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A CONCISE ROUTE TO TWO DISTINCT E-RING STRUCTURES OF CIGUATOXINS

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This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

Abstract – Ciguatoxins, the causative toxins of ciguatera seafood poisoning, are large ladder-like polycyclic ethers, and known to have more than 20 structurally distinct congeners. In this paper, we describe a new concise synthesis of the two E-ring structures, of different ring sizes, found in ciguatoxins. From the common oxepane intermediate, the seven-membered E-ring was prepared in three steps, and the eight-membered E-ring was synthesized in seven steps using ring expansion and olefin isomerization as key reactions.

The scarcity of ciguatoxins [e.g. CTX1B[1] (**1**), CTX3C[2] (**2**) and 51-hydroxyCTX3C[3] (**3**), Figure 1], their extraordinary ladder-shaped architecture, their potent neurotoxicity, and association with ciguatera seafood poisoning render these marine natural products formidable targets for a synthesis-driven investigation at the chemistry/biology interface.[4] To date, more than 20 congeners of ciguatoxins have been structurally determined.[5] While all the congeners share the common FGHIJ-ring structures, the ring sizes and the functional group patterns of the other parts of the congeners are diverse. For instance, **2** and **3** not only lack the additional side chain of **1**, but have an eight-membered E-ring instead of the seven-membered ring found in **1**.

In earlier work, we reported the total syntheses of **1**-**3** by applying unified synthetic strategies; AB-, E-, HI-, and LM-ring fragments were assembled with construction of the CD-, FG-, and JK-ring systems to

generate the entire structures of these ciguatoxins.[6,7] Obviously, for practical use of this convergent synthesis, an efficient synthesis of the four fragments is crucial.[8] Here we report a new concise route to two structurally distinct E-ring structures of ciguatoxins.[9]

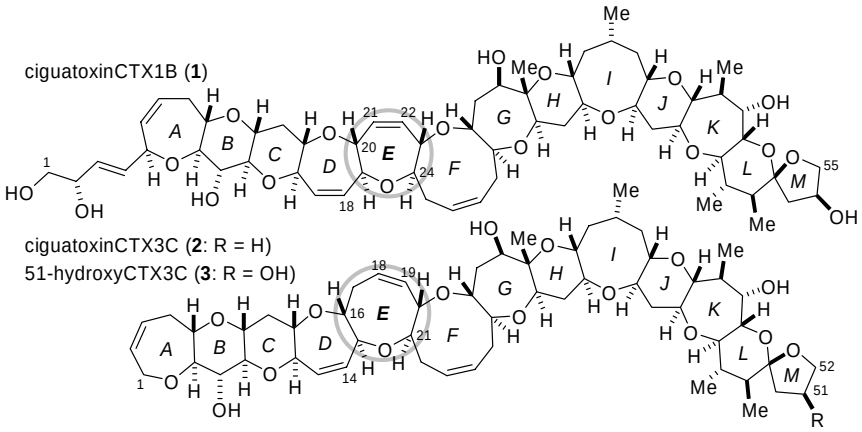
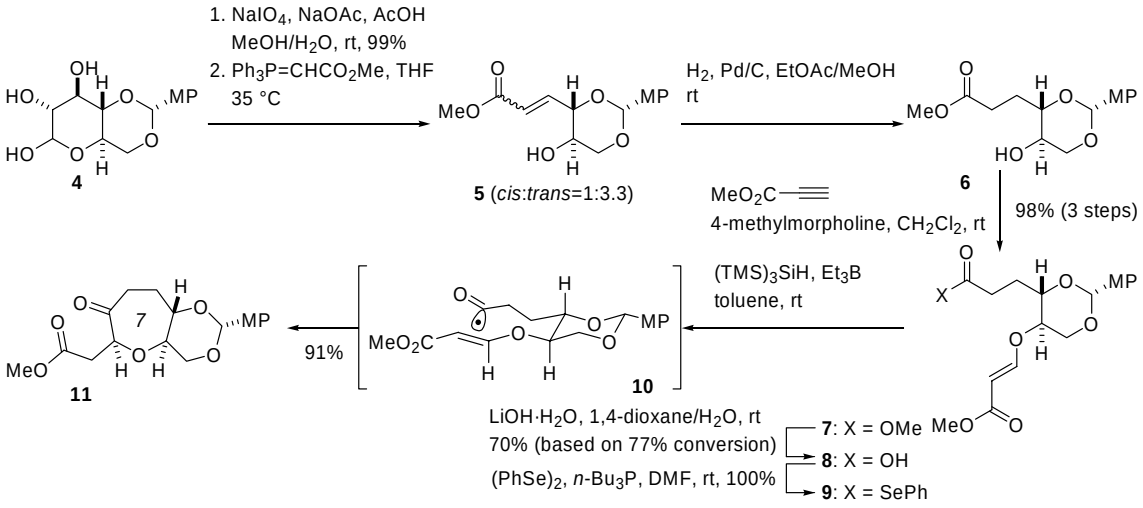


