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Stereoselective 6-exo Radical Cyclization Using *cis*-Vinyl Sulfoxide: Practical Total Synthesis of CTX3C

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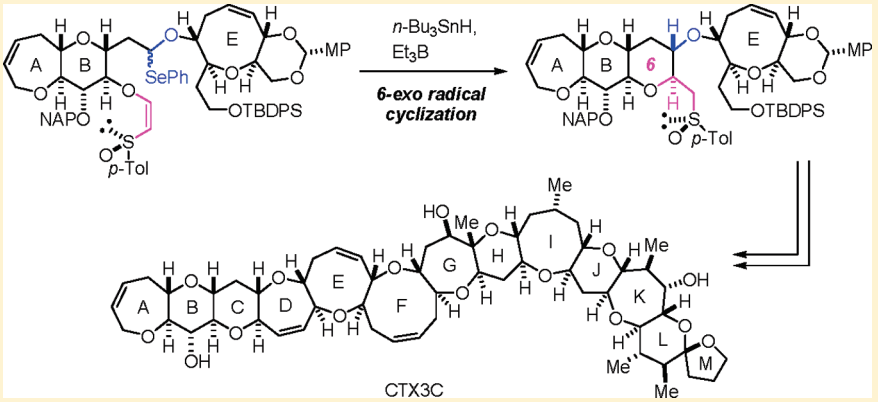
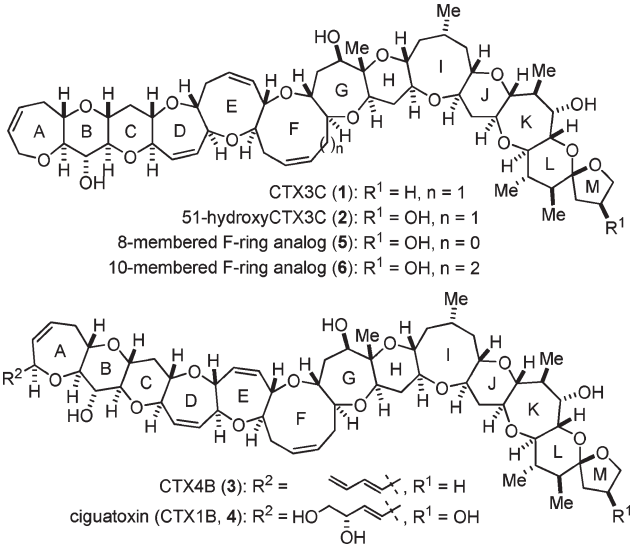
Supporting Information

ABSTRACT: Ciguatoxins, the principal causative toxins of ciguatera seafood poisoning, are large ladder-like polycyclic ethers. We report a highly stereoselective 6-exo radical cyclization/ring-closing olefin metathesis sequence to construct the *syn*/*trans*-fused polyether system. The new method was applied to the practical synthesis of ciguatoxin CTX3C.



Ciguatera seafood poisoning is a foodborne illness that afflicts more than 50 000 people annually in tropical and subtropical areas.[1] Ciguatoxins are regarded as the causative toxins of ciguatera (**1**−**4**).[2] Yasumoto and co-workers demonstrated that these toxins are originally produced by an epiphytic dinoflagellate, *Gambierdiscus toxicus*, and are transferred to various fish and eventually to humans by the food chain.[3] In 1989, the Yasumoto group successfully determined the structures of ciguatoxins CTX4B (**3**) and CTX1B (**4**), which were found to be large ladder-like polycyclic ethers 3 nm in length with 13 rings ranging from five- to nine-membered.[4] Subsequently, more than 20 ciguatoxin congeners were structurally identified, including CTX3C (**1**) and 51-hydroxyCTX3C (**2**).[5] Ciguatoxins exhibit their potent toxicities (LD_{50} = 0.25−4 μg/kg, mice) by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes.[6−8] However, the very limited supply of ciguatoxins from natural sources has hampered detailed biological studies and the development of therapeutic treatments for ciguatera.

The unique bioactivities and intriguing molecular structures of the ciguatoxins prompted us to investigate their synthesis. We have successfully achieved the total syntheses of three important congeners (**1**, **2**, and **4**)[9] and the analogues (**5**, **6**)[10] utilizing a unified strategy. These synthetic ciguatoxins and their fragments enabled us to develop anti-ciguatoxin antibodies as well as sandwich enzyme-linked immunosorbent assay (ELISA) detection methods without cross-reactivity against other marine toxins.[11] SAR and electrophysiological studies using the synthetic materials were also performed in order to understand ciguatoxin−VSSC interactions.[10,12] However, more practical and secure methods to prepare sufficient amounts of congeners and analogues are still required for further detailed studies.



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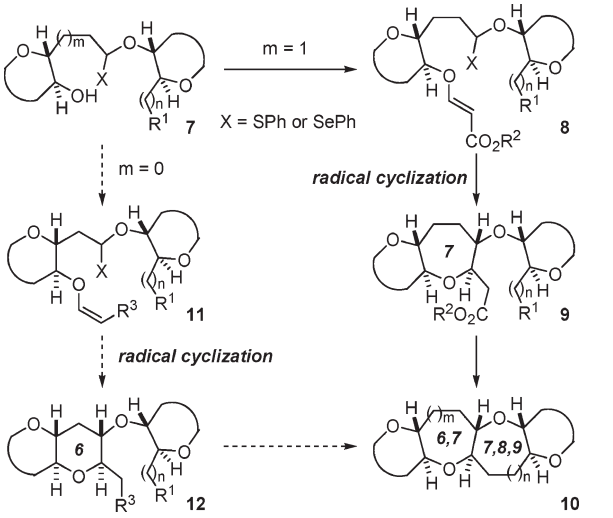
Scheme 1. Complementary Radical Routes for Construction of *trans*-Fused Polyether Systems



Recently, we developed two efficient routes for constructing *trans*-fused polyethers based on *O*,*S*-acetal intermediates: (i) an acyl radical cyclization/reductive etherification sequence for 6/6- and 7/6-rings;[13] (ii) a 7-exo radical cyclization/ring-closing olefin metathesis (RCM) sequence for 7/7-, 7/8-, and 7/9-ring systems (**8** → **9** → **10**, Scheme 1).[9,14] While the former acyl radical cyclization can create six- and seven-membered rings, the latter radical reaction affords only seven-membered ethers. To increase the utility and diversity of the radical cyclization/RCM strategy, a complementary method for assembling 6/7- and 6/8-membered ring systems (**11** → **12** → **10**, Scheme 1), which are inaccessible by the previous methodologies, was investigated. Herein, we describe the development of a *trans*-selective 6-exo radical reaction leading to such systems and its application to the practical total synthesis of **1**.

