) to afford compound **33** (7.40 g, 98%) as a colorless liquid; R_f = 0.8 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2955, 2932, 2893, 2858, 1738, 1468, 1254, 1167, 1109, 1075, 833, 703, 613 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 6.8 Hz, 4 H), 7.39–7.33 (m, 6 H), 5.64 (t, *J* = 6.0 Hz, 1 H), 4.47 (q, *J* = 4.5 Hz, 1 H), 4.19 (m, 2 H), 4.09 (q, *J* = 6.8 Hz, 2 H), 2.47 (dd, *J* = 13.6, 9.0 Hz, 1 H), 2.28 (dd, *J* = 14.3, 4.5 Hz, 1 H),

1.45 (s, 3 H), 1.26 (t, J = 6.8 Hz, 3 H), 1.03 (s, 9 H), 0.86 (s, 9 H), 0.01 (d, J = 10.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 137.6, 135.6, 133.8, 127.6, 125.8, 74.9, 60.6, 60.3, 42.4, 26.7, 25.7, 19.1, 18.0, 14.2, 11.3, –5.3, –4.7 ppm. MS (ESI): m/z = 563 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{31}H_{48}O_4Si_2Na$ $[M + Na]^+$ 563.2988; found 563.2999.

Ethyl (*E*)-3-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-4-methylhex-4-enoate (34): To a stirred solution of **33** (5.0 g, 9.2 mmol) in anhydrous MeOH (30 mL) was added NH_4F (1.70 g, 46.0 mmol) at 25 °C, and the reaction was stirred for 12 h. After complete removal of the *tert*-butyldiphenylsilyl group (checked by TLC), saturated NH_4Cl solution (10 mL) was added, and the MeOH was removed under vacuum. The crude reaction mixture was diluted with EtOAc (30 mL), and the organic layer was washed with brine (5 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10→20% EtOAc in hexane) to yield **34** (2.70 g, 97% yield) as a colorless oil; R_f = 0.3 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3429, 2933, 2895, 2858, 1734, 1466, 1374, 1255, 1081, 835, 777, 669 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (t, J = 6.8 Hz, 1 H), 4.47 (q, J = 4.5 Hz, 1 H), 4.12 (d, J = 6.8 Hz, 2 H), 4.08 (q, J = 6.8 Hz, 2 H), 2.50 (dd, J = 14.3, 8.3 Hz, 1 H), 2.34 (dd, J = 13.6, 4.5 Hz, 1 H), 1.65 (s, 3 H), 1.43 (br. s, 1 H), 1.26 (t, J = 6.8 Hz, 3 H), 0.85 (s, 9 H), 0.02 (d, J = 11.3 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 139.2, 125.1, 74.8, 60.4, 58.7, 42.3, 25.5, 17.9, 14.0, 11.1, –5.5, –4.8 ppm. MS (ESI): m/z = 325 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$ 325.1811; found 325.1800.

2-(Octylsulfonyl)benzo[*d*]thiazole (35): To a stirred solution of octyl bromide (5.0 g, 25.9 mmol, 1.0 equiv.) in THF (60 mL) were successively added Et_3N (5.42 mL, 38.8 mmol) and benzothiazole (5.20 g, 31.1 mmol) at 0 °C, and the reaction mixture was allowed to reach room temperature. After stirring for 2 h, the mixture was quenched by the addition of water (20 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 2→5% EtOAc in hexane) to give the sulfide (6.80 g, 95% yield) as a yellow liquid. To a stirred solution of the sulfide (5.0 g, 17.92 mmol) in CH_2Cl_2 (50 mL) was added *m*CPBA (*meta*-chloroperoxybenzoic acid, 13.2 g, 53.7 mmol) portionwise at 0 °C for 10 min. The reaction mixture was stirred for 4 h at room temperature. After the completion of the reaction, saturated $NaHCO_3$ (10 mL) and saturated $NaHSO_3$ (10 mL) solutions were added successively, and the solution was stirred for another 30 min at room temperature. After the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10→20% EtOAct in hexane) to give **35** (5.0 g, 90%) as a semisolid compound; R_f = 0.4 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.9 Hz, 1 H), 8.02 (d, J = 8.9 Hz, 1 H), 7.68–7.57 (m, 2 H), 3.51 (t_{app}, J = 7.9 Hz, 2 H), 1.93–1.82 (m, 2 H), 1.46–1.24 (m, 10 H), 0.87–0.83 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 152.5, 136.4, 127.8, 127.4, 125.0, 122.1, 54.4, 31.3, 28.5, 27.9, 22.2, 21.9, 13.8 ppm. MS (ESI): m/z = 312 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{21}O_2NS_2Na$ $[M + Na]^+$ 334.0911; found 334.0902.