Figure 1. Structures of ciguatoxins

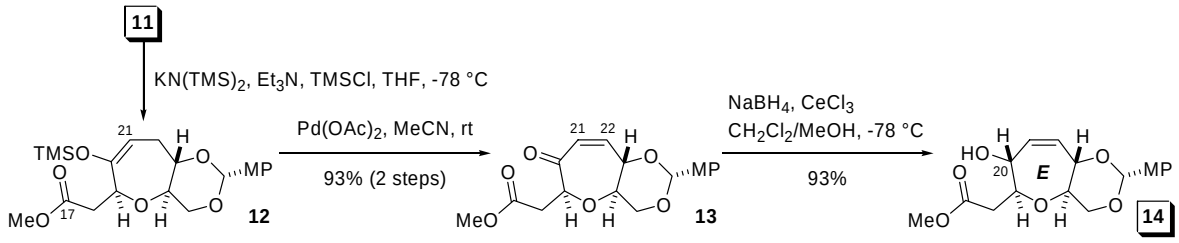


Scheme 1. Synthesis of the common oxepane intermediate

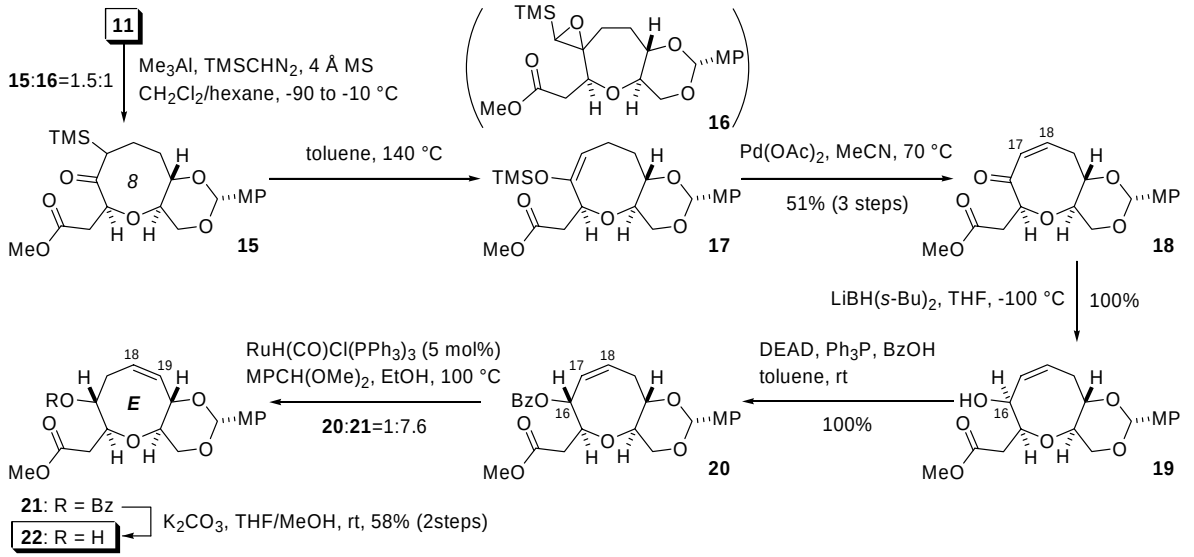
We planned to synthesize both the seven-membered and eight-membered E-rings from the common oxepane intermediate **11** (Scheme 1). Synthesis of **11** started with the oxidative cleavage of the *p*-methoxybenzylidene (MP)-protected D-glucose **4**, followed by Wittig reaction, to produce α,β-unsaturated ester **5**. Hydrogenation of olefin **5** and subsequent hetero-Michael reaction of secondary alcohol **6** to methyl propiolate yielded **7**.[10] Then, treatment of diester **7** with LiOH in aqueous dioxane selectively led to monocarboxylic acid **8**,[11] which was converted into phenylselenyl ester **9** by the action of $(PhSe)_2$ and *n*-Bu_3P.[12] According to the method developed by Evans,[13] homolytic cleavage of the C-Se bond of **9** was induced by a reagent combination of $(TMS)_3SiH$ and Et_3B to produce acyl radical **10**, which reacted with β-alkoxy acrylate to afford the seven-membered ring **11** in 91% yield as a sole isomer.[14] The excellent stereochemical control observed here is ascribed to the strongly favored

