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Total synthesis of trifluoromethylated analogs of macrosphelide A

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Abstract—Trifluoromethylated analogs of macrosphelide A **1** and **2** were designed and synthesized. The key segment **6** was efficiently constructed via a series of high stereoselective transformations from trifluoromethylated diol **8**. Methoxymethylation of compound **9** with 1.0 equiv of sodium hydride gave optically pure compound **23a** in 73% yield. From **23a** a novel route was developed to prepare key segment **7**. The condensation and macrolactonization were smoothly proceeded under our modified Keck's protocol.

1. Introduction

Currently more than half of the prescription drugs are of natural product origin[1] and the expectations from combinatorial libraries in drug screening have not been realized.[2] Therefore, the natural product-inspired drug discovery and development has received renewed attention in recent years.[2] The synthesis of natural products' analogs by removing suspected sites of toxicity or by introducing additional structural features may enhance potency or stability of natural medicines. The most versatile approach to analogs preparation is the design of a synthetic route to a given natural product that allow for the introduction of deep-seated structural variations en route to the target molecule, termed by Danishefsky et al. as diverted total synthesis.[3] The interest of fluorinated analogs of natural products is increasing continuously, because the incorporation of fluorine atom(s) or fluoroalkyl groups may greatly modify the chemical properties and biological activities of those molecules.[4,5] A notable recent example is diverted total synthesis of trifluoromethylated analog of epothilone B: 'fludelone'.[6] Fludelone shows an extremely high therapeutic efficacy against various carcinomas.

Macrosphelide A (Fig. 1), isolated from the *Macrosphaeropsis* sp. FO-5050 by the Omura group, strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells (HUVEC) in a dose-dependent manner.[7] The total synthesis of macrosphelide A has been reported by several groups.[8] Furthermore, macrosphelide A served as a lead compound for the development of new anti-cancer drugs.[9] In view of strong electron-withdrawing character and large hydrophobic parameter of trifluoromethyl (CF_3) group,[10] we were interested in the replacement of methyl group of macrosphelide A by trifluoromethyl group. Herein we report on the total synthesis of trifluoromethylated macrosphelide A **1** and **2** (Fig. 1).

2. Results and discussion

To explore a flexible synthetic strategy not only for trifluoromethylated macrosphelide A **1** and **2**, but also for various analogs of macrosphelide for in-depth investigation of the structure–activity relationship, a convergent route to **1** and **2** was designed as shown in Scheme 1. Key elements

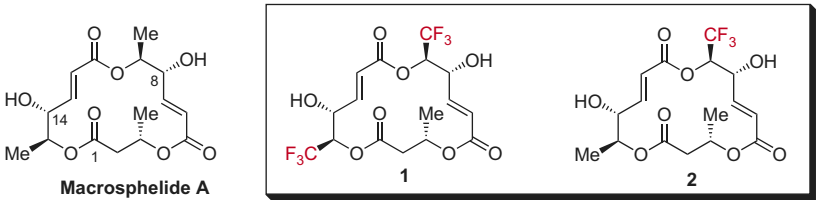

Figure 1.

Keywords: Asymmetric synthesis; Keck reaction; Kinetic resolution; Macrosphelide A; Trifluoromethyl group.
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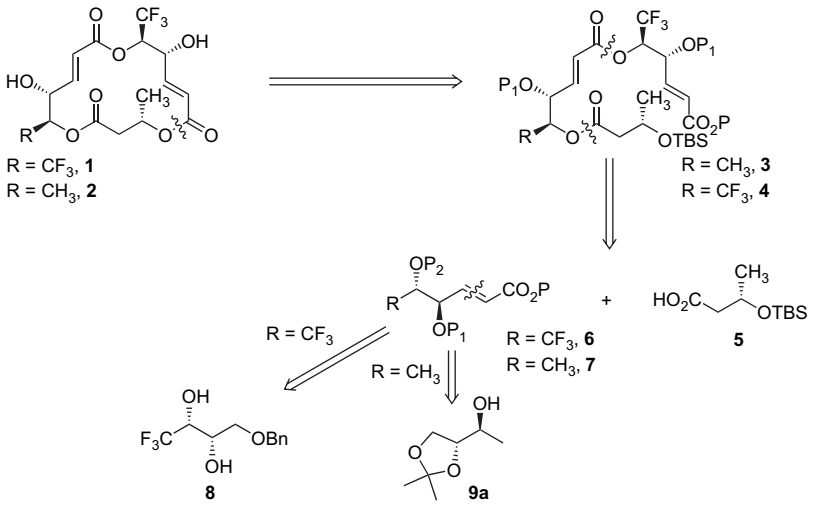
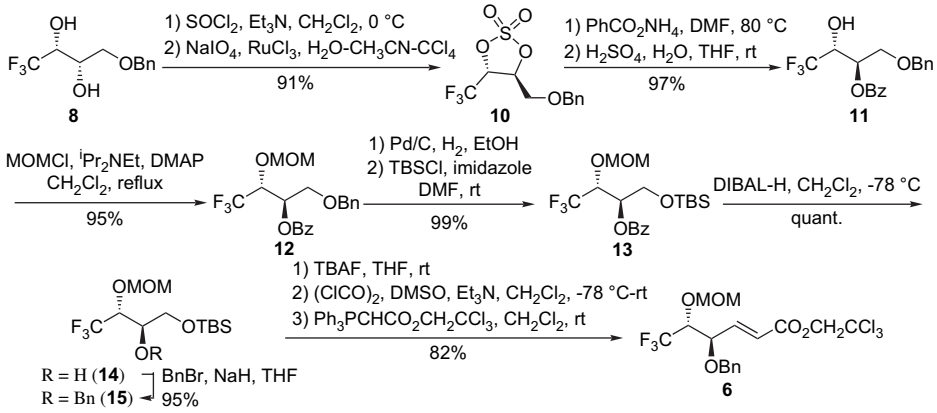


Scheme 1.

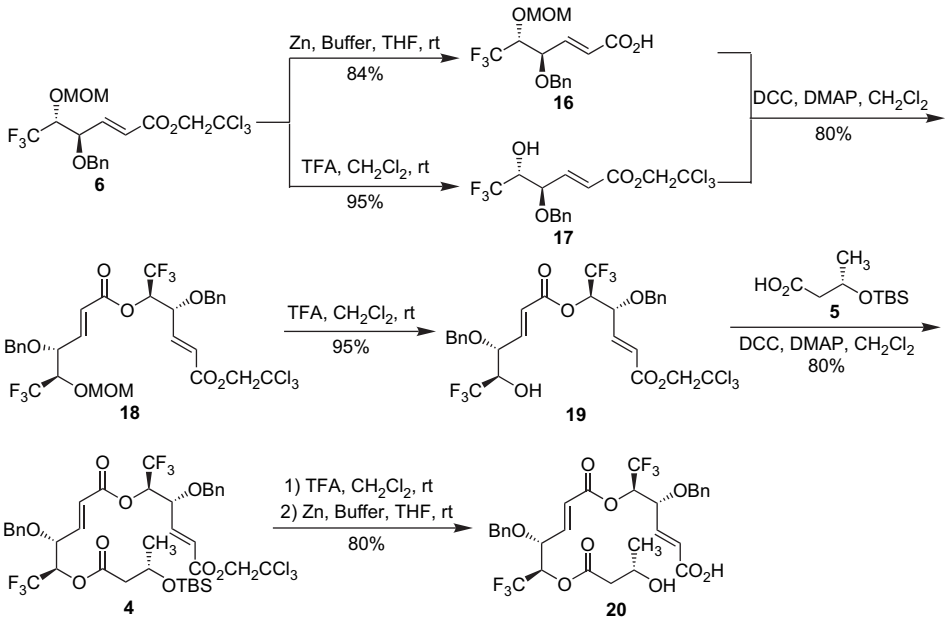
of this approach include efficient construction of the stereocenters, suitable choice of protection groups, and sequential coupling of the fragments followed by macrolactonization. Trifluoromethylated building block **6** is central moiety for the synthesis of target molecules **1** and **2**. We envisioned that trifluoromethylated α,β-unsaturated ester **6** would be prepared from trifluoromethylated diol **8** via inversion of hydroxy configuration and lengthening of terminal carbon. The common intermediate **7** for target molecule **2** and other congeners of macrosphelide was expected to be derived from chiral alcohol **9a**. The third fragment, acid **5**, can be prepared according to the published procedures.[11]