RESULTS AND DISCUSSION

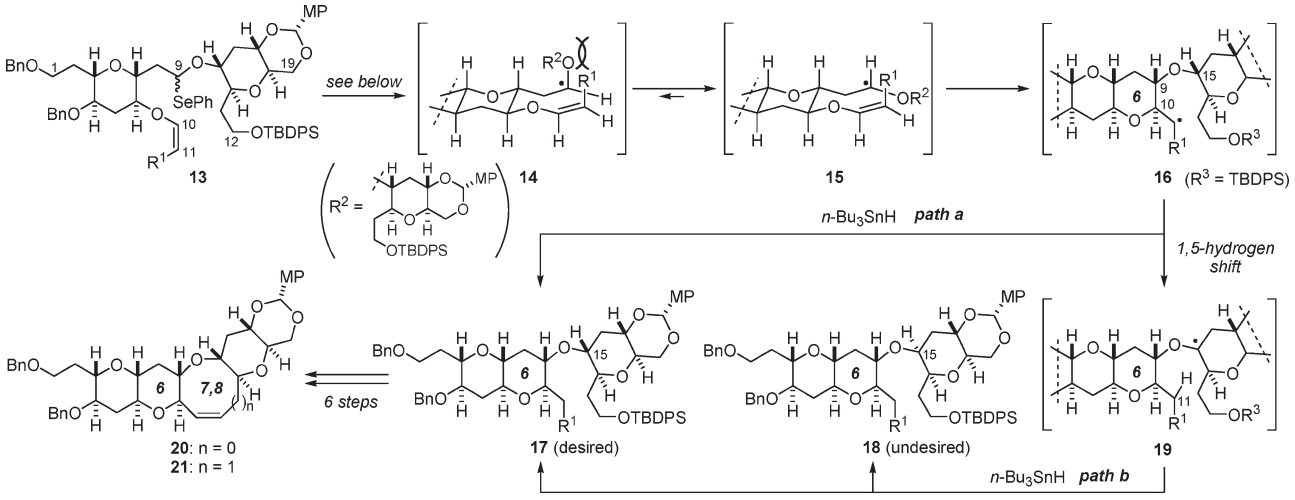
We first investigated the *trans*-selective radical cyclization using model compounds (Table 1).[15] Previously, the Sasaki and Tachibana group reported that the 6-exo radical cyclization using a *trans*-acrylate selectively provided the undesired *cis*-substituted pyran ring.[16] With this result in mind, we examined the reaction using *cis*-olefins as radical acceptors. It was envisioned that an α-oxy radical, generated from *O*,*Se*-acetal **13**, would react with a radical acceptor through the transition state **15** to alleviate the steric repulsion between bulky R^1 and R^2O groups in **14**, resulting in *trans*-substituted pyran ring **17** via **16** (path a). Indeed, when **13a** [R^1 = *p*-tolyl (*S*)-sulfoxide] was treated with *n*-Bu_3SnH and Et_3B in benzene at room temperature (entry 1), we found that the tetracyclic compound **17a** with the desired configurations was obtained in 59% yield. Unfortunately, an isomeric product was also obtained in 23% yield, which was determined to be the C15-epimer **18a** by NMR experiments. These observations can be explained by the proposed mechanism (paths a and b) in Table 1. While the 6-exo cyclization should proceed with complete stereocontrol at both C9 and C10, the resultant intermediate **16** appeared to undergo, in addition to a direct formation of **17** (path a), the unexpected 1,5-hydrogen atom transfer from C15 to C11 to generate tertiary radical **19**. The intermediacy of **19** would result in the formation of **17** and **18** via unselective hydrogen addition (path b). Attempts to improve the stereoselectivity of this reaction using (*R*)-sulfoxide **13b** (entry 2), bulky mesityl sulfoxide **13c** (entry 3), and sulfone **13d** (entry 4) led to unfruitful results. The corresponding *cis*-methylacrylate (R^1 = CO_2Me) could not be prepared. After careful screening of substrates and conditions, we finally found that treatment of **13a** with *n*-Bu_3SnH and Et_3B in toluene at low temperature provided **17a** almost exclusively in high yield (entry 5).[17] Sulfoxide **17a** was successfully converted to 6/7- and 6/8-ring systems (**20** and **21**, respectively), both in six steps.[18]

Having successfully established the new method, we applied it to the synthesis of CTX3C (**1**). The modified synthesis of the E-ring moiety of **1** is shown in Scheme 2. Ester **22** was prepared from D-glucose according to known procedures.[19] Alkylation of **22** with iodide **23**[20] gave **24** as a 1.2:1 diastereomeric mixture. DIBAL reduction of ester **24** and nucleophilic addition of allylmagnesium bromide to the corresponding aldehyde afforded alcohol **25** in 56% yield. RCM reaction of **25** using Grubbs' first-generation catalyst **26**[21] provided the eight-membered E-ring **27** (56%) with recovery of the starting material (21%). Diastereomeric mixture **27** was oxidized using Dess−Martin periodinane[22] and then was isomerized at the C15 position to provide the desired ketone **28** in 86% overall yield. After several experiments, we found that DIBAL reduction of **28** at low temperature afforded E-ring alcohol **29** in 87% yield.

The coupling partner of **29** was easily prepared from the known AB-ring **30**[13b] (Scheme 3). After the protection of secondary alcohol **30** as its TES ether, DIBAL reduction of **31** led to the aldehyde, which was oxidized to carboxylic acid **32** in 79% overall yield. Efficient condensation of AB-ring carboxylic acid **32** and E-ring alcohol **29** was realized using the Yamaguchi protocol[23] to produce the ester **33** in 95% yield. Following Rychnovsky's report,[24] acetal **34** was prepared by DIBAL reduction of ester **33** and subsequent acetylation of the resulting hemiacetal. Selective *O*,*Se*-acetal formation was successfully accomplished by the action of *i*-$Bu_2AlSePh$[25,16] to provide **35** without destruction of the *p*-anisyl (MP) acetal moiety. Treatment of **35** with TBAF at low temperature gave secondary alcohol **37** along with the corresponding diol **36**, which was selectively protected with TBDPS chloride to deliver **37** in 92% combined yield from **35**. The reaction of lithium alkoxide, which was generated from alcohol **37** and MeLi, with acetylene sulfoxide (*S*)-**38**[26] furnished the *cis*-oriented radical acceptor **39**. Treatment of **39** under the optimum radical conditions exclusively constructed the desired six-membered ring **40** in 86% yield. Pummerer rearrangement[27] of sulfoxide **40** and Wittig reaction of the resulting aldehyde afforded olefin **41**. Three-step conversion of **41** to the terminal diene **42** was conducted in 97% overall yield. Finally, RCM reaction of **42** and subsequent acid treatment produced the ABCDE-ring diol **43**, which afforded the left wing **44** according to the previously reported protocol.[13b]

Total synthesis of **1** was completed as shown in Scheme 4. The left wing **44** was assembled with the right wing α-chlorosulfide **46**, generated from sulfide **45**,[9c] by the action of AgOTf and DTBMP to furnish *O*,*S*-acetal **47** in 70% yield.[9e,14,28] After the TIPS group of **47** was removed, the pentafluorophenyl acrylate was installed to the resulting secondary alcohol **48** and gave **49** in 86% overall yield. We previously demonstrated that the electron-withdrawing pentafluorophenyl group promoted 7-exo radical cyclization over the entropically favored 6-exo cyclization by enhancing SOMO/LUMO interactions.[9g] Actually, treatment of **49** with AIBN and *n*-Bu_3SnH formed the G-ring stereoselectively