transition state conformation of **10**, in which the $A^{1,3}$-strain is minimized. Overall, the functionalized oxepane intermediate **11** was synthesized from **4** in seven steps.

The seven-membered E-ring **14** was prepared in a straightforward manner from **11** in three steps (Scheme 2).[15] Chemo- and regioselective TMS-enolization of ketone **11** was realized using $TMSCl/Et_3N/KN(TMS)_2$, leading to **12** with the intact C17-ester. Saegusa oxidation[16] of **12** introduced the requisite C21-22 olefin to give α,β-unsaturated ketone **13**, which was stereoselectively reduced under Luche conditions[17] to deliver the appropriately functionalized E-ring **14**.



Scheme 2. Synthesis of the seven-membered E-ring



Scheme 3. Synthesis of the eight-membered E-ring

On the other hand, the eight-membered E-ring **22** was synthesized from **11** in seven steps (Scheme 3).[18] The selective ring-expansion from the seven-membered ketone **11** was realized by applying $TMSCHN_2$ in the presence of Me_3Al,[19] leading to the eight-membered α-silyl ketone **15** along with the seven-membered epoxide **16** (**15**:**16**=1.5:1). Heating of **15** at 140 °C in toluene resulted in formation of TMS-enol ether **17** via [1,3]-silyl migration.[20] Pd^{2+}-mediated oxidation of **17** introduced the C17-18 olefin, generating **18** (51% overall yield from **11**). Stereoselective introduction of the C16-stereocenter of **20**, starting from **18**, required the following two steps; chemo- and stereoselective reduction of

α,β-unsaturated ketone **18** with LiBH(*s*-Bu)$_2$, and subsequent Mitsunobu reaction[21] of **19** to produce **20**. Finally, relocation of the olefin from C17-18 to C18-19 was achieved through use of the ruthenium hydride catalyst,[22,23] which selectively converted **20** into **21**, the benzoyl group of which was removed to furnish the eight-membered E-ring **22**.

The regioselectivity of the successful olefin isomerization of **20** is worthy of note (Figure 2). Interestingly, oxocene **21** was found to be thermodynamically more stable than its pseudo-enantiomer **20**. The ^{1}H-^{1}H coupling constants and the molecular modeling study (MacroModel ver. 8.6)[24] suggested that the conformations of the eight-membered ring portions of **20** and **21** are slightly deviated from their enantiomeric relationship; the distance between the C16-oxygen and the C14-methylene is shorter in the case of **20**, whereas the distance between the C20- and the C22-substituents is constant due to the constraint of the rigid six-membered MP-acetal. This conformational bias is likely to contribute to the more unfavorable steric interaction in **20**, resulting in selective formation of **21** upon olefin isomerization.

In conclusion, a new general and practical approach to the synthesis of both seven- and eight-membered E-rings of ciguatoxins has been described. The common oxepane intermediate **11** was prepared from the protected D-glucose in seven steps and 62% yield employing acyl radical cyclization. From **11**, **14** was synthesized in three steps and 86% yield, while **22** was synthesized in seven steps and 30% yield using the ring expansion and regioselective olefin isomerization as key reactions.