Ethyl (4*E*,6*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyltetradeca-4,6-dienoate (36): To a stirred solution of IBX (4.20 g, 14.6 mmol) in anhydrous DMSO (9 mL) under nitrogen was added alcohol **34** (2.40 g, 7.97 mmol) in anhydrous CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred for 2 h and then diluted with an excess amount of ether (30 mL). The resulting mixture was filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution (5 mL), water (5 mL), and brine solution (5 mL). The organic layer was dried with Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to give the pure aldehyde (3.70 g, 90%) as a colorless liquid. To a solution of the aldehyde (3.50 g, 11.6 mmol) and sulfone **35** (2.60 g, 8.30 mmol) in dry THF (60 mL) was bubbled argon for 30 min to degas the reaction mixture. The mixture was then cooled at –78 °C, and KHMDS (0.5 M in toluene, 18.2 mL, 9.12 mmol) was added dropwise. The reaction was warmed to 0 °C, stirred for 1 h at room temperature, and then quenched with a saturated NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, and concentrated to a residue. Purification by flash column chromatography on silica gel (5% EtOAc/Hexane) afforded Julia product **36** (3.29 g, 72%) as a yellow liquid; R_f = 0.9 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2927, 2857, 1739, 1633, 1372, 1254, 1167, 1077, 962, 835, 669 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.13 (dd, J = 14.9, 10.7 Hz, 1 H), 5.92 (d, J = 10.7 Hz, 1 H), 5.66–5.56 (m, 1 H), 4.54–4.46 (m, 1 H), 4.09 (q, J = 6.8 Hz, 2 H), 2.53 (dd, J = 14.2, 9.0 Hz, 1 H), 2.35 (dt, J = 14.3, 10.2, 4.1 Hz, 1 H), 2.17–2.05 (m, 2 H), 1.70 (s, 3 H), 1.42–1.23 (m, 13 H), 0.89–0.85 (m, 12 H), 0.02 (d, J = 13.4 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 136.0, 135.2, 125.8, 125.7, 75.3, 60.2, 42.5, 32.9, 31.8, 29.6, 29.3, 29.1, 27.6, 25.6, 22.6, 14.1, 14.0, 11.4, –4.8, –5.4 ppm. MS (ESI): m/z = 419 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{44}O_3SiNa$ $[M + Na]^+$ 419.2957; found 419.2957.