Table 1. Development of 6-exo Radical Cyclization



Entry	R^1		Conditions	Yield of **17**	Yield of **18**	**17**:**18**
1	*p*-Tol (*S*)	**13a**	*n*-Bu_3SnH, Et_3B, air, benzene, RT	59% (**17a**)	23% (**18a**)	2.6:1
2	*p*-Tol (*R*)	**13b**	*n*-Bu_3SnH, Et_3B, air, benzene, RT	39% (**17b**)	28% (**18b**)	1.4:1
3	Mes (*S*)	**13c**	*n*-Bu_3SnH, Et_3B, air, benzene, RT	39% (**17c**)	18% (**18c**)	2.2:1
4	*p*-Tol	**13d**	*n*-Bu_3SnH, Et_3B, air, benzene, RT	40% (**17d**)	34% (**18d**)	1.2:1
5	*p*-Tol (*S*)	**13a**	*n*-Bu_3SnH, Et_3B, air, toluene, -40 to -15 °C	86% (**17a**)	trace (**18a**)	>15:1

in 74% yield along with a small amount of 6-exo product **51** (7%). The resulting carboxylic acid **50** was converted to pentaene **52** through a three-step functional group manipulation. Lastly, the RCM reaction constructed the nine-membered F-ring, and oxidative removal of the three 2-naphthylmethyl (NAP)[9b,29] groups using DDQ provided **1** in 59% yield from **52**.

In summary, we have devised an efficient method to construct polyether systems through a 6-exo radical cyclization of a *cis*-vinyl sulfoxide and subsequent RCM reaction. This neutral and reliable reaction sequence secures multimilligram quantities of **1**. The strategy developed here will facilitate the practical total syntheses of ciguatoxin congeners and other polycyclic ethers.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates. Column chromatography was performed using 100−210 μm silica gel 60N (Kanto Chemical Co., Inc.), and for flash column chromatography 40−50 μm silica gel 60N (Kanto Chemical Co., Inc.) was used. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Optical rotations were recorded on a JASCO P-2200 polarimeter. ^{1}H NMR spectra were recorded on Varian INOVA 500 (500 MHz) and Varian 400-MR (400 MHz) spectrometers. Chemical shifts are reported in δ (ppm) downfield from tetramethylsilane with reference to solvent signals [^{1}H NMR: $CHCl_3$ (7.26), C_6D_5H (7.16), C_5HD_4N (7.56); ^{13}C NMR: $CDCl_3$ (77.16), C_6D_6 (128.06), C_5D_5N (123.5)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. MALDI-TOF MS spectra were measured on an Applied Biosystems Voyager DE STR SI-3 instrument. High-resolution mass spectra were measured on a Themo Fisher Scientific Orbitrap Discovery (ESI LTQ Orbitrap).

Vinyl Sulfoxide 39. To a solution of alcohol **37** (47.5 mg, 43.9 μmol) in THF (1.0 mL) at −78 °C was added MeLi (0.96 M in Et_2O, 82.3 μL, 79 μmol) and warmed to room temperature. After being stirred for 1 h, the mixture was slowly added to sulfoxide (*S*)-**38** (21.6 mg, 132 μmol) in THF (0.5 mL). After being stirred for 40 min, the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc, 10:1−2:1) gave vinyl sulfoxide **39** (45.7 mg, 36.7 μmol) in 84% yield: colorless, amorphous solid; ^{1}H NMR (400 MHz, C_6D_6) δ 7.84−7.23 (23H, m, MP, NAP, SePh, TBDPS, *p*-Tol), 6.87−6.79 (5H, m, SePh, *p*-Tol), 6.70 (2H, d, J = 8.0 Hz, MP), 6.26 (1/2H, d, J = 5.6 Hz, H12), 6.14 (1/2H, dd, J = 11.2, 4.8 Hz, H19), 6.07 (1/2H, d, J = 5.6 Hz, H12), 6.06 (1/2H, m, H18), 6.02 (1/2H, dd, J = 10.8, 4.4 Hz, H19), 5.87 (1/2H, m, H18), 4.66

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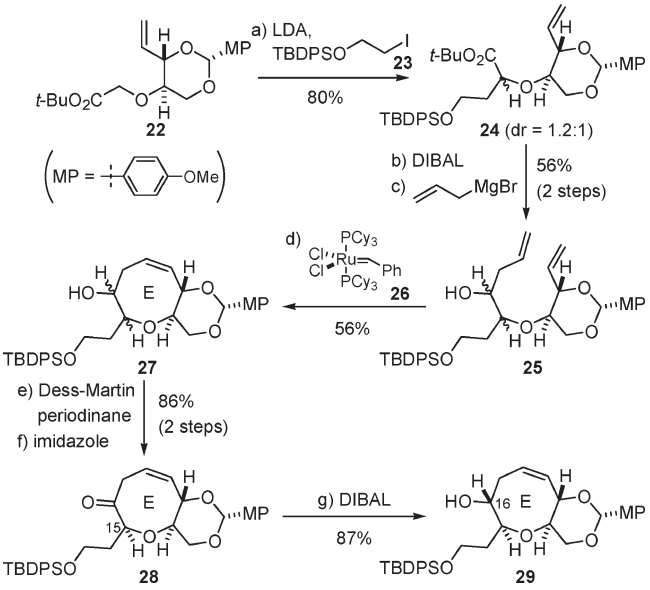
Scheme 2. Synthesis of E-Ring[a]



[a] Reagents and conditions: (a) **23** (1.3 equiv), lithium diisopropylamide (LDA), THF/HMPA (4:1), −78 to −50 °C, 80%; (b) DIBAL, CH_2Cl_2, −78 °C; (c) allylmagnesium bromide, THF, −78 °C, 56% (2 steps); (d) **26**, CH_2Cl_2, 40 °C, 56%; (e) Dess−Martin periodinane, CH_2Cl_2, RT, 87%; (f) imidazole, toluene, 70 °C, 99%; (g) DIBAL, CH_2Cl_2, −95 °C, 87%.