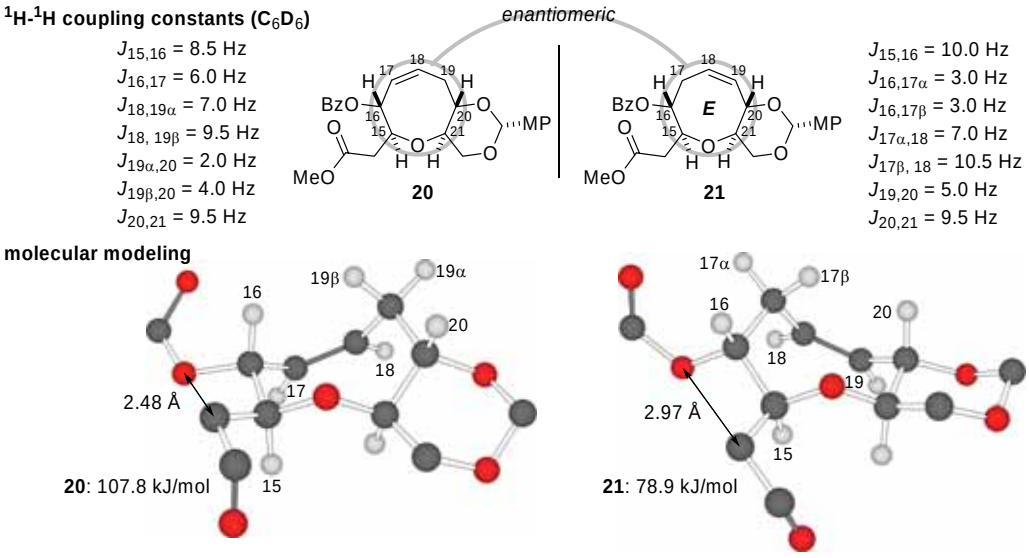


Figure 2. ^{1}H-^{1}H coupling constants and molecular modeling of **20** and **21** (MM2*, MacroModel Ver. 8.6). The *p*-methoxyphenyl group was not included on the energy calculation. The phenyl group of Bz, the methoxy group at C13 and the hydrogens of C14 and the six-membered acetal were omitted for visual clarity.

EXPERIMENTAL

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. Toluene was distilled from calcium hydride, and DMF from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated 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.

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian INOVA 500 (500 MHz) spectrometer and a Varian Mercury 200 (200 MHz) spectrometer. Chemical shifts are reported in δ (ppm) down field from tetramethylsilane (TMS) with reference to solvent signals [^{1}H NMR: $CHCl_3$ (7.26), C_6D_6 (7.16); ^{13}C NMR: $CDCl_3$ (77.16)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. ESI-TOF mass spectra were measured on a BRUKER DALTONICS APEX III. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

Diester 7. To a mixture of **4** (2.00 g, 6.70 mmol), AcOH (38 μl, 0.67 mmol) and NaOAc (1.10 g, 13.4 mmol) in MeOH/H_2O (10:1, 34 mL) at rt was added $NaIO_4$ (2.87 g, 13.4 mmol). After being stirred for 17 h at rt, the reaction mixture was treated with saturated aqueous $NaHCO_3$, and extracted with EtOAc (x4). The organic layer was washed with brine, dried over Na_2SO_4, concentrated, and passed through a short pad of silica gel (EtOAc). The eluent was concentrated to afford the aldehyde (1.58 g, 6.63 mmol) in 99% yield.

To a solution of the aldehyde (13.5 g, 56.8 mmol) in THF (116 mL) at rt was added Ph_3PCHCO_2Me (28.5 g, 85.3 mmol). After being stirred for 4.5 h at 35 °C, the mixture was treated with saturated aqueous $NaHCO_3$, and then extracted with EtOAc (x2). The organic layer was washed with brine and dried over $MgSO_4$. After concentration, triphenylphosphine oxide was filtered out. The filtrate was concentrated and purified with silica gel chromatography (hexane/EtOAc 10:1-3:1) to give α,β-unsaturated ester **5** (*cis*:*trans*=1:3.3) including triphenylphosphine oxide. It was used in the next reaction without further purification.

A mixture of α,β-unsaturated ester **5** and 10% Pd/C (1.7 g) in EtOAc/MeOH (50:1, 58 mL) was stirred under H_2 atmosphere at rt for 1 d. The mixture was passed through Celite, and concentrated to afford crude alcohol **6**, which was used without further purification.