Ethyl (4*E*,6*E*)-3-Hydroxy-4-methyltetradeca-4,6-dienoate (37): To an ice cooled solution of silyl ether **36** (4.50 g, 11.4 mmol) in dry THF (35 mL) was added TBAF (1 M solution in THF, 17 mL, 17.0 mmol). After 15 min of stirring, the reaction mixture was warmed to room temperature and then stirred for another 2 h. After completion, the reaction mixture was cooled and then quenched with an ammonium chloride solution (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (10% EtOAc/hexane) to give alcohol **37** (3.0 g, 95%) as a yellow oil; R_f = 0.2 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3453, 2925, 2855, 1734, 1460, 1271, 1165, 1035, 888, 770, 536 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (dd, J = 14.9, 10.7 Hz, 1 H), 5.99 (d, J = 10.7 Hz, 1 H), 5.69–5.59 (m, 1 H), 4.48–4.39 (m, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 2.53–2.48 (m, 2 H), 2.08 (q, J = 7.0 Hz, 2 H), 1.73 (s, 3 H), 1.40–1.24 (m, 13 H), 0.90–0.86 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 135.8, 133.1, 125.8, 125.6, 73.1, 60.6, 40.1, 32.9, 31.7, 29.6, 29.3, 29.1, 22.6, 14.1, 14.0, 12.3 ppm. MS (ESI): m/z = 305 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{30}O_3Na$ $[M + Na]^+$ 305.2092; found 305.2095.

Ethyl (*R*,4*E*,6*E*)-3-Acetoxy-4-methyltetradeca-4,6-dienoate (38): To a suspension of racemic alcohol **37** (3.0 g, 10.6 mmol) in hexane (150 mL) were added Amano lipase PS-C (2.0 g) and molecular sieves (4 Å, 5.50 g), followed by vinyl acetate (5.50 g, 63.6 mmol) as the acylating agent. The reaction mixture was stirred at 30 °C for 30 h, filtered through Celite, and concentrated. Purification by chromatography on silica gel (5% ethyl acetate in hexane) yielded allylic (*R*)-acetate **38** (1.50 g, 45% yield) and the unreacted (*S*)-alcohol (1.80 g, 53% yield); R_f = 0.3 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.18 (dd, J = 14.3, 10.6 Hz, 1 H), 6.06 (d, J = 10.6 Hz, 1 H), 5.78–5.67 (m, 1 H), 5.58 (dd, J = 9.1, 5.3 Hz, 1 H), 4.12 (q, J = 6.8 Hz, 2 H), 2.72 (dd, J = 15.1, 9.1 Hz,

1 H), 2.57 (dd, J = 15.1, 5.3 Hz, 1 H), 2.13–2.04 (m, 2 H), 2.04 (s, 3 H), 1.74 (s, 3 H), 1.42–1.21 (m, 13 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 169.7, 136.9, 134.2, 128.3, 125.2, 75.1, 60.6, 38.6, 32.9, 31.7, 29.6, 29.2, 29.1, 22.6, 21.0, 14.1, 14.0, 12.3 ppm. MS (ESI): m/z = 347 [M + Na]$^+$.

Methyl (*R*,4*E*,6*E*)-3-Hydroxy-4-methyltetradeca-4,6-dienoate (39): To a suspension of K_2CO_3 (0.21 g) in methanol (1.5 mL) was added allylic (*R*)-acetate **38** (0.20 g, 0.62 mmol). The reaction mixture was stirred for 15 min at –10 °C and then was filtered. EtOAc (10 mL) was added. The combined filtrate was washed with water (2 mL) and brine (2 mL) and then dried with Na_2SO_4. The solvents were removed in vacuo, and the resulting residue was purified by chromatography on silica gel (10% ethyl acetate in hexane) to give allylic (*R*)-alcohol **39** (0.15 g, 92% yield) as a yellow oil; R_f = 0.15 (20% EtOAc/hexane). $[\alpha]_D^{24}$ = +1.3 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3453, 2925, 2854, 1737, 1638, 1438, 1272, 1164, 965 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (dd, J = 14.7, 10.7 Hz, 1 H), 6.00 (d, J = 10.8 Hz, 1 H), 5.70–5.60 (m, 1 H), 4.43–4.40 (m, 1 H), 3.70 (s, 3 H), 2.69 (br. s, 1 H), 2.53–2.50 (m, 2 H), 2.08 (q, J = 6.8 Hz, 2 H), 1.74 (s, 3 H), 1.38–1.28 (m, 10 H), 0.90–0.86 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 136.0, 134.8, 125.9, 125.6, 73.1, 51.7, 40.0, 32.9, 31.8, 29.6, 29.3, 29.1, 22.6, 14.0, 12.4 ppm. MS (ESI): m/z = 291 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{16}H_{28}O_3Na$ [M + Na]$^+$ 291.1936; found 291.1942.