Our synthesis commenced with the preparation of the trifluoromethylated α,β-unsaturated ester **6** (Scheme 2). We have developed an efficient and practical route to diol **8** in high enantioselectivity (99% ee) by Sharpless asymmetric dihydroxylation of trifluoromethylated olefin.[12] The inversion of a hydroxy configuration was based upon the regioselective and stereoselective nucleophilic ring opening of the trifluoromethylated cyclic sulfate recently developed in our laboratory.[13] Treatment of the vicinal diol **8** with $SOCl_2$ followed by oxidation with RuO_4 (generated in situ from $NaIO_4$/catalytic $RuCl_3$) provided cyclic sulfate **10** in 91% yield. The regioselective and stereoselective nucleophilic ring opening of the cyclic sulfate **10** with $PhCO_2NH_4$ and then acidic hydrolysis gave compound **11** in 97% yield. The resulting hydroxy group was protected as a methoxymethyl (MOM) ether, **12**, in 95% yield. Hydrogenation of compound **12** for the cleavage of the benzyl group followed by treatment with *tert*-butyldimethylsilyl chloride and imidazole afforded the *tert*-butyldimethylsilyl (TBS) ether **13** in quantitative yield. Removal of the benzoyl group of **13** with DIBAL-H in CH_2Cl_2 at −78 °C produced alcohol **14**, which was benzylated to give benzyl ether **15**. Removal of TBS of compound **15** followed by Swern oxidation of the resulting alcohol and then Wittig reaction gave the desired fragment **6** in 82% yield over three steps.

With the key fragment **6** in hand, we embarked on the synthesis of target molecule **1** as shown in Scheme 3. Selective cleavage of trichloroethyl ester **6** gave the acid **16** in 84% yield,[14] whereas desilylation generated the alcohol **17** in 95% yield. At this point, we focused our efforts on the coupling of **16** and **17**. The condensation of carboxylic acids and alcohols via Keck protocol[15] had been successfully used in total synthesis of macrosphelide A.[8a–c,8k] Unfortunately, the coupling of **16** and **17** by esterification employing the Keck procedure (the addition of the solution of **16** and **17** in CH_2Cl_2 to the solution of DCC/DMAP in CH_2Cl_2 at room temperature) failed to give the desired product **18**, but the dehydrated product of alcohol **17** was isolated. In



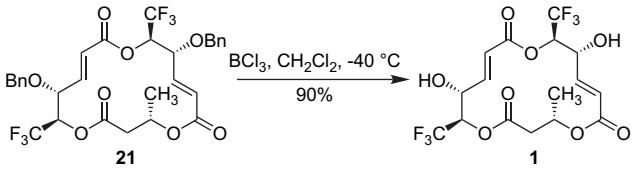
Scheme 2.



Scheme 3.

our opinion, the failure of condensation was attributed to the fact that the acidity of hydroxy group of compound **17** was enhanced greatly by the adjacent trifluoromethyl, which made alcohol **17** to react with DCC prior to acid **16** and led to dehydration. We envisioned that the first activation of carboxylic acid **16** and the condensation at low temperature should furnish our desired product. To our delight, treatment of **16** with DCC/DMAP at 0 °C followed by addition of alcohol **17** produced compound **18** in 80% yield. Subsequent removal of MOM group afforded alcohol **19** in 95% yield. The condensation of **19** and **5** via Keck procedures also failed to provide compound **4**. When the reaction conditions of the formation of **19** were used for the coupling of **19** and **5**, the desired product **4** was isolated in 80% yield. Removal of the TBS and 2,2,2-trichloroethyl groups of compound **4** provided seco acid **20**.

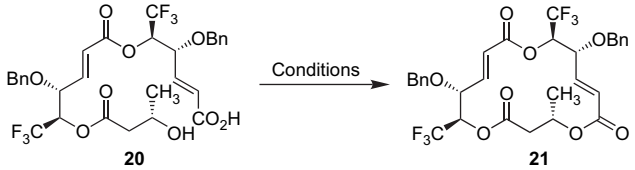
Yamaguchi's macrolactonization protocol[16] had been successfully used for macrolactone construction of macrosphelide.[8a–h,8k] However, all attempts on macrolactonization of seco acid **20** under the conditions of Yamaguchi failed. The change of reaction conditions such as solvent and reaction temperature had no pronounced beneficial effect on the reaction outcome (Table 1, entries 1–5). ^{19}F NMR spectra of the reaction mixture showed that the reaction was complex and elimination reaction took place. The mild reaction conditions without strong base such as Et_3N was expected to avoid the side reaction. Therefore, the macrolactonization of seco acid **20** under the conditions of Keck[15] was investigated. Although treatment of seco acid **20** with typical Keck's conditions (at reflux in $CHCl_3$) still resulted in a complex mixture (Table 1, entry 6), the reaction was proceeded at 25 °C to give the desired product **21** in 30% yield (Table 1, entry 7). We were pleased to find that the isolated yield of compound **21** was improved to 50% when the reaction temperature was lowered to 0 °C (Table 1, entry 8). Finally, deprotection of the Bn groups of **21** with BCl_3 in CH_2Cl_2 afforded the trifluoromethylated macrosphelide A **1** in 90% yield (Scheme 4).



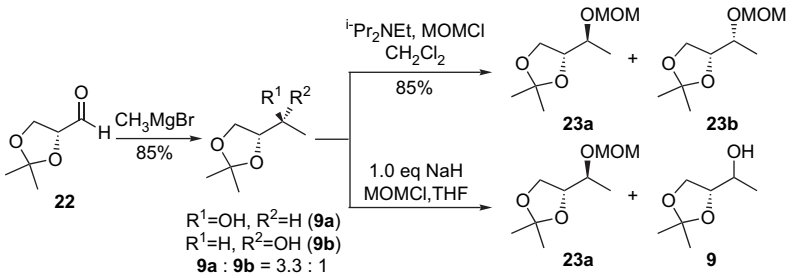
Scheme 4.