To a solution of **6** in CH_2Cl_2 (114 mL) at rt were added methyl propiolate (7.6 mL, 85.0 mmol) and 4-methylmorpholine (3.1 mL, 28.0 mmol). After being stirred for 3 h at rt, the mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc (x2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and open column chromatography (hexane/EtOAc 20:1-7:1) gave diester **7** (19.2 g, 50.4 mmol) in 98% yield over 3 steps: colorless oil; $[\alpha]_D^{30}$ = -34.6 (*c* 1.02, $CHCl_3$); IR (film) ν 2952, 2849, 1737, 1714, 1644, 1518, 1251, 1197, 1133, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.87 (1H, dddd, *J* = 15.0, 9.0, 8.5, 6.0 Hz, H22), 2.19 (1H, dddd, *J* = 15.0, 8.5, 8.0, 3.0 Hz, H22), 2.44-2.58 (2H, m, H21, H21), 3.64 (3H, s, MeO), 3.65 (1H, dd, *J* = 11.0, 10.0 Hz, H25), 3.71 (3H, s, MeO), 3.77 (1H, ddd, *J* = 9.5, 9.0, 3.0 Hz, H23), 3.80 (3H, s, MeO), 3.88 (1H, ddd, *J* = 10.0, 9.5, 5.0 Hz, H24), 4.36 (1H, dd, *J* = 11.0, 5.0 Hz, H25), 5.39 (1H, d, *J* = 12.5 Hz, H19), 5.44 (1H, s, MP), 6.89 (2H, d, *J* = 9.0 Hz, MP), 7.37 (2H, d, *J* = 9.0 Hz, MP), 7.48 (1H, d, *J* = 12.5 Hz, H18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.1, 29.5, 51.4, 51.8, 55.4, 68.2, 75.4, 78.3, 98.9, 101.2, 113.8, 127.5, 129.7, 160.3, 161.1, 167.9, 173.6; HRMS (ESI), calcd for $C_{19}H_{24}O_8Na$ 403.1363 ($M+Na^+$), found 403.1364.

Monocarboxylic acid 8. To a solution of **7** (1.64 g, 4.31 mmol) in 1,4-dioxane/H_2O (2:1, 9.0 mL) at rt was added $LiOH \cdot H_2O$ (199 mg, 4.74 mmol). After being stirred for 1 h at rt, the mixture was diluted with EtOAc and quenched with saturated aqueous NH_4Cl. After being extracted with EtOAc (x2), the combined organic layer was washed with brine, and dried over Na_2SO_4. Concentration and open column chromatography (hexane/EtOAc 7:1-0:1) gave monocarboxylic acid **8** (774 mg, 2.11 mmol) in 70% yield, based on recovered diester **7** (23%): colorless solid; $[\alpha]_D^{30}$ = -32.0 (*c* 0.91, $CHCl_3$); IR (film) ν 2954, 2871, 1740, 1714, 1615, 1518, 1250, 1107, 1031, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.87 (1H, m, H22), 2.18 (1H, dddd, *J* = 14.5, 8.0, 8.0, 3.0 Hz, H22), 2.48-2.62 (2H, m, H21, H21), 3.65 (1H, dd, *J* = 10.5, 10.0 Hz, H25), 3.70 (3H, s, MeO), 3.78 (1H, ddd, *J* = 9.5, 5.0, 3.0 Hz, H23), 3.79 (3H, s, MeO), 3.89 (1H, ddd, *J* = 10.0, 9.5, 5.0 Hz, H24), 4.37 (1H, dd, *J* = 10.5, 5.0 Hz, H25), 5.39 (1H, d, *J* = 13.0 Hz, H19), 5.45 (1H, s, MP), 6.88 (2H, d, *J* = 9.0 Hz, MP), 7.37 (2H, d, *J* = 9.0 Hz, MP), 7.49 (1H, d, *J* = 13.0 Hz, H18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 29.4, 51.4, 55.4, 68.1, 75.4, 78.2, 98.9, 101.2, 113.8, 127.5, 129.6, 160.3, 161.2, 170.0, 178.7; HRMS (ESI), calcd for $C_{18}H_{22}O_8Na$ 389.1207 ($M+Na^+$), found 389.1206.