(*R*,4*E*,6*E*)-3-Hydroxy-4-methyltetradeca-4,6-dienoic Acid (5): To a stirred solution of the previously obtained methyl ester (*R*)-**39** (0.11 g, 0.40 μmol, 1.0 equiv.) in a mixture of THF/MeOH/H_2O (2:2:1, 25 mL) was added solid LiOH (0.19 g, 8.10 mmol, 20 equiv.) in one portion at 0 °C. The resulting yellow mixture was allowed to reach room temperature, and the stirring was continued for 2 h. The mixture was then concentrated under reduced pressure to remove the THF and MeOH, diluted with EtOAc (25 mL), and acidified with a saturated aqueous solution of NaH_2PO_4 (pH = 4.5, 15 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to provide the corresponding crude carboxylic acid fragment **5** (0.10 g, 100%), which was used without further purification in the next step.

***tert*-Butyl (*R*)-5-{(*S*)-1-[(3*E*,5*E*,7*E*)-9-Ethoxy-9-oxonona-3,5,7-trienylamino]-1-oxopropan-2-yl}-2,2-dimethyloxazolidine-3-carboxylate (40):** A stirred solution of trienic ester fragment **3** (0.25 g, 0.85 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under nitrogen was treated with CF_3COOH (0.8 mL), and the resulting mixture was stirred at room temperature for 45 min. The reaction mixture was concentrated, and the residue was dried under high vacuum. The amine salt was basified with DIPEA (*N*,*N*-diisopropylethylamine, 0.26 mL, 1.27 mmol) in dry CH_2Cl_2 (3 mL) to generate the corresponding free amine. In another round-bottomed flask, to acid fragment **4** (0.25 g, 0.90 mmol) in dry CH_2Cl_2 (3 mL) were added sequentially HOBT (0.16 g, 1.04 mmol) and EDCI (0.20 g, 1.04 mmol) at 0 °C under nitrogen. After 15 min, the above-mentioned free amine in dry CH_2Cl_2 (3 mL) was added to the reaction mixture. The reaction mixture was allowed to reach room temperature and stirred for an additional 4 h under nitrogen. The mixture was diluted with $CHCl_3$ (10 mL), and the resulting solution was washed with HCl (1 N solution, 3 mL), water (2 mL), $NaHCO_3$ (5% aqueous solution, 2 mL), and brine solution (5 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography (ethyl acetate/hexane, 50:50) of the residue gave the desired amide **40** (0.36 g, 95% yield) as a waxy solid; R_f = 0.5 (50% EtOAc/hexane). $[\alpha]_D^{25}$ = –2.1 (c = 0.9, MeOH). IR (KBr): $\tilde{\nu}$ = 3444, 2928, 2863, 1699, 1651, 1549, 1460, 1391, 1259, 1175, 1137, 1055, 1011, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 1 H), 6.49 (dd, J = 14.5, 10.8 Hz, 1 H), 6.27–6.09 (m, 2 H, NH), 5.85 (m, 1 H), 5.85 (d, J = 15.5 Hz, 1 H), 4.17 (q, J = 7.0 Hz, 2 H), 4.07 (m, 1 H), 3.67 (br. s, 1 H), 3.35 (m, 2 H), 3.07 (t, J = 9.6 Hz, 1 H), 2.35 (m, 3 H), 1.53 (br. s, 3 H), 1.46 (br. s, 3 H), 1.46 (s, 9 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.12 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 167.0, 152.1, 151.8, 144.2, 140.1, 135.8, 131.8, 128.8, 120.8, 93.8, 93.7, 80.3, 80.0, 75.0, 60.2, 49.5, 49.3, 44.2, 44.0, 38.5, 33.0, 28.4, 27.2, 26.2, 25.2, 24.2, 14.2, 13.3 ppm. MS (ESI): m/z = 473 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{38}O_6N_2Na$ [M + Na]$^+$ 473.2627; found 473.2621.