(1/2H, dd, *J* = 6.2, 6.2 Hz, H11), 5.56 (1H, m, H2), 5.54 (1/2H, m, H11), 5.51 (1H, m, H3), 5.31 (1/2H, d, *J* = 5.6 Hz, H13), 5.31 (1/2H, m, MP), 5.25 (1/2H, m, MP), 5.21 (1/2H, d, *J* = 5.6 Hz, H13), 5.08 (1/2H, d, *J* = 11.2 Hz, NAP), 5.05 (1/2H, d, *J* = 11.2 Hz, NAP), 4.76 (1/2H, d, *J* = 11.2 Hz, NAP), 4.74 (1/2H, d, *J* = 11.2 Hz, NAP), 4.28 (1H, m, H20), 4.24 (1/2H, m, H16), 4.11 (1/2H, dd, *J* = 11.2, 5.0 Hz, H22), 4.08 (1/2H, m, H1), 4.03 (1/2H, m, H1), 3.99 (1/2H, m, H15), 3.93−3.87 (3/2H, m, H5, H9, H15), 3.85−3.68 (9/2H, m, H1, H7, H14′×2, H16, H22), 3.63 (1/2H, dd, *J* = 8.8, 8.8 Hz, H7), 3.57 (1/2H, m, H21), 3.53 (1/2H, m, H9), 3.51−3.43 (1H, m, H6, H22), 3.37 (1/2H, dd, *J* = 10.4, 10.4 Hz, H22), 3.30 (1/2H, m, H6), 3.29 (3/2H, s, MP), 3.28 (3/2H, s, MP), 3.28−3.24 (1H, m, H8, H21), 3.24−3.18 (3/2H, m, H5, H8, H17), 2.77 (1/2H, m, H10), 2.71 (1/2H, m, H17), 2.69−2.62 (1H, m, H4, H10), 2.59 (1H, m, H17), 2.46 (1/2H, m, H4), 2.43 (1/2H, m, H14), 2.34 (1/2H, m, H4), 2.30 (1/2H, m, H10), 2.24 (1/2H, m, H4), 2.19 (1/2H, m, H10), 2.09 (1/2H, m, H14), 1.87 (3H, s, *p*-Tol), 1.64 (1/2H, m, H14), 1.54 (1/2H, m, H14), 1.22 (9/2H, s, TBDPS), 1.15 (9/2H, s, TBDPS); HRESIMS *m*/*z* 1269.4081 $[M + Na]^+$ (calcd for $C_{71}H_{78}O_{11}SSeSiNa$ 1269.4092).

Sulfoxide 40. To a mixture of **39** (45.7 mg, 36.7 μmol) and *n*-Bu_3SnH (98.6 μL, 367 μmol) in toluene (12.2 mL) at −78 °C was added Et_3B (1.0 M in THF, 293 μL, 293 μmol). After being stirred for 3 h, the reaction mixture was concentrated and directly subjected to flash column chromatography (hexane/EtOAc, 4:1−1:1) to give sulfoxide **40** (34.3 mg, 31.4 μmol) in 86% yield: colorless oil; $[\alpha]^{28}_D$ −50.2 (*c* 1.25, $CHCl_3$); IR (film) *ν* 2929, 2856, 1616, 1518, 1427, 1387, 1249, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.90−7.81 (4H, m, NAP), 7.68−7.62 (4H, m, TBDPS), 7.58 (2H, d, *J* = 8.0 Hz, *p*-Tol), 7.45 (2H, d, *J* = 8.4 Hz, MP), 7.45−7.38 (9H, m, NAP, TBDPS), 7.19 (2H, d, *J* = 8.0 Hz, *p*-Tol), 6.89 (2H, d, *J* = 8.4 Hz, MP), 5.89 (1H, m, H2), 5.79 (1H, dd, *J* = 10.8, 4.8 Hz, H19), 5.77 (1H, m, H3), 5.63 (1H, m, H18), 5.36 (1H, s, MP), 5.13 (1H, d, *J* = 11.6 Hz, NAP), 5.06 (1H, d, *J* = 11.6 Hz, NAP), 4.37 (1H, dd, *J* = 16.0, 5.8 Hz, H1), 4.35 (1H, m, H20), 4.10 (1H, dd, *J* = 16.0, 1.6 Hz, H1), 3.91 (1H, dd, *J* = 10.8, 5.2 Hz, H22), 3.80 (3H, s, MP), 3.76−3.66 (2H, m, H14′), 3.59 (1H, dd, *J* = 8.4, 8.4 Hz, H7), 3.56 (1H, m, H15), 3.55 (1H, m, H16), 3.53 (1H, m, H11), 3.43 (1H, dd, *J* = 10.8, 10.8 Hz, H22), 3.41 (1H, dd, *J* = 8.4, 8.4 Hz, H6), 3.35 (1H, m, H13), 3.34 (1H, m, H5), 3.32 (1H, m, H21), 3.19 (1H, ddd, *J* = 11.6, 8.8, 4.4 Hz, H9), 3.05 (1H, dd, *J* = 8.8, 8.4 Hz, H8), 3.04 (1H, m, H12), 3.01 (1H, m, H13), 2.66 (1H, m, H4), 2.62 (1H, m, H17), 2.47 (1H, ddd, *J* = 11.6, 4.4, 4.4 Hz, H10), 2.35 (1H, m, H4), 2.32 (1H, m, H17), 2.31 (3H, s, *p*-Tol), 1.95 (1H, m, H14), 1.48 (1H, m, H14), 1.44 (1H, ddd, *J* = 11.6, 11.6, 11.6 Hz, H10), 1.06 (9H, s, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.2 (C, MP), 141.9 (C), 140.4 (C), 136.5 (C), 135.70 (CH, TBDPS), 135.68 (CH, TBDPS), 133.75 (C), 133.68 (C), 133.6 (C), 133.4 (CH, C19), 133.2 (C), 131.4 (CH, C2), 130.3 (C), 130.2 (CH×2, *p*-Tol), 129.88 (CH), 129.86 (CH), 128.11 (CH), 128.05 (CH), 127.93 (CH), 127.88 (CH), 127.8 (CH), 127.6 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 124.6 (CH×2, *p*-Tol), 113.8 (CH×2, MP), 100.9 (CH, MP), 87.4 (CH, C6), 83.8 (CH, C15 or C16), 81.9 (CH, C7), 81.4 (CH, C12), 79.8 (CH, C20), 77.4 (CH, C15 or C16), 77.1 (CH, C5), 76.8 (CH, C8), 75.72 (CH, C21), 75.66 (CH_2, NAP), 75.4 (CH, C11), 72.8 (CH, C9), 69.3 (CH_2, C22), 68.6 (CH_2, C1), 60.7 (CH_2, C13), 60.3 (CH_2, C14′), 55.4 (CH_3, MP), 37.4 (CH_2, C10), 36.8 (CH_2, C14), 34.8 (CH_2, C4), 30.5 (CH_2, C17), 27.1 (CH_3×3, TBDPS), 21.5 (CH_3, *p*-Tol), 19.3 (C, TBDPS); HRESIMS *m*/*z* 1113.4601 $[M + Na]^+$ (calcd for $C_{65}H_{74}O_{11}SSiNa$ 1113.4613).