Seven-membered ketone 11. To a solution of **8** (388 mg, 1.06 mmol) in DMF (21 mL) at rt were added $(PhSe)_2$ (662 mg, 2.12 mmol) and *n*-Bu_3P (0.40 mL, 1.59 mmol). After being stirred for 1.5 h at rt, the mixture was concentrated and subjected to open column chromatography (hexane/EtOAc 30:1-5:1) to give phenylselenyl ester **9** (556 mg, 1.06 mmol) in 100% yield.

To a solution of phenylselenyl ester **9** in toluene (21 mL) were added $(TMS)_3SiH$ (392 μl, 1.27 mmol) and Et_3B (1.0M in THF, 0.53 mL, 0.530 mmol), and the mixture was stirred for 1 h at rt. The solution was concentrated and subjected to open column chromatography (hexane/EtOAc 30:1-5:1) to give

seven-membered ketone **11** in 91% yield: colorless needle; mp 150-151 °C; $[\alpha]_D^{29}$ = -86.1 (*c* 1.06, $CHCl_3$); IR (film) ν 2954, 2871, 1740, 1714, 1518, 1250, 1172, 1107, 1031, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.81 (1H, dddd, *J* = 14.0, 14.0, 11.0, 1.5 Hz, H22), 2.23 (1H, dddd, *J* = 14.0, 7.0, 4.0, 2.5 Hz, H22), 2.58 (1H, ddd, *J* = 14.0, 7.0, 1.5 Hz, H21), 2.75 (1H, dd, *J* = 16.5, 7.0 Hz, H18), 2.79 (1H, dd, *J* = 16.5, 5.0 Hz, H18), 2.98 (1H, ddd, *J* = 14.0, 14.0, 2.5 Hz, H21), 3.40 (1H, ddd, *J* = 10.5, 10.5, 5.0 Hz, H24), 3.67 (1H, dd, *J* = 10.5, 9.5 Hz, H25), 3.71 (3H, s, MeO), 3.77 (1H, ddd, *J* = 11.0, 10.5, 4.0 Hz, H23), 3.80 (3H, s, MeO), 4.25 (1H, dd, *J* = 9.5, 5.0 Hz, H25), 4.27 (1H, dd, *J* = 7.0, 5.0 Hz, H19), 5.47 (1H, s, MP), 6.89 (2H, d, *J* = 9.0 Hz, MP), 7.40 (2H, d, *J* = 9.0 Hz, MP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 37.6, 38.2, 52.2, 55.5, 69.2, 78.1, 81.5, 83.9, 101.3, 113.9, 127.6, 129.9, 160.3, 170.6, 213.6; HRMS (ESI), calcd for $C_{18}H_{22}O_7Na$ 373.1258 ($M+Na^+$), found 373.1258.

α,β-Unsaturated ketone 13. To a mixture of **11** (285 mg, 0.814 mmol), Et_3N (2.5 mL, 17.9 mmol) and TMSCl (2.1 mL, 16.3 mmol) in THF (27 mL) at -78 °C was added $KN(TMS)_2$ (0.5 M in toluene, 6.5 mL, 3.26 mmol). After being stirred for 0.5 h at –78 °C, the reaction mixture was quenched with pH 7.4 phosphate buffer. The mixture was extracted with EtOAc (x2), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude TMS-enol ether **12** was used in the next reaction without further purification.