Ethyl 9-(2*E*,4*E*,6*E*)-{(2*S*,3*R*)-3-Hydroxy-4-[(*R*,4*E*,6*E*)-3-hydroxy-4-methyltetradeca-4,6-dienamido]-2-methylbutanamido}nona-2,4,6-trienoate (41): A stirred solution of the amide **40** (0.05 g, 0.12 mmol) in dry CH_2Cl_2/MeOH (1:1, 2 mL) at 0 °C under nitrogen was treated with CF_3COOH (0.8 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated, and the residue was dried under high vacuum. The amine salt was basified with DIPEA (0.03 mL, 0.18 mmol) in dry CH_2Cl_2 (2 mL) to generate the corresponding free amino alcohol. In another round-bottomed flask, to the previously obtained carboxylic acid **5** (0.03 g, 0.13 mmol) in dry CH_3CN (2 mL) was added sequentially 1-hydroxybenzotriazole (0.02 g, 0.13 mmol, 1.1 equiv.), *O*-(1*H*-benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (0.05 g, 0.13 mmol, 1.1 equiv.), and *N*-methylmorpholine (40 μL, 0.36 mmol, 3.0 equiv.). The solution was warmed to room temperature, and after stirring for 6 h, the resulting brown mixture was hydrolyzed by the addition of water (2 mL). CH_3CN was removed under reduced pressure, and the resulting aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), a saturated aqueous solution of NH_4Cl (5 mL), and brine solution (5 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness under reduced pressure. The residue, thus obtained, was purified by flash chromatography on silica gel (hexane/EtOAc, from 80:20 to 50:50), which provided the desired diamide **41** (0.06 g, 90% over 2 steps) as a colorless oil; R_f = 0.35 (10% MeOH/$CHCl_3$). $[\alpha]_D^{24}$ = +4.2 (c = 0.985, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3430, 2926, 2857, 1641, 1558, 1438, 1259, 1140, 843, 756, 561 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (dd, J = 15.1, 11.3 Hz, 1 H), 6.72 (br. m, 1 H, NH), 6.57 (br. t, J = 6.0 Hz, 1 H, NH), 6.44 (dd, J = 15.1, 10.6 Hz, 1 H), 6.18 (dd, J = 15.1, 11.3 Hz, 1 H), 6.18–6.08 (m, 2 H), 5.97 (d, J = 10.6 Hz, 1 H), 5.78 (d, J = 15.1 Hz, 1 H), 5.77 (m, 1 H), 5.64 (dt, J = 14.3, 7.5 Hz, 1 H), 5.05 (m, 1 H, OH), 4.34 (dd, J = 9.0, 3.7 Hz, 1 H), 4.12 (q, J = 6.8 Hz, 2 H), 3.62 (m, 1 H), 3.48 (m, 1 H), 3.34–3.25 (m, 2 H), 3.05 (m, 1 H), 2.40–2.18 (m, 5 H), 2.01 (m, 2 H), 1.66 (s, 3 H), 1.35–1.14 (m, 16 H), 0.81 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 173.0, 167.1, 144.3, 140.1, 136.0, 135.5, 135.5, 132.1, 129.0, 125.6, 125.0, 120.8, 73.7, 73.0, 60.4, 60.3, 44.0, 43.3, 41.6, 38.5, 32.9, 31.8, 29.6, 29.4, 29.1, 22.6, 15.5, 14.2, 14.0, 12.6 ppm. MS (ESI): m/z = 569 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{31}H_{50}O_6N_2Na$ [M + Na]$^+$ 569.3566; found 569.3556.