As outlined in Scheme 1, compound **7** was another key intermediate for the completion of the synthesis of trifluoromethylated macrosphelide A **2**. Although several groups have reported the preparation of fragment **7** for total synthesis of macrosphelide A,[8a–h,8k] we sought another practical method for accessing the key intermediate **7**. The preparation of **9a** in an optically active fashion was key

Table 1. Macrolactionization of compound **20**



Entry	Conditions	Yield
1	(a) **21**, 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt (b) DMAP, toluene, reflux	Complex
2	(a) **21**, 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt (b) DMAP, benzene, reflux	Complex
3	(a) **21**, 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt (b) DMAP, benzene, 40 °C	Complex
4	(a) **21**, 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt (b) DMAP, toluene, 25 °C	Complex
5	(a) **21**, 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, rt (b) DMAP, Toluene, 0 °C	Complex
6	DCC, DMAP, DMAP·HCl, $CHCl_3$, reflux	Complex
7	DCC, DMAP, DMAP·HCl, $CHCl_3$, 25 °C	30%
8	DCC, DMAP, DMAP·HCl, $CHCl_3$, 0 °C	50%
9	DCC, DMAP, DMAP·HCl, $CHCl_3$, −10 °C	35%

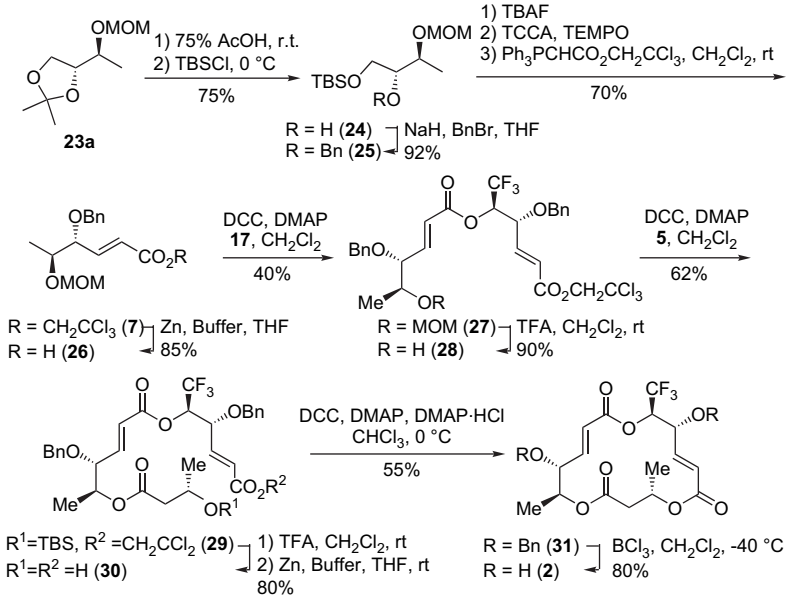


Scheme 5.

step for preparation of **7** (Scheme 1). We anticipated that compound **7** could be made from the nucleophilic addition of methyl metal reagent to 1-(*R*)-glyceraldehyde acetonide **22**. Accordingly, treatment of **22** with MeMgBr provided predominantly the desired *anti*-adduct **9a** (**9a/9b**=3.3:1, determined by ^{1}H NMR) (Scheme 5).[17] However, the two diastereomers could not be separated by column chromatography. Protection of the hydroxy group of **9** with MOMCl/^{i}Pr$_2$NEt provided methoxymethyl ethers **23a** and **23b**, which were still very difficult to be separated. Enlightened by our previous work,[18] epimerization of compound **9** in the methoxymethylation under different equivalents of sodium hydride was investigated. To our delight, a kinetic resolution was discovered and reactivity of **9a** seemed to be much more active than that of **9b**. The single **23a** was obtained by controlling the amount of sodium hydride. When 1.0 equiv of sodium hydride was used in the methoxymethylation of **9**, compound **23a** was isolated in 73% yield along with 15% recovered **9**.

Acidic hydrolysis of the isopropylidene group of **23a** with 75% acetic acid followed by the selective protection of primary hydroxy group with TBSCl gave **24**, which was further benzylated to provide compound **25** (Scheme 6). Removal of TBS of compound **25** followed by oxidation of the resulting alcohol in the presence of excessive trichloroisocyanuric acid (TCCA) and catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO),[19] and then Wittig reaction gave the desired fragment **7** in 70% yield over three steps. With three coupling partners in hand and our experience in total synthesis of the target molecule **1**, the synthesis of trifluoromethylated macrosphelide A **2** proceeded in a straightforward manner (Scheme 6). Selective cleavage of trichloroethyl ester **7** provided acid **26** in 85% yield. The condensation of **26** with alcohol **17** using our modified Keck's procedure gave compound **27** in 40% yield. Removal of MOM group of **27** afforded alcohol **28** in 90% yield. The coupling **28** with **5** produced compound **29** in 62% yield. Removal of the TBS and 2,2,2-trichloroethyl groups of **29** gave seco acid **30**. To our delight, our modified Keck's protocol in synthesis of compound **21** smoothly promoted the macrolactonation of seco acid **30** to afford macrolactone **31** in 55% yield, which was then subjected to BCl_3 in CH_2Cl_2 at −40 °C to give the desired trifluoromethylated macrosphelide A **2**.

In conclusion, we accomplished the total synthesis of trifluoromethylated macrosphelide A **1** and **2**. Our approach integrated highly effective asymmetric reaction to generate key chiral trifluoromethylated building block **6**, a novel route to common intermediate **7** via a kinetic resolution in methoxymethylation of alcohol **9** and elaborate manipulations



Scheme 6.

of protection groups. Notably the unexpected side reactions in coupling reactions and macrolactonization were well overcome under our improved reaction conditions. The synthesis of other trifluoromethylated analogs of macrosphelide and their biological evaluation are in progress in our group.

3. Experimental section

3.1. General information

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum heat-dried glassware under nitrogen atmosphere. Reaction mixtures were stirred magnetically. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR was recorded on a Bruker AM300 spectrometer ($FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are in Hertz. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

3.2. (2*R*,3*R*)-1-(Benzyloxy)-4,4,4-trifluoro-3-(methoxymethoxy)butan-2-yl benzoate (12)

To a solution of **11** (3.19 g, 9.0 mmol) and (^{i}Pr)$_2$NEt (2.07 g, 18 mmol) in CH_2Cl_2 (50 mL) was added MOMCl (1.46 g, 18 mmol). After stirring at reflux for 30 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=30:1) to afford **12** (3.37 g, 95%) as a clear oil. $[\alpha]_D^{20}$ +18.4 (c 0.370, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J=7.5, 1.5 Hz, 2H), 7.6 (t, J=7.5 Hz, 1H), 7.47 (t, J=7.5 Hz, 2H), 7.28–7.32 (m, 5H), 5.57–5.61 (m, 1H), 4.81 (d, J=6.9 Hz, 1H), 4.75 (d, J=6.9 Hz, 1H), 4.61 (d, J=12.3 Hz, 1H), 4.55 (d, J=12.3 Hz, 1H), 4.45–4.50 (m, 1H), 3.85–3.91 (m, 2H), 3.41 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.42 (d, J=7.8 Hz); IR (thin film) ν_{max} 2905, 1728, 1275 cm^{-1}; MS (EI) m/z 399 (M^++1, <1), 91 (100). Anal. Calcd for $C_{20}H_{21}O_5F_3$: C, 60.30; H, 5.31. Found: C, 60.54; H, 5.18.