To a solution of TMS-enol ether **12** in MeCN (27 mL) at rt was added $Pd(OAc)_2$ (366 mg, 1.63 mmol). After being stirred for 0.5 h at rt, the reaction mixture was passed through a pad of silica gel. The solution was concentrated and purified with open column chromatography (hexane/EtOAc 15:1-5:1) to give α,β-unsaturated ketone **13** in 93% yield over 2 steps: colorless solid; $[\alpha]_D^{30}$ = 92.5 (*c* 0.97, $CHCl_3$); IR (film) ν 2953, 2839, 1740, 1663, 1518, 1251, 1116, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.81 (1H, dd, *J* = 17.0, 7.0 Hz, H18), 2.90 (1H, dd, *J* = 17.0, 4.0 Hz, H18), 3.68 (1H, m, H25), 3.68 (3H, s, MeO), 3.77 (1H, m, H24), 3.78 (3H, s, MeO), 4.31 (1H, dd, *J* = 10.5, 5.0 Hz, H25), 4.40 (1H, ddd, *J* = 8.5, 2.5, 2.5 Hz, H23), 4.51 (1H, dd, *J* = 7.0, 4.0 Hz, H19), 5.48 (1H, s, MP), 6.08 (1H, *J* = 13.0, 2.5 Hz, H22), 6.54 (1H, dd, *J* = 13.0, 2.5 Hz, H21), 6.88 (2H, d, *J* = 9.0 Hz, MP), 7.40 (2H, dd, *J* = 9.0 Hz, MP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.2, 51.9, 53.3, 68.8, 74.5, 80.0, 83.5, 101.6, 113.7, 127.5, 128.5, 129.4, 144.0, 160.3, 170.7, 201.2; HRMS (ESI), calcd for $C_{18}H_{20}O_7Na$ 371.1101 ($M+Na^+$), found 371.1102.

Seven-membered E-ring 14. To a solution of **13** (709 mg, 2.04 mmol) in $MeOH/CH_2Cl_2$ (1:2, 15 mL) at -78 °C was added $CeCl_3 \cdot 7H_2O$ (798 mg, 2.14 mmol). Then $NaBH_4$ (77 mg, 2.04 mmol) in MeOH (5 mL) was added to the mixture portionwise over 5 min. After being stirred for 5 min at -78 °C, the mixture was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (x2). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 10:1-5:1) afforded seven-membered E-ring **14** (663 mg, 1.89 μmol) in 93% yield: colorless needle crystal; mp 137-138 °C; $[\alpha]_D^{29}$ = 8.9 (*c* 0.87, $CHCl_3$); IR (film) ν 3468, 2953, 1736, 1518,

1250, 1119, 1032, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.14 (1H, d, *J* = 7.0 Hz, OH), 2.58 (1H, dd, *J* = 15.5, 7.5 Hz, H18), 2.85 (1H, dd, *J* = 15.5, 4.0 Hz, H18), 3.53 (1H, ddd, *J* = 10.0, 10.0, 4.5 Hz, H24), 3.57 (1H, dd, *J* = 10.0, 10.0 Hz, H25), 3.71 (3H, s, MeO), 3.80 (3H, s, MeO), 3.87 (1H, ddd, *J* = 9.5, 7.5, 4.0 Hz, H19), 4.16 (1H, dd, *J* = 10.0, 4.5 Hz, H25), 4.22-4.28 (2H, m, H20, H23), 5.41 (1H, s, MP), 5.77 (2H, m, H21, H22), 6.89 (2H, d, *J* = 9.0 Hz, MP), 7.41 (2H, d, *J* = 9.0 Hz, MP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 37.6, 38.2, 52.2, 55.5, 69.2, 78.1, 81.5, 83.9, 101.3, 113.9, 127.6, 129.9, 160.3, 170.6, 213.6; HRMS (ESI), calcd for $C_{18}H_{22}O_7Na$ 373.1258 ($M+Na^+$), found 373.1258.

α,β-Unsaturated ketone 18. To a mixture of **11** (1.13 g, 3.23 mmol) and 4 Å MS (1 g) in CH_2Cl_2/hexane (2.5:1, 8.3 mL) at -90 °C were added $TMSCHN_2$ (2.0 M in hexane, 3.2 mL, 6.50 mmol) and Me_3Al (1.0 M in hexane, 6.5 mL, 6.50 mmol). The reaction mixture was allowed to warm to -10 °C over 4.5 h, and then quenched with saturated aqueous NH_4Cl and aqueous Rochelle's salt. After being stirred for 1 h at rt, the mixture was extracted with EtOAc (x2). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the crude α-silyl ketone **15**, which was used in the next reaction without further purification.

A solution of **15** in toluene (10 mL) was heated to 140 °C in sealed tube. After being stirred for 1.5 h at 140 °C, the mixture was cooled to rt and concentrated to give TMS-enol ether **17**, which was used in the next reaction without further purification.