(2*E*,4*E*,6*E*)-9-{(2*S*,3*R*)-3-Hydroxy-4-[(*R*,4*E*,6*E*)-3-hydroxy-4-methyltetradeca-4,6-dienamido]-2-methylbutanamido}nona-2,4,6-trienoic Acid (2): To a stirred solution of **41** (0.05 g, 0.09 mmol, 1.0 equiv.) in a mixture of THF/MeOH/H_2O (2:2:1, 12.5 mL) was added solid LiOH (0.04 g, 1.82 mmol, 20 equiv.) in one portion at 0 °C, and the resulting yellow mixture was allowed to reach room temp. After stirring for 12 h, the mixture was concentrated under reduced pressure to remove the 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 with $MgSO_4$, filtered, and concentrated in vacuo to provide the corresponding crude *seco* carboxylic acid **2** (0.05 g, 99%) as a white solid with a satisfying level of purity; R_f = 0.15 (10% MeOH/$CHCl_3$). $[\alpha]_D^{24}$ = +6.7 (*c* = 0.475, MeOH); ref.[5] $[\alpha]_D^{20}$ = +7.7 (*c* = 1.2, MeOH). IR (KBr): $\tilde{\nu}$ = 3385, 2925, 2856, 1711, 1642, 1556, 1458, 1376, 1257, 1096, 805, 406 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 7.91–7.80 (m, 2 H, NH), 7.27 (dd, *J* = 14.8, 10.9 Hz, 1 H), 6.59 (dd, *J* = 15.8, 11.9 Hz, 1 H), 6.38–6.22 (m, 3 H), 6.02 (d, *J* = 10.9 Hz, 1 H), 5.96–5.91 (m, 1 H), 5.83 (d, *J* = 14.8 Hz, 1 H), 5.67 (dt, *J* = 14.8, 7.0 Hz, 1 H), 4.41 (dd, *J* = 8.0, 5.0 Hz, 1 H), 3.69 (m, 1 H), 3.40 (dd, *J* = 13.8, 3.0 Hz, 1 H), 3.30–3.24 (m, 2 H), 3.14 (dd, *J* = 12.8, 7.0 Hz, 1 H), 2.51–2.33 (m, 5 H), 2.10 (q_{app}, *J* = 7.0 Hz, 2 H), 1.74 (s, 3 H), 1.38 (m, 2 H), 1.35–1.24 (m, 8 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 0.90 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 177.5, 174.3, 170.6, 146.6, 142.2, 137.6, 137.3, 136.2, 133.1, 129.8, 127.3, 126.8, 121.6, 75.1, 73.3, 45.4, 44.5, 43.2, 39.7, 34.0, 33.0, 30.7, 30.6, 30.3, 23.7, 15.2, 14.5, 12.4 ppm. MS (ESI): *m*/*z* = 541 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{29}H_{46}O_6N_2Na$ $[M + Na]^+$ 541.3253; found 541.3241.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds and HPLC chromatogram of compound **38**.

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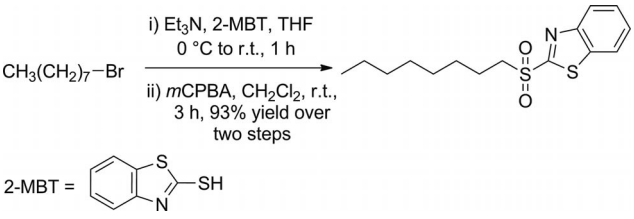
[18] Sulfone **35** was readily prepared from octyl bromide in two steps:



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[21] The enantiomeric excess was determined by chiral HPLC (chiral column AD-H, Diacel). The optical and spectroscopic data of **39** were in full agreement with those reported by J. Cossy et al.[6b]

[22] The hydrolysis of compound **38** required very mild conditions, as elimination to the conjugated diene occurred as a competing reaction.

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