3.3. (2*R*,3*R*)-1-(*tert*-Butyldimethylsilyloxy)-4,4,4-trifluoro-3-(methoxymethoxy)butan-2-yl benzoate (13)

A suspension of 10% palladium on charcoal (674 mg) and **12** (3.37 g, 8.6 mmol) in EtOH (40 mL) was stirred under a hydrogen atmosphere for 10 h. Filtration of the mixture and removal of the solvent in filtrate in vacuo gave a residue, which was used without further purification. To a 0 °C solution of the above residue and DMAP (110 mg, 0.9 mmol) in DMF (10 mL) was added imidazole (1.17 g, 17.2 mmol) followed by TBDMSCl (1.94 g, 12.9 mmol). Then, the mixture was warmed to room temperature and stirred for 8 h. EtOAc (40 mL) was added and the resulting mixture was washed with brine twice. The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to afford **13** (3.54 g, 99%) as a clear oil. $[\alpha]_D^{20}$ +20.7 (c 0.600, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J=7.5, 1.5 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.5 Hz, 2H), 5.40–5.44 (m, 1H), 4.86 (d, J=6.6 Hz, 1H), 4.77 (d, J=6.6 Hz, 1H), 4.41–4.50 (m, 1H), 4.00 (d, J=4.5 Hz, 2H), 3.45 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.51 (d, J=6.2 Hz); IR (thin film) ν_{max} 2957, 1730, 1276 cm^{-1}; MS (EI) m/z 423 (M^++1, <1), 45 (100). Anal. Calcd for $C_{19}H_{29}O_5F_3Si$: C, 54.01; H, 6.92. Found: C, 54.33; H, 6.49.

3.4. (2*R*,3*R*)-1-(*tert*-Butyldimethylsilyloxy)-4,4,4-trifluoro-3-(methoxymethoxy)butan-2-ol (14)

To a solution of **13** (2.66 g, 6.3 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DIBAL-H (10 mL, 1.0 M in hexane, 10 mmol) dropwise. After stirring for 1.5 h, the reaction was quenched with saturated Rochelle's salt (20 mL) at −78 °C. Warming up to room temperature, the mixture was stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) to provide **14** (2.03 g, quant.) as a clear oil. $[\alpha]_D^{20}$ −3.90 (c 0.850, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72–4.81 (m, 2H), 4.04–4.14 (m, 1H), 3.90–3.96 (m, 1H), 3.67–3.83 (m, 2H), 3.44 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{19}F NMR (282 MHz, CDCl3) δ −73.83 (d, J=7.5 Hz); IR (thin film) ν_{max} 3500, 2934, 1271 cm^{-1}; MS (EI) m/z 319 (M^++1, <1), 45 (100). Anal. Calcd for $C_{12}H_{25}O_4F_3Si$: C, 45.26; H, 7.91. Found: C, 45.45; H, 8.01.

3.5. ((2*R*,3*R*)-2-(Benzyloxy)-4,4,4-trifluoro-3-(methoxymethoxy)butoxy)(*tert*-butyl)dimethylsilane (15)

To a suspension of NaH (378 mg, 0.19 mol) in THF (20 mL) at 0 °C was added a solution of alcohol **14** (2.03 g, 6.3 mol) in THF (5 mL). After the mixture was stirred for about 1 h, Bu_4NI (0.28 g, 0.63 mmol) and BnBr (1.28 g, 7.6 mol) were added. After stirring at room temperature for 5 h, the reaction mixture was diluted with Et_2O (20 mL), washed with water, brine, and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent provided the compound **15** (2.44 g, 95%) as a clear oil. $[\alpha]_D^{20}$ +6.10 (c 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.37 (m, 5H), 4.81 (d, J=6.6 Hz, 1H), 4.73 (d, J=6.6 Hz, 1H), 4.70 (d, J=2.7 Hz, 2H), 4.22–4.25 (m, 1H), 3.78–3.90 (m, 3H), 3.41 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.37 (d, J=7.3 Hz); IR (thin film) ν_{max} 2932, 1473, 1363, 1258 cm^{-1}; MS (EI) m/z 407 (M^+−1, <1), 91 (100). Anal. Calcd for $C_{19}H_{31}O_4F_3Si$: C, 55.86; H, 7.65. Found: C, 56.23; H, 7.56.

3.6. (4*R*,5*R*,*Z*)-2,2,2-Trichloroethyl 4-(benzyloxy)-6,6,6-trifluoro-5-(methoxymethoxy)hex-2-enoate (6)

To an ice-cold solution of **15** (2.03 g 4.8 mmol) in THF (20 mL) was added a solution of TBAF (4.8 mL, 1.0 M in THF, 4.8 mmol) dropwise. After the mixture was warmed

to room temperature, the reaction was stirred for 1 h. Filtration of the mixture and removal of the solvent in filtrate in vacuo gave a residue, which was used in next step without further purification. To a solution of dimethyl sulfoxide (1.74 g, 19.2 mmol) in CH_2Cl_2 (30 mL) was added a solution of oxalyl chloride (1.23 g, 9.6 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After continuous stirring for 30 min, the above residue was added dropwise to the solution. After 1 h, Et_3N (4.70 mL, 38.7 mmol) was added and the mixture was warmed to 0 °C, and stirred for 2 h. Then, $Ph_3PCHCO_2CH_2CCl_3$ (3.25 g, 7.20 mmol) was added at 0 °C. Warming up to room temperature, the mixture was stirred overnight. Et_2O (20 mL) was added and the resulting mixture was washed with water and brine, and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to give ester **6** (2.12 g, 82%) as a clear oil. $[\alpha]_D^{20}$ +24.6 (*c* 0.950, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.38 (m, 5H), 7.12 (dd, *J*=15.6, 6.3 Hz, 1H), 6.05 (d, *J*=15.6 Hz, 1H), 4.76–4.90 (m, 4H), 4.51–4.62 (m, 2H), 4.27–4.35 (m, 2H), 3.40 (s, 3H); ^{19}F NMR (282 MHz, CDCl3) δ −73.97 (d, *J*=7.2 Hz); IR (thin film) ν_{max} 2960, 1741, 1660, 1273 cm^{-1}; MS (EI) *m*/*z* 466 (M^+, <1), 91 (100). Anal. Calcd for $C_{17}H_{18}O_5F_3Cl_3$: C, 43.84; H, 3.89. Found: C, 43.83; H, 3.99.

3.7. (4*R*,5*R*,*E*)-4-(Benzyloxy)-6,6,6-trifluoro-5-(methoxymethoxy)hex-2-enoic acid (16)

A solution of **6** (240 mg, 0.50 mmol) in THF (3 mL) was added to a mixture of Zn dust (260 mg, 4.0 mmol) and AcOH/AcONa buffer (5 mL) in THF (3 mL) at 0 °C. Warming up to room temperature, the reaction was stirred for 20 h. The mixture was filtered and the filtrate was acidified with 1 M aqueous HCl and extracted with Et_2O. The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to afford **16** (140 mg, 84%) as a clear oil. $[\alpha]_D^{20}$ +33.8 (*c* 0.801, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.40 (m, 5H), 7.07 (dd, *J*=15.9, 6.0 Hz, 1H), 6.05 (d, *J*=15.9 Hz, 1H), 4.81 (d, *J*=7.2 Hz, 1H), 4.77 (d, *J*=7.2 Hz, 1H), 4.63 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 4.27–4.33 (m, 2H), 3.41 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.01 (d, *J*=5.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.68, 144.65. 136.74, 128.58, 128.20, 127.85, 123.89, 124.35, 97.24, 75.15, 71.82, 67.97, 56.47; IR (thin film) ν_{max} 3300, 2906, 1703, 1662, 1272 cm^{-1}; MS (ESI) *m*/*z* 357 $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{17}O_5F_3Na$: 357.0920, found: 357.0928.