Pentafluorophenylacrylate 49. To a solution of alcohol **48** (31 mg, 18.2 μmol) and pentafluorophenyl propiolate (17.2 mg, 72.8 μmol) in CH_2Cl_2 (610 μL) at room temperature was added PMe_3 (1.0 M solution in toluene, 36.4 μL, 36.4 μmol). Further pentafluorophenyl propiolate (34.4 mg, 145.6 μmol) and PMe_3 (1.0 M solution in toluene, 72.8 μL, 72.8 μmol) was added. After 1 h, the reaction mixture was concentrated, and column chromatography (hexane/Et_2O, 3:1−0:1, containing 1% Et_3N) gave pentafluorophenylacrylate **49** (33.3 mg, 17.3 μmol) in 95% yield: colorless, amorphous solid; $[\alpha]^{26}_D$ −20.1 (*c* 0.42, CH_2Cl_2); IR (film) *ν* 3055, 2925, 1752, 1638, 1521, 1087, 1006 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ* 7.94−7.00 (33H, m, NAP×4, PhS), 7.75 (1H, d, *J* = 12.0 Hz, H26), 5.96 (1H, ddt, *J* = 16.5, 10.5, 7.0 Hz, H23), 5.95 (1H, m, H13), 5.92 (1H, m, H19), 5.80 (1H, m, H18), 5.78 (1H, m, H14), 5.60 (1H, d, *J* = 12.0 Hz, H25), 5.54 (1H, dddd, *J* = 12.0, 5.5, 3.0, 3.0 Hz, H2), 5.47 (1H, m, H3), 5.35 (1H, dd, *J* = 10.0, 3.5 Hz, H27), 5.22 (1H, d, *J* = 12.5 Hz, NAP), 5.17 (1H, m, H23′), 5.15 (1H, d, *J* = 12.5 Hz, NAP), 5.14 (1H, m, H23′), 5.02 (1H, d, *J* = 12.0 Hz, NAP), 4.91 (1H, d, *J* = 12.0 Hz, NAP), 4.84 (2H, s, NAP), 4.32 (2H, s, NAP), 4.30 (1H, m, H20), 4.22 (1H, ddd, *J* = 11.5, 9.5, 5.0 Hz, H41), 4.12 (1H, dd, *J* = 16.0, 5.5 Hz, H1), 4.11 (1H, m, H31), 4.07 (1H, m, H15), 4.06 (1H, m, H52), 4.00 (1H, t, *J* = 10.0 Hz, H29), 3.99 (1H, d, *J* = 9.5 Hz, H45), 3.81 (1H, dd, *J* = 9.5, 9.5 Hz, H46), 3.80 (1H, m, H52), 3.78 (1H, m, H1), 3.74 (1H, dddd, *J* = 9.0, 2.5, 2.5, 2.5 Hz, H12), 3.65 (1H, dd, *J* = 9.0, 9.0 Hz, H7), 3.65 (1H, d, *J* = 3.0 Hz, H44), 3.46 (1H, dddd, *J* = 8.5, 2.5, 2.5, 2.5 Hz, H16), 3.39 (1H, m, H21), 3.37 (1H, dd, *J* = 9.0, 9.0 Hz, H6), 3.26 (1H, ddd, *J* = 9.0, 9.0, 4.0 Hz, H5), 3.23 (1H, m, H34), 3.19 (1H, dd, *J* = 9.0, 9.0 Hz, H8), 3.06 (1H, m, H42), 3.05 (1H, m, H11), 3.03 (1H, m, H38), 2.91 (1H, ddd, *J* = 12.0, 9.0, 4.5 Hz, H9), 2.87 (1H, m, H39), 2.77 (1H, m, H22), 2.75 (1H, m, H33), 2.63 (1H, m, H28), 2.59 (1H, m, H17), 2.55 (1H, m, H4), 2.53 (1H, m, H43), 2.34 (1H, m, H40), 2.32 (1H, m, H28), 2.30 (1H, m, H10), 2.29 (1H, m, H22), 2.25 (1H, m, H4), 2.23 (1H, m, H50), 2.22 (1H, m, H50), 2.14 (1H, m, H17), 2.04 (1H, m, H47), 2.00 (1H, m, H37), 1.99 (1H, m, H51), 1.88 (1H, m, H32), 1.80 (1H, m, H35), 1.75 (1H, m, H36), 1.72 (1H, m, H51), 1.69 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H40), 1.64 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H10), 1.57 (1H, m, H32), 1.57 (1H, m, H37), 1.55 (1H, m, H48), 1.38 (1H, m, H35), 1.24 (3H, d, *J* = 6.0 Hz, Me56), 1.16 (3H, d, *J* = 7.5 Hz, Me55), 1.14 (3H, d, *J* = 7.0 Hz, Me57), 1.07 (3H, s, Me53), 0.92 (3H, d, *J* = 7.0 Hz, Me54); ^{13}C NMR (125 MHz, C_6D_6) *δ* 165.2, 163.5, 142.8, 139.1, 138.3, 137.8, 136.5, 136.4, 135.9, 135.80, 135.76, 134.01, 133.93, 133.91, 133.7, 133.58, 133.56, 133.3, 131.7, 131.2, 129.2, 128.7, 128.6, 128.5,

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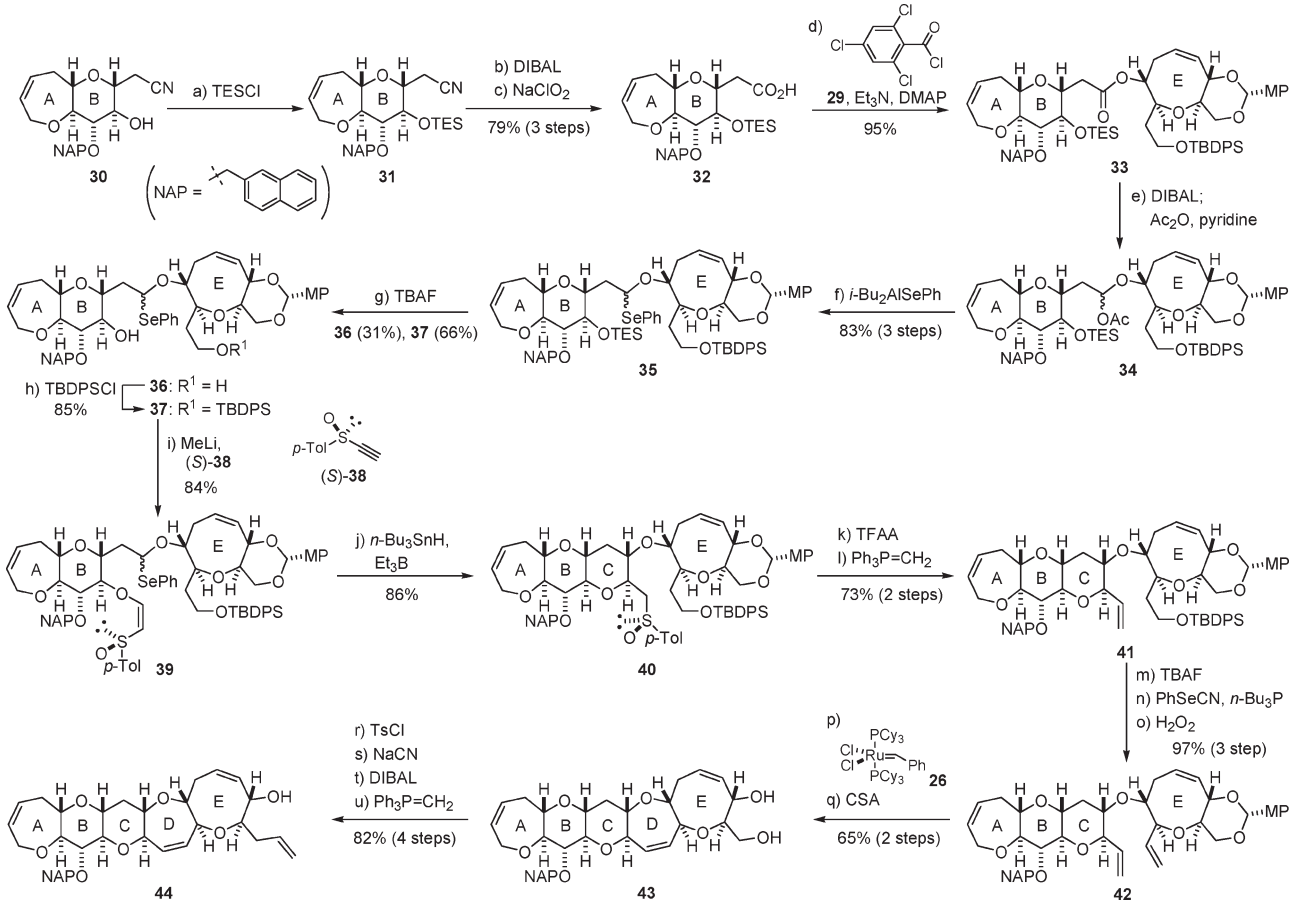
Scheme 3. Synthesis of Left Wing of CTX3C[a]



[a] Reagents and conditions: (a) TESCl, imidazole, DMF, 50 °C; (b) DIBAL, CH_2Cl_2, −78 °C; (c) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), RT, 79% (3 steps); (d) **29** (1.1 equiv), 2,4,6-trichlorobenzoyl chloride, Et_3N, 4-(dimethylamino)pyridine (DMAP), toluene, RT, 95% from **32**; (e) DIBAL, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyridine, CH_2Cl_2, −78 to −60 °C; (f) DIBAL, $(PhSe)_2$, CH_2Cl_2/hexane, 0 °C, 83% (3 steps); (g) TBAF, THF, −30 °C, **36**, 31%; **37**, 66%; (h) TDBPSCl, imidazole, DMF, RT, 85%; (i) (*S*)-**38**, MeLi, THF, −78 °C to RT, 84%; (j) *n*-Bu_3SnH, Et_3B, toluene, −78 °C, 86%; (k) TFAA, pyridine, MeCN, 0 °C; KOAc, H_2O, RT; (l) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 73% (2 steps); (m) TBAF, THF, 40 °C, 99%; (n) PhSeCN, *n*-Bu_3P, THF, RT; (o) H_2O_2(aq), $NaHCO_3$, THF, RT to 40 °C, 98% (2 steps); (p) **26**, CH_2Cl_2, 40 °C; (q) CSA, MeOH/CH_2Cl_2, 65% (2 steps); (r) TsCl, pyridine, 4 Å molecular sieves, RT, 94%; (s) NaCN, DMSO, 45 °C, 97%; (t) DIBAL, CH_2Cl_2, −80 °C; (u) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 90% (2 steps).

128.4, 128.14, 128.12, 128.0, 127.2, 126.9, 126.6, 126.54, 126.51, 126.47, 126.46, 126.36, 126.26, 126.18, 126.15, 126.09, 125.92, 125.87, 125.84, 125.76, 117.5, 109.5, 95.8, 88.4, 87.8, 87.5, 85.6, 85.5, 84.9, 83.7, 82.4, 81.8, 81.7, 81.6, 81.5, 81.0, 79.5, 79.3, 79.1, 78.6, 78.3, 77.8, 77.3, 75.2, 74.7, 74.4, 73.8, 73.4, 73.0, 72.8, 71.8, 71.3, 68.6, 46.6, 46.1, 43.3, 42.2, 41.2, 40.9, 39.2, 38.0, 37.6, 36.3, 35.2, 34.7, 32.9, 30.5, 30.2, 28.4, 27.9, 27.2, 23.1, 20.2, 16.3, 13.8; MALDI-TOF MS *m*/*z* 1785.5879 $[M + Na]^+$ (calcd for $C_{114}H_{119}F_5NaO_{19}S$ 1785.6101).

Pentaene 52. AIBN (7.6 mg, 46 μmol) was added to a degassed solution of pentafluorophenylacrylate **49** (8.8 mg, 4.58 μmol) and *n*-Bu_3SnH (62 μL, 230 μmol) in toluene (4.6 mL). After being stirred for 3 h at 85 °C, the reaction mixture was concentrated, and column chromatography (hexane/EtOAc, 10:1−0:1) gave oxepane carboxylic acid **50** (5.6 mg, 3.4 μmol) in 74% yield and tetrahydropyran **51** (0.6 mg, 0.33 μmol) in 7% yield. To a solution of oxepane carboxylic acid **50** (9.0 mg, 6.04 μmol) in MeOH (400 μL) and benzene (1 mL) at room temperature was added $TMSCHN_2$ (2.0 M solution in hexane, 6 μL, 12 μmol). After being stirred for 30 min at room temperature, the reaction mixture was quenched with AcOH, diluted with EtOAc and saturated aqueous $NaHCO_3$, and extracted with EtOAc (×3). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 10:1−1:1) gave the oxepane methyl ester (9.1 mg, 6.04 μmol) in 100% yield.

To a solution of the above methyl ester (4.4 mg, 2.93 μmol) in CH_2Cl_2 (1.0 mL) at −90 °C was added DIBAL (15 μL, 14.6 μmol). After being stirred for 30 min at −90 °C, the reaction mixture was quenched with EtOAc and aqueous NH_4Cl. The mixture was extracted with EtOAc (×3), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration gave the aldehyde, which was used in the next reaction without further purification. To a suspension of Ph_3PCH_3Br (52 mg, 146 μmol) in THF (1.0 mL) at 0 °C was added *t*-BuOK (8.2 mg, 73.3 μmol). After 15 min, a solution of the above aldehyde in THF (300 μL) at 0 °C was added dropwise to the reaction mixture. After being stirred for 30 min at 0 °C, the reaction mixture was quenched with aqueous NH_4Cl. The mixture was extracted with EtOAc (×3), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and column chromatography (hexane/EtOAc, 20:1−10:1) gave the pentaene **52** (4.0 mg, 2.71 μmol) in 92% yield over two steps: white, amorphous solid; $[\alpha]^{19}_D$ −5.1 (*c* 0.21, $CHCl_3$); IR (film) *ν* 2927, 2872, 1641, 1509, 1456, 1090, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.85−7.65 (12H, m, NAP), 7.58−7.42 (9H, m, NAP) 5.88 (1H, m, H2), 5.82 (1H, m, H23), 5.79−5.74 (2H, m, H3, H13), 5.69 (1H, m, H24),