3.8. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl 4-(benzyloxy)-6,6,6-trifluoro-5-hydroxyhex-2-enoate (17)

To a solution of **6** (700 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added CF_3COOH (3 mL). The solution was stirred at room temperature for 5 h and concentrated. The resulting oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to afford **17** (600 mg, 95%) as a clear oil. $[\alpha]_D^{20}$ +21.1 (*c* 0.500, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.45 (m, 5H), 7.11 (dd, *J*=16.5, 7.5 Hz, 1H), 6.05 (dd, *J*=16.5, 1.2 Hz, 1H), 4.81–4.89 (m, 2H), 4.69 (d, *J*=11.7 Hz, 1H), 4.50 (d, *J*=11.7 Hz, 1H), 4.31–4.35 (m, 1H), 4.13–4.23 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.33 (d, *J*=6.9 Hz); IR (thin film) ν_{max} 3466, 2876, 1739, 1660, 1272 cm^{-1}; MS (EI) *m*/*z* 421 (M^+−1, <1), 91 (100). Anal. Calcd for $C_{15}H_{14}O_4F_3Cl_3$: C, 42.73; H, 3.47. Found: C, 42.94; H, 3.71.

3.9. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-((4*R*,5*R*,*E*)-4-(benzyloxy)-6,6,6-trifluoro-5-(methoxymethoxy)hex-2-enoyloxy)-6,6,6-trifluorohex-2-enoate (18)

To a solution of 1,3-dicyclohexylcarbodiimide (DCC) (1.08 g, 5.2 mmol) and 4-dimethylaminopyridine (DMAP) (318 mg, 2.61 mmol) in CH_2Cl_2 (20 mL) was added a solution of **16** (924 mg, 2.8 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After stirring for 30 min at 0 °C, a solution of **17** (1.10 g, 2.61 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the mixture. The solution was stirred for 6 h at room temperature. After filtration, the filtrate was washed with 1 M aqueous HCl and saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) to afford **18** (1.53 g, 80%) as a clear oil. $[\alpha]_D^{20}$ +30.4 (*c* 0.675, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.41 (m, 10H), 6.99–7.10 (m, 2H), 6.24 (dd, *J*=16.8, 1.2 Hz, 1H), 6.19 (dd, *J*=15.9, 0.9 Hz, 1H), 5.64–5.72 (m, 1H), 4.74–4.87 (m, 4H), 4.49–4.63 (m, 4H), 4.41–4.45 (m, 1H), 4.24–4.32 (m, 2H), 3.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.18 (d, *J*=6.2 Hz, 3F), −74.03 (d, *J*=7.1 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.50, 163.16, 145.59, 143.48, 136.63, 136.32, 128.63, 128.42, 128.32, 128.06, 127.94, 127.65, 123.90, 124.00, 122.72, 122.51, 97.22, 94.78, 76.19, 75.55, 74.38, 74.08, 71.94, 69.90, 56.45; IR (thin film) ν_{max} 2963, 2877, 1744, 1661, 1244 cm^{-1}; MS (ESI) *m*/*z* 759 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{29}O_8F_6Cl_3Na$: 759.0724, found: 759.0722.

3.10. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-((4*R*,5*R*,*E*)-4-(benzyloxy)-6,6,6-trifluoro-5-hydroxyhex-2-enoyloxy)-6,6,6-trifluorohex-2-enoate (19)

To a solution of **18** (735 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added CF_3COOH (5 mL). The solution was stirred at room temperature for 10 h and concentrated. The resulting oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to afford **19** (658 mg, 95%) as a clear oil. $[\alpha]_D^{20}$ +21.7 (*c* 0.501, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.43 (m, 10H), 7.16 (dd, *J*=15.9, 5.4 Hz, 1H), 7.11 (dd, *J*=16.2, 6.0 Hz, 1H), 6.33 (d, *J*=15.9 Hz, 1H), 6.24 (d, *J*=16.2 Hz, 1H), 5.72–5.79 (m, 1H), 4.89 (d, *J*=12.3 Hz, 1H), 4.84 (d, *J*=12.3 Hz, 1H), 4.69 (d, *J*=11.1 Hz, 2H), 4.62 (d, *J*=11.1 Hz, 2H), 4.49–4.54 (m, 1H), 4.30–4.45 (m, 1H), 4.10–4.16 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.26 (d, *J*=7.3 Hz, 3F), −75.52 (d, *J*=6.7 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.80, 163.37, 145.70, 143.70, 137.08, 136.45, 128.70, 128.57, 128.46, 128.07, 127.94, 127.83, 124.17, 123.75, 122.72, 122.49, 94.77, 74.78, 74.10, 72.45, 72.23, 72.16, 69.97, 65.93; IR (thin film) ν_{max} 3482, 2876, 1743, 1660, 1247 cm^{-1}; MS (ESI) *m*/*z* 715 $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{25}O_7F_6Cl_3Na$: 715.0462, found: 715.0452.

3.11. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-((4*R*,5*R*,*E*)-4-(benzyloxy)-5-((*S*)-3-(*tert*-butyldimethylsilyloxy)butanoyloxy)-6,6,6-trifluorohex-2-enoyloxy)-6,6,6-trifluorohex-2-enoate (4)

To a solution of 1,3-dicyclohexylcarbodiimide (DCC) (142 mg, 0.69 mmol) and 4-dimethylaminopyridine (DMAP) (84 mg, 0.69 mmol) in CH_2Cl_2 (1 mL) was added a solution of **5** (100 mg, 0.46 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 30 min at 0 °C, a solution of **19** (318 mg, 0.46 mmol) was added dropwise to the mixture. The solution was stirred for 6 h at room temperature. The mixture was filtered and the filtrate was washed with 1 M aqueous HCl and saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) to afford **4** (328 mg, 80%) as a clear oil. $[\alpha]_D^{20}$ +40.7 (*c* 1.100, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.33 (m, 10H), 6.86–6.99 (m, 2H), 6.08–6.21 (m, 2H), 5.52–5.61 (m, 2H), 4.75 (s, 1H), 4.46–4.60 (m, 4H), 4.34–4.37 (m, 1H), 4.27–4.30 (m, 1H), 4.15–4.21 (m, 1H), 2.36–2.55 (m, 2H), 1.12 (d, *J*=5.1 Hz, 3H), 0.80 (s, 9H), 0.04 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.79 (d, *J*=6.8 Hz, 3F), −72.87 (d, *J*=8.2 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.10, 163.44, 162.99, 144.26, 143.46, 136.40, 136.34, 128.74, 128.65, 128.37, 128.32, 128.03, 127.98, 124.65, 123.52, 123.18, 94.89, 74.79, 74.64, 74.13, 71.99, 69.49, 65.27, 44.03, 30.80, 25.75, 23.57, 18.00, −4.60, −5.03; IR (thin film) ν_{max} 2959, 1744, 1656, 1252, 835 cm^{-1}; MS (ESI) *m*/*z* 915 [M+Na]$^+$; HRMS (ESI) calcd for $C_{38}H_{45}SiO_9F_6Cl_3Na$: 915.1681, found: 915.1695.

3.12. (4*R*,5*R*,*E*)-4-(Benzyloxy)-5-((4*R*,5*R*,*E*)-4-(benzyloxy)-6,6,6-trifluoro-5-((*S*)-3-hydroxybutanoyloxy)hex-2-enoyloxy)-6,6,6-trifluorohex-2-enoic acid (20)

To a solution of **4** (200 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added CF_3COOH (1 mL). The solution was stirred at room temperature for 2 h and diluted with Et_2O. The reaction mixture was quenched with saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue, which was used without further purification. A solution of the above residue in THF (1 mL) was added to a mixture of Zn dust (57 mg, 0.88 mmol) and AcOH/AcONa buffer (1 mL) in THF (1 mL) at 0 °C. Warming up to room temperature, the reaction was stirred for 24 h. After filtration, the filtrate was acidified with 1 M aqueous HCl and extracted with Et_2O. The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=2:1) to afford **20** (142 mg, 80%) as a white solid. $[\alpha]_D^{20}$ +46.3 (*c* 3.240, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.38 (m, 10H), 6.84–6.92 (m, 2H), 6.12 (dd, *J*=15.9, 6.0 Hz, 2H), 5.54–5.63 (m, 2H), 4.75 (s, 1H), 4.47–4.64 (m, 4H), 4.30–4.41 (m, 2H), 4.11–4.22 (m, 1H), 2.52–2.56 (m, 2H), 1.12 (d, *J*=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.52 (d, *J*=6.8 Hz, 3F), −73.71 (d, *J*=6.5 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.99, 169.22, 162.87, 144.04, 142.97, 136.30, 136.24, 128.63, 128.61, 128.35, 128.33, 128.01, 127.96, 125.29, 123.70, 122.35, 94.89, 74.76, 74.65, 72.01, 71.88, 70.16, 64.51, 42.51, 22.44; IR (thin film) ν_{max} 3066, 2962, 1745, 1707, 1662, 1272, 982 cm^{-1}; MS (ESI) *m*/*z* 649 [M+H]$^+$; HRMS (ESI) calcd for $C_{30}H_{30}O_9F_6Na$: 671.1682, found: 671.1686.

3.13. Bn ether of trifluoromethylated analog of macrosphelide A (21)

To a stirring solution of dicyclohexylcarbodiimide (DCC) (79 mg, 0.39 mmol), 4-dimethylaminopyridine (DMAP) (47 mg, 0.39 mmol) and 4-dimethylaminopyridine hydrochloride (61 mg, 0.39 mmol) in ethanol-free chloroform (2 mL) at 0 °C was added via syringe pump a solution of **20** (50 mg, 0.077 mmol) in ethanol-free chloroform (14 mL) over a period of 5 h. Warming up to room temperature, the mixture was stirred overnight. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=6:1) to give **21** (24 mg, 50%) as an oil. $[\alpha]_D^{20}$ +55.1 (*c* 0.950, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.39 (m, 10H), 6.66–6.85 (m, 2H), 6.02–6.13 (m, 2H), 5.36–5.48 (m, 3H), 4.57–4.66 (m, 2H), 4.40–4.50 (m, 2H), 4.30–4.38 (m, 1H), 4.25–4.29 (m, 1H), 2.65–2.69 (m, 2H), 1.32 (d, *J*=6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.96 (d, *J*=6.5 Hz, 3F), −74.12 (d, *J*=6.5 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.26, 163.59, 162.04, 144.51, 142.07, 136.31, 136.11, 128.61, 128.56, 128.35, 128.27, 128.07, 127.83, 123.84, 121.51, 121.23, 74.84, 74.51, 72.27, 72.09, 72.16, 67.27, 40.11, 19.38; IR (thin film) ν_{max} 2927, 2855, 1747, 1662, 1272, 982 cm^{-1}; MS (ESI) *m*/*z* 648 [M+NH$_4$]$^+$; HRMS (ESI) calcd for $C_{30}H_{28}O_8F_6Na$: 653.1578, found: 653.1581.

3.14. Trifluoromethylated analog of macrosphelide A (1)

To a solution of **21** (24 mg, 0.038 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added BCl_3 (0.38 mL, 1.0 M in toluene, 0.38 mmol) dropwise. After stirring for 0.5 h, the reaction was quenched with methanol at −78 °C. Warming up to room temperature, the mixture was stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=2:1) to provide **1** (15 mg, 90%) as a white solid. $[\alpha]_D^{20}$ −43.9 (*c* 0.350, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.86 (dd, *J*=15.3, 5.7 Hz, 1H), 6.79 (dd, *J*=15.6, 5.1 Hz, 1H), 6.15 (dd, *J*=15.3, 1.2 Hz, 1H), 5.98 (dd, *J*=15.9, 1.5 Hz, 1H), 5.26–5.34 (m, 2H), 5.18–5.23 (m, 1H), 4.61–4.66 (m, 1H), 2.26–2.81 (m, 2H), 1.25 (d, *J*=2.1 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.72 (d, *J*=7.6 Hz, 3F), −75.08 (d, *J*=7.3 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3OD) δ 168.81, 164.49, 162.89, 147.30, 144.85, 136.31, 136.11, 122.68, 121.33, 71.87, 70.47, 67.40, 39.29, 18.10; IR (thin film) ν_{max} 2927, 1747, 1728, 1662, 1388, 1272, 982 cm^{-1}; MS (ESI) *m*/*z* 451 [M+H]$^+$; HRMS (ESI) calcd for $C_{16}H_{16}O_8F_6Na$: 473.0650, found: 473.0642.

3.15. (*R*)-4-((*S*)-1-(Methoxymethoxy)ethyl)-2,2-dimethyl-1,3-dioxolane (23a)

To a suspension of NaH (60% in oil, 575 mg, 14.4 mmol) in anhydrous THF (50 mL) was added a solution of **9** (2.10 g,

14.4 mmol) in anhydrous THF (20 mL) slowly at 0 °C. After the mixture was stirred for 30 min at the same temperature, it was allowed to warm to room temperature and stirred for 30 min. Then the resulting reaction mixture was cooled to 0 °C, and treated with MOMCl (1.28 g, 15.8 mmol). After stirring at room temperature for 20 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=8:1) to afford **23a** (2.00 g, 73%) as a clear oil and recovered **9** (15% recovery). $[\alpha]_D^{26}$ +19.1 (*c* 1.400, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (dd, *J*=18.9, 6.9 Hz, 2H), 3.92–4.04 (m, 2H), 3.78–3.82 (m, 1H), 3.63–3.71 (m, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 3.31 (s, 3H), 1.16 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 109.21, 95.23, 78.78, 73.49, 66.45, 55.41, 26.45, 25.28, 16.63; IR (thin film) ν_{max} 2927, 1189 cm^{-1}; MS (ESI) *m/z* 191 $[M+H]^+$; HRMS (ESI) calcd for $C_9H_{18}O_4Na$: 213.1103, found: 213.1115.

3.16. (2*R*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-(methoxymethoxy)butan-2-ol (24)

A mixture of **23a** (1.52 g, 8.0 mmol) and 75% of aqueous AcOH (40 mL) was stirred at room temperature for 15 h. The solvent was then removed in vacuo. To a 0 °C solution of the residue and DMAP (98 mg, 0.80 mmol) in DMF (40 mL) was added imidazole (654 mg, 9.6 mmol), followed by TBDMSCl (1.21 g, 8.0 mmol). Then, the mixture was stirred for 30 h at 0 °C. EtOAc (80 mL) was added and the resulting mixture was washed with brine. The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (petroleum ether) to afford **24** (1.59 g, 75%) as a clear oil. $[\alpha]_D^{27}$ +16.5 (*c* 1.600, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.61–4.71 (m, 2H), 3.49–3.77 (m, 4H), 3.35 (s, 3H), 2.51 (br, 1H), 2.21 (d, *J*=5.7 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 95.40, 75.02, 74.32, 63.84, 55.45, 25.86, 18.26, −5.39, −5.41; IR (thin film) ν_{max} 3510, 2934, 1260, 838 cm^{-1}; MS (ESI) *m/z* 287 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{28}SiO_4Na$: 287.1655, found: 287.1663.