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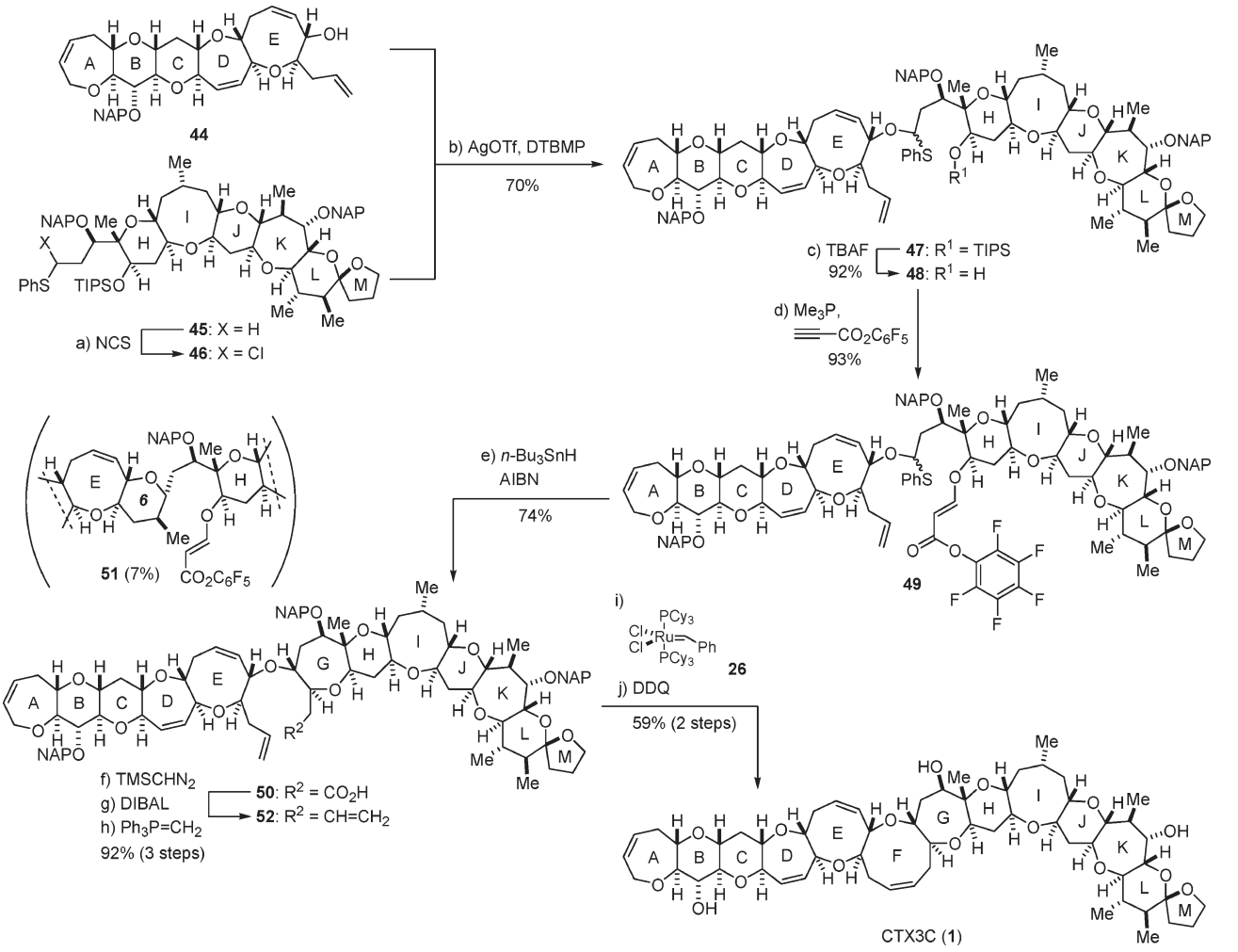
Scheme 4. Practical Total Synthesis of CTX3C (1)[a]



[a] Reagents and conditions: (a) *N*-Chlorosuccinimide (NCS), CCl_4/CH_2Cl_2 (6:1), RT; (b) AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), CH_2Cl_2/CCl_4 (5:1), 4 Å molecular sieves, −70 to 0 °C, 70% from **44**; (c) TBAF, THF, 35 °C, 92%; (d) Me_3P, pentafluorophenyl propiolate, CH_2Cl_2, RT, 93%; (e) *n*-Bu_3SnH, 2,2′-azobisisobutyronitrile (AIBN), toluene, 85 °C, **50**, 74%; **51**, 7%; (f) trimethylsilyl diazomethane ($TMSCHN_2$), benzene/MeOH (2.5:1), RT, quant; (g) DIBAL, CH_2Cl_2, −90 °C; (h) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, 92% (2 steps); (i) **26**, CH_2Cl_2, 40 °C, 90%; (j) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O (10:1), RT, 65%.

5.67−5.61 (2H, m, H14, H18), 5.19 (1H, dd, *J* = 10.5, 5.5 Hz, H19), 5.11−5.06 (2H, m, H23′, H23′), 5.05 (1H, d, *J* = 12.0 Hz, NAP), 5.00 (1H, d, *J* = 12.0 Hz, NAP), 5.01−4.97 (2H, m, H24′, H24′), 4.95 (1H, d, *J* = 12.5 Hz, NAP), 4.84 (1H, d, *J* = 12.5 Hz, NAP), 4.81 (1H, d, *J* = 12.5 Hz, NAP), 4.77 (1H, d, *J* = 12.5 Hz, NAP), 4.31 (1H, dd, *J* = 15.5, 5.5 Hz, H1), 4.05 (1H, m, H1), 3.84−3.88 (2H, m, H41, H52), 3.83−3.77 (2H, m, H12, H15), 3.75 (1H, m, H52), 3.70 (1H, m, H27), 3.66 (1H, d, *J* = 10.5 Hz, H45), 3.64 (1H, m, H20), 3.56 (1H, m, H26), 3.53 (1H, m, H16), 3.49 (1H, d, *J* = 3.5 Hz, H44), 3.49 (1H, dd, *J* = 9.5, 9.5 Hz, H7), 3.43−3.34 (4H, m, H6, H29, H34, H46), 3.29 (1H, ddd, *J* = 9.5, 9.5, 4.0 Hz, H5), 3.21 (1H, dd, *J* = 11.5, 4.5 Hz, H31), 3.20 (1H, m, H11), 3.16−3.06 (4H, m, H8, H9, H33, H39), 2.99 (1H, ddd, *J* = 9.5, 9.5, 2.5 Hz, H38), 2.93 (1H, ddd, *J* = 9.0, 9.0, 3.0 Hz, H21), 2.87 (1H, dd, *J* = 9.0, 4.5 Hz, H42), 2.65 (1H, ddd, *J* = 16.5, 7.0, 4.0 Hz, H4), 2.56 (1H, m, H17), 2.48 (1H, m, H22), 2.35 (1H, m, H4), 2.30−2.25 (2H, m, H10, H40), 2.20 (1H, m, H17), 2.17 (1H, m, H43), 2.14 (1H, m, H25), 2.02−1.85 (9H, m, H22, H25, H28, H32, H35, H36, H37, H50, H51), 1.84−1.75 (3H, m, H28, H50, H51), 1.64−1.50 (6H, m, H10, H32, H35, H37, H47, H48), 1.41 (1H, m, H40), 1.26 (3H, s, Me53), 1.11 (3H, d, *J* = 7.5 Hz, Me55), 1.09 (3H, d, *J* = 7.0 Hz, Me54), 1.03 (3H, d, *J* = 6.0 Hz, Me56), 0.91 (3H, d, *J* = 6.5 Hz, Me57); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 136.9, 136.68, 136.64, 136.62, 135.7, 135.3, 135.2, 134.1, 133.3, 133.28, 133.26, 132.9, 132.1, 131.4, 130.3, 129.0, 128.5, 128.4, 128.2, 127.89, 127.84, 127.82, 127.69, 127.67, 126.8, 126.6, 126.3, 126.10, 126.08, 126.06, 126.03, 125.91, 125.89, 125.70, 125.64, 125.62, 125.60, 117.7, 117.0, 108.3, 87.5, 86.87, 86.85, 84.6, 84.59, 84.55, 83.6, 82.5, 82.0, 80.98, 80.96, 80.92, 80.7, 79.9, 79.7, 78.4, 78.28, 78.27, 78.26, 78.21, 78.1, 77.97, 77.95, 77.94, 77.8, 75.2, 74.4, 73.7, 73.2, 72.2, 72.1, 71.9, 68.4, 67.39, 67.35, 41.9, 40.5, 40.3, 39.6, 35.6, 37.7, 36.9, 35.1, 34.6, 32.4, 29.7, 27.7, 24.4, 20.0, 15.8, 13.5; HRFABMS *m*/*z* 1493.7698 $[M + Na]^+$ (calcd for $C_{92}H_{110}O_{16}Na$ 1493.7686).