3.17. ((2*R*,3*S*)-2-(Benzyloxy)-3-(methoxymethoxy)-butoxy)(*tert*-butyl)dimethylsilane (25)

It was prepared using the same condition as described for compound **15**, clear oil. $[\alpha]_D^{26}$ +21.1 (*c* 1.260, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.35 (m, 5H), 4.61–4.80 (m, 5H), 3.85–3.89 (m, 1H), 3.68–3.81 (m, 2H), 3.36 (s, 3H), 1.19 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); IR (thin film) ν_{max} 2948, 1272, 1176, 837 cm^{-1}; MS (ESI) *m/z* 377 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.52; H, 9.59.

3.18. (4*R*,5*S*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-(methoxymethoxy)hex-2-enoate (7)

To an ice-cold solution of **25** (636 mg 1.8 mmol) in THF (10 mL) was added a solution of TBAF (1.8 mL, 1.0 M in THF, 1.8 mmol) dropwise. After the mixture was warmed to room temperature, the reaction was stirred for 1 h. Filtration of the mixture and removal of the solvent in filtrate in vacuo gave a residue, which was used without further purification. The above residue and trichloroisocyanuric acid (TCCA) (497 mg, 2.14 mmol) were dissolved in CH_2Cl_2 (10 mL), then, to this solution was added 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (3 mg, 0.018 mmol) at 0 °C. After the mixture was warmed to room temperature, the reaction was stirred for 15 min. Filtration of the mixture and removal of the solvent in filtrate in vacuo gave a residue. Then, $Ph_3PCHCO_2CH_2CCl_3$ (1.22 g, 2.70 mmol) was added to a solution of the residue in CH_2Cl_2 (10 mL) at 0 °C. Warming up to room temperature, the mixture was stirred overnight. Et_2O (20 mL) was added and the resulting mixture was washed with water and brine, and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the resultant residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=15:1) to give ester **7** (481 mg, 70%) as a clear oil. $[\alpha]_D^{20}$ −43.8 (*c* 0.950, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 7.12 (dd, *J*=15.9, 5.7 Hz, 1H), 6.20 (d, *J*=15.9 Hz, 1H), 4.82 (s, 2H), 4.49–4.69 (m, 4H), 3.97–4.00 (m, 1H), 3.85–3.89 (m, 1H), 3.34 (s, 3H), 1.22 (d, *J*=5.7 Hz, 3H); IR (thin film) ν_{max} 2958, 1741, 1660, 1273 cm^{-1}; MS (ESI) *m/z* 411 $[M+H]^+$. Anal. Calcd for $C_{17}H_{21}O_5Cl_3$: C, 49.59; H, 5.14. Found: C, 49.70; H, 5.31.

3.19. (4*R*,5*S*,*E*)-4-(Benzyloxy)-5-(methoxymethoxy)-hex-2-enoic acid (26)

It was prepared using the same condition as described for compound **16**, clear oil. $[\alpha]_D^{27}$ −54.4 (*c* 0.750, $CHCl_3$); ^1H NMR (300 MHz, CD_3COCD_3) δ 7.28–7.41 (m, 5H), 6.93 (dd, *J*=15.9, 6.3 Hz, 1H), 6.09 (d, *J*=15.9 Hz, 1H), 4.52–4.68 (m, 4H), 4.07–4.10 (m, 1H), 3.85–3.93 (m, 1H), 3.30 (s, 3H), 1.18 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 167.16, 145.61, 137.51, 127.86, 127.17, 123.19, 94.76, 80.63, 74.02, 70.92, 54.84, 15.90; IR (thin film) ν_{max} 3200, 2907, 1703, 1662 cm^{-1}; MS (ESI) *m/z* 451 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{16}O_8F_6Na$: 473.0650, found: 473.0642.

3.20. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-((4*R*,5*S*,*E*)-4-(benzyloxy)-5-hydroxyhex-2-enoyloxy)-6,6,6-trifluorohex-2-enoate (28)

To a solution of DCC (28 mg, 0.13 mmol) and DMAP (16 mg, 0.13 mmol) in CH_2Cl_2 (0.6 mL) was added a solution of **26** (30 mg, 0.11 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C. After stirring for 30 min at 0 °C, a solution of **17** (45 mg, 0.09 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise to the mixture. The solution was stirred for 6 h at room temperature. Filtration of the mixture and removal of the solvent in filtrate in vacuo gave a crude product (30 mg, 40%), which was used without further purification. To a solution of the crude product in CH_2Cl_2 (1.0 mL) was added CF_3COOH (0.3 mL). The solution was stirred at room temperature for 8 h and concentrated. The resulting oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=8:1) to afford **28** (25 mg, 90%) as a clear oil. $[\alpha]_D^{27}$ +33.6 (*c* 1.250, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.40 (m, 10H), 6.93 (dt, *J*=15.6, 6.0 Hz, 2H), 6.25 (d, *J*=15.9 Hz, 1H), 6.13 (d, *J*=15.9 Hz, 1H), 5.62–5.71

(m, 1H), 4.81 (s, 2H), 4.55–4.70 (m, 3H), 4.38–4.45 (m, 2H), 3.73–3.83 (m, 2H), 3.34 (br, 1H), 1.15 (d, J=6.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.88 (d, J=6.8 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.42, 163.14, 147.96, 143.50, 137.09, 136.20, 128.55, 128.45, 128.26, 128.05, 127.93, 127.85, 123.83, 122.77, 121.70, 94.68, 83.02, 75.03, 74.00, 71.88, 71.82, 70.35, 69.27, 18.30; IR (thin film) ν_{max} 3225, 2972, 1744, 1656 cm^{-1}; MS (ESI) m/z 656 $[M+NH_4]^+$; HRMS (ESI) calcd for $C_{28}H_{28}O_7F_3Cl_3Na$: 661.0739, found: 661.0742.

3.21. (4*R*,5*R*,*E*)-2,2,2-Trichloroethyl-4-(benzyloxy)-5-((4*R*,5*S*,*E*)-4-(benzyloxy)-5-((*S*)-3-(*tert*-butyldimethylsilyloxy)butanoyloxy)hex-2-enoyloxy)-6,6,6-trifluorohex-2-enoate (29)

It was prepared using the same condition as described for compound **4**, clear oil. $[\alpha]_D^{25}$ +10.4 (c 1.050, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.41 (m, 10H), 6.94 (dt, J=15.9, 6.3 Hz, 2H), 6.18 (d, J=15.9 Hz, 1H), 6.11 (d, J=15.9 Hz, 1H), 5.59–5.70 (m, 1H), 4.74 (s, 2H), 4.48–4.66 (m, 3H), 4.39–4.43 (m, 1H), 4.22–4.29 (m, 1H), 4.08–4.11 (m, 1H), 2.46–2.53 (m, 1H), 2.31–2.38 (m, 1H), 1.17 (d, J=6.0 Hz, 6H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.89 (d, J=6.8 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.92, 163.59, 163.34, 147.23, 143.58, 137.20, 136.33, 128.65, 128.55, 128.39, 128.32, 127.94, 127.86, 121.66, 121.26, 120.86, 94.82, 78.70, 74.75, 74.17, 72.09, 71.99, 70.62, 70.01, 64.27, 43.03, 25.07, 22.48, 15.58, −4.58, −5.01; IR (thin film) ν_{max} 2959, 1744, 1656, 1252 cm^{-1}; MS (ESI) m/z 861 $[M+Na]^+$; HRMS (ESI) calcd for $C_{38}H_{48}SiO_9F_3Cl_3Na$: 861.1972, found: 861.1985.