CTX3C. To a solution of tris-NAP CTX3C **S18** (3.3 mg, 2.29 μmol) in CH_2Cl_2 (1.6 mL) and H_2O (800 μL) at room temperature was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (5.1 mg, 22.9 μmol). After being stirred for 3 h at room temperature, the mixture was quenched with saturated aqueous $Na_2S_2O_3$ at room temperature, diluted with EtOAc and saturated aqueous $NaHCO_3$, and extracted with EtOAc (×6). The organic layer was washed with brine. Concentration and reversed-phase column chromatography (Shodex Asahipak ODP 50-6D, 6.0 × 150 mm, UV 210 nm, CH_3CN/H_2O, 75:25, 1.0 mL/min)

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gave pure synthetic CTX3C (**1**) (t_R = 19.7 min, 1.83 mg, 1.79 μmol) in 65% yield: colorless, amorphous solid; $[\alpha]^{32}_D$ −42.6 (*c* 0.10, MeOH); ^{1}H NMR (600 MHz, C_5D_5N) δ 6.02 (1H, m, H24), 6.02 (1H, m, H23), 5.96 (1H, dd, *J* = 10.8, 5.4 Hz, H19), 5.91 (1H, m, H14), 5.86 (1H, m, H2), 5.83 (1H, m, H13), 5.82 (1H, m, H18), 5.72 (1H, m, H3), 4.44 (1H, m, H41), 4.32 (1H, dd, *J* = 15.0, 6.0 Hz, H1), 4.19 (1H, m, H44), 4.15 (1H, m, H15), 4.14 (1H, m, H20), 4.12 (1H, m, H29), 4.06 (1H, m, H12), 4.07 (1H, m, H7), 4.01 (1H, d, *J* = 9.6 Hz, H45), 4.06 (1H, m, H1), 3.53 (1H, dd, *J* = 9.6, 9.6 Hz, H46), 3.86 (1H, m, H52), 3.86 (1H, m, H52), 3.76 (1H, m, H26), 3.70 (1H, m, H16), 3.58 (1H, m, H27), 3.58 (1H, m, H21), 3.53 (1H, dd, *J* = 9.0, 9.0 Hz, H6), 3.45 (1H, m, H5), 3.43 (1H, m, H34), 3.41 (1H, m, H11), 3.41 (1H, dd, *J* = 9.0, 9.0 Hz, H8), 3.33 (1H, m, H9), 3.32 (1H, m, H39), 3.32 (1H, m, H33), 3.30 (1H, m, H31), 3.18 (1H, m, H38), 3.17 (1H, m, H42), 3.02 (1H, m, H25), 2.98 (1H, m, H22), 2.83 (1H, m, H17), 2.65 (1H, m, H4), 2.56 (1H, m, H43), 2.54 (1H, m, H40), 2.53 (1H, m, H10), 2.53 (1H, m, H28), 2.49 (1H, m, H28), 2.42 (1H, m, H4), 2.30 (1H, m, H25), 2.27 (1H, m, H17), 2.23 (1H, m, H22), 2.22 (1H, m, H32), 1.98 (1H, m, H37), 1.91 (1H, m, H47), 1.90 (1H, m, H50), 1.89 (1H, m, H51), 1.87 (1H, m, H32), 1.85 (1H, m, H36), 1.83 (1H, m, H50), 1.82 (1H, m, H10), 1.80 (1H, m, H35), 1.75 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H40), 1.68 (1H, m, H37), 1.66 (1H, m, H51), 1.59 (1H, m, H48), 1.51 (1H, m, H35), 1.25 (3H, m, Me53), 1.26 (3H, m, Me55), 1.25 (3H, m, Me56), 0.94 (3H, d, *J* = 6.6 Hz, Me57), 0.88 (3H, d, *J* = 6.6 Hz, Me54); ^{13}C NMR (150 MHz, C_5D_5N) δ 137.9, 136.5, 132.1, 131.0, 128.7, 128.5, 127.1, 125.8, 108.8, 88.7, 87.7, 86.1, 85.3, 84.5, 84.0, 83.8, 83.7, 83.4, 82.5, 81.7, 81.6, 81.1, 80.9, 79.3, 78.6, 78.2, 77.0, 76.9, 74.9, 74.7, 74.3, 73.5, 73.1, 72.6, 68.5, 67.5, 46.6, 46.1, 44.0, 42.3, 41.4, 40.0, 39.0, 37.6, 36.4, 35.1, 34.9, 32.8, 32.7, 32.4, 28.4, 28.0, 24.6, 20.3, 16.2, 13.7, 9.9; HRESIMS *m/z* 1045.5496 $[M + Na]^+$ (calcd for $C_{57}H_{82}O_{16}Na$ 1045.5495).

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and NMR spectra for new compounds are available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

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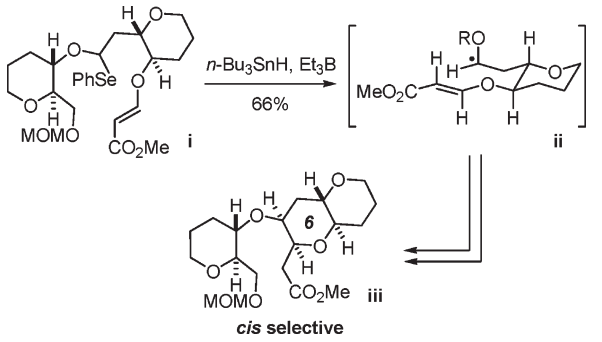

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