3.22. (4*R*,5*R*,*E*)-4-(Benzyloxy)-5-((4*R*,5*S*,*E*)-4-(benzyloxy)-5-((*S*)-3-hydroxybutanoyloxy)hex-2-enoyloxy)-6,6,6-trifluorohex-2-enoic acid (30)

It was prepared using the same condition as described for compound **20**, clear oil. $[\alpha]_D^{25}$ +58.9 (c 0.250, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.28–7.38 (m, 10H), 6.84 (dd, J=15.6, 6.6 Hz, 2H), 6.21 (d, J=15.6 Hz, 2H), 5.64–5.73 (m, 2H), 4.56–4.70 (m, 5H), 4.15–4.23 (m, 2H), 4.31–3.42 (br, 2H), 2.50–2.64 (m, 3H), 1.19 (d, J=6.3 Hz, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.71 (d, J=6.8 Hz, 3F); IR (thin film) ν_{max} 3076, 2964, 1745, 1666 cm^{-1}; MS (ESI) m/z 617 $[M+Na]^+$. Anal. Calcd for $C_{30}H_{33}O_9F_3$: C, 60.60; H, 5.59. Found: C, 60.46; H, 5.29.

3.23. Bn ether of trifluoromethylated analog of macrosphelide A (31)

It was prepared using the same condition as described for compound **21**, clear oil. $[\alpha]_D^{25}$ −36.3 (c 0.260, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.39 (m, 10H), 6.72 (dt, J=15.6, 6.3 Hz, 2H), 6.04 (dd, J=15.6, 6.3 Hz, 2H), 5.38–5.42 (m, 1H), 5.19–5.25 (m, 1H), 4.97–5.02 (m, 1H), 4.31–4.58 (m, 5H), 4.16–4.19 (m, 1H), 2.56 (d, J=5.7 Hz, 2H), 1.30 (d, J=6.3 Hz, 3H), 1.11 (d, J=6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.07 (d, J=6.8 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.20, 165.09, 163.18, 147.56, 143.38, 137.38, 136.93, 128.61, 128.56, 128.35, 128.27, 127.98, 127.83, 123.84, 122.35, 121.23, 75.52, 74.85, 72.17, 72.09, 71.86, 69.95, 65.81, 40.93, 23.64, 18.48; IR (thin film) ν_{max} 3032, 2927, 1749, 1664 cm^{-1}; MS (ESI) m/z 577 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{31}O_8F_3Na$: 599.1869, found: 599.1872.

3.24. Trifluoromethylated analog of macrosphelide A (2)

It was prepared using the same condition as described for compound **1**, white solid. $[\alpha]_D^{25}$ −72.5 (c 0.560, CH_3COCH_3); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.02 (dd, J=15.6, 3.6 Hz, 1H), 6.78 (dd, J=15.6, 5.4 Hz, 1H), 6.07 (dd, J=15.6, 7.2 Hz, 2H), 5.28–5.35 (m, 1H), 5.14–5.21 (m, 1H), 4.95–5.02 (m, 1H), 4.69–4.83 (m, 1H), 4.49–4.52 (m, 1H), 2.57–2.61 (m, 2H), 1.35 (d, J=6.3 Hz, 3H), 1.17 (d, J=6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.77 (d, J=6.2 Hz, 3F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.90, 167.64, 166.08, 148.36, 145.98, 137.62, 136.13, 121.93, 76.12, 74.05, 71.45, 66.85, 66.01, 40.06, 23.62, 16.18; IR (thin film) ν_{max} 3462, 2924, 1746, 1663, 1388, 1275, 1148 cm^{-1}; MS (ESI) m/z 414 $[M+NH_4]^+$; HRMS (ESI) calcd for $C_{16}H_{19}O_8F_3Na$: 419.0924, found: 419.0924.

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References and notes

1. (a) Cragg, G. M.; Newman, D. J. *Pure Appl. Chem.* **2005**, *77*, 7; (b) Bulter, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162; (c) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.
2. (a) Tiztze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996; (b) Rouhi, A. M. *Chem. Eng. News* **2003**, 77; (c) Paterson, I.; Anderson, E. *Science* **2005**, *310*, 451; (d) Koehn, F.; Carter, G. T. *Nat. Rev. Drug Discov.* **2005**, *4*, 206.
3. Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X. Y.; Danishefsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 1038.
4. For recent reviews, see: (a) Begue, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992; (b) Ojima, I. *ChemBioChem* **2004**, *5*, 628.
5. For excellent overviews, see: (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004; (b) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.
6. (a) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T. C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913; (b) Rivkin, A.; Chou, T. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2838; (c) Cho, Y. S.; Wu, K. D.; Moore, M. A.; Chou, T. C.; Danishefsky, S. J. *Drugs Future* **2005**, *30*, 737; (d) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329.
7. Hayashi, M.; Kim, Y. P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435.
8. (a) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1997**, *119*, 10247; (b) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett.*

2000, *41*, 1559; (c) Kobayashi, Y.; Kumar, B. G.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011; (d) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 4381; (e) Ono, M.; Nakamura, H.; Konno, F.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2753; (f) Nakamura, H.; Ono, M.; Shiba, Y.; Akita, H. *Tetrahedron: Asymmetry* **2002**, *13*, 705; (g) Nakamura, H.; Ono, M.; Makino, M.; Akita, H. *Heterocycles* **2002**, *57*, 327; (h) Sharma, G. V. M.; Mouli, C. C. *Tetrahedron Lett.* **2002**, *43*, 9159; (i) Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939; (j) Kawaguchi, T.; Funamori, N.; Matsuya, Y.; Nemoto, H. *J. Org. Chem.* **2004**, *69*, 505; (k) Peak, S.-M.; Seo, S.-Y.; Kim, S.-H.; Jung, J.-W.; Lee, Y.-S.; Jung, J.-K.; Suh, Y.-G. *Org. Lett.* **2005**, *7*, 3159.

9. (a) Takahashi, T.; Kusaka, S.-i.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230; (b) Ishihara, K.; Kawaguchi, T.; Matsuya, Y.; Sakurai, H.; Saiki, I.; Nemoto, H. *Eur. J. Org. Chem.* **2004**, *19*, 3973; (c) Matsuya, Y.; Kawaguchi, T.; Ishihara, K.; Ahmed, K.; Zhao, Q. L.; Kondo, T.; Nemoto, H. *Org. Lett.* **2006**, *8*, 4609.
10. Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
11. (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163; (b) Liu, L.; Tanake, R. S.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 5332.
12. (a) Wang, B. L.; Yu, F.; Qiu, X. L.; Jiang, Z. X.; Qing, F. L. *J. Fluorine Chem.* **2006**, *127*, 580; (b) Jiang, Z. X.; Qin, Y. Y.; Qing, F. L. *J. Org. Chem.* **2003**, *68*, 7544.
13. Jiang, Z. X.; Qing, F. L. *J. Org. Chem.* **2004**, *69*, 5486.
14. Just, G.; Grozinger, K. *Synthesis* **1976**, 457.
15. (a) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394; (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.
16. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
17. Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.
18. Zhang, X.; Xia, H.; Dong, X. C.; Jin, J.; Meng, W. D.; Qing, F. L. *J. Org. Chem.* **2003**, *68*, 9026.
19. Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041.