To a solution of **17** in MeCN (6 mL) at rt was added $Pd(OAc)_2$ (798 mg, 3.55 mmol). After being stirred for 30 min at 70 °C, the mixture was cooled to rt, and passed through a pad of silica gel. Concentration and flash column chromatography (hexane/EtOAc 16:1-10:1) gave α,β-unsaturated ketone **18** (592 mg, 1.63 mmol) in 51% yield from **11**: colorless solid; $[\alpha]_D^{26}$ = -124.8 (*c* 1.04, $CHCl_3$); IR (film) ν 2953, 2860, 1737, 1673, 1518, 1250, 1094, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.64 (1H, dd, *J* = 17.0, 9.0 Hz, H14), 2.65 (1H, dd, *J* = 14.0, 10.5 Hz, H19), 2.98 (1H, dddd, *J* = 14.0, 9.5, 7.5, 1.5 Hz, H19), 3.01 (1H, dd, *J* = 17.0, 3.5 Hz, H14), 3.60 (1H, dd, *J* = 10.5, 10.0 Hz, H22), 3.64 (1H, dd, *J* = 9.5, 9.5 Hz, H20), 3.74 (3H, s, MeO), 3.80 (3H, s, MeO), 3.94 (1H, ddd, *J* = 10.0, 9.5, 5.0 Hz, H21), 4.14 (1H, dd, *J* = 10.5, 5.0 Hz, H22), 4.81 (1H, dd, *J* = 9.0, 3.5 Hz, H15), 5.43 (1H, s, MP), 5.95 (1H, dd, *J* = 13.0, 1.5 Hz, H17), 6.57 (1H, ddd, *J* = 13.0, 10.5, 7.5 Hz, H18), 6.89 (2H, d, *J* = 9.0 Hz, MP), 7.40 (2H, d, *J* = 9.0 Hz, MP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.2, 37.8, 52.1, 55.5, 69.6, 77.6, 82.8, 84.0, 101.7, 113.9, 127.6, 129.9, 130.5, 137.8, 160.3, 171.6, 199.8; HRMS (ESI), calcd for $C_{19}H_{22}O_7Na$ 385.1258 ($M+Na^+$), found 385.1258.

Alcohol 19. To a solution of **18** (2.47 g, 6.82 mmol) in THF (34 mL) at -100 °C was added $LiBH(s\text{-}Bu)_2$ (1.0 M in THF, 7.50 mL, 7.50 mmol) over 5 min. Additional $LiBH(s\text{-}Bu)_2$ (0.70 mL) was then introduced. After being stirred for 5 min at -100 °C, the mixture was quenched with saturated aqueous NH_4Cl. After being stirred for 1 h at rt, the mixture was extracted with EtOAc (x2), washed

with brine, and dried over Na_2SO_4. The combined organic layer was concentrated and subjected to open column chromatography (hexane/EtOAc 10:1-3:1) to give alcohol **19** (2.48 g, 6.82 mmol) in 100% yield: colorless solid; $[\alpha]_D^{26}$ = -43.8 (*c* 1.02, $CHCl_3$); IR (film) ν 3468, 2953, 2867, 1738, 1615, 1518, 1250, 1107, 1030, 830 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 2.28 (1H, m, H19), 2.29 (1H, dd, *J* = 16.5, 9.5 Hz, H14), 2.39 (1H, ddd, *J* = 13.0, 9.0, 3.0 Hz, H19), 2.79 (1H, dd, *J* = 16.5, 3.5 Hz, H14), 3.26-3.34 (2H, m, H21, H20) 3.28 (3H, s, MeO), 3.35 (3H, s, MeO), 3.44 (1H, dd, *J* = 11.0, 10.0 Hz, H22), 4.07 (1H, ddd, *J* = 9.5, 6.0, 3.5 Hz, H15), 4.22 (1H, dd, *J* = 11.0, 5.0 Hz, H22), 4.31 (1H, ddd, *J* = 7.5, 6.0, 1.5 Hz, H16), 5.27 (1H, s, MP), 5.40 (1H, ddd, *J* = 10.5, 7.5, 1.5 Hz, H17), 5.62 (1H, dddd, *J* = 10.5, 9.0, 7.5, 1.5 Hz, H18), 6.83 (2H, d, *J* = 9.0 Hz, MP), 7.55 (2H, d, *J* = 9.0 Hz, MP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.5, 34.8, 51.9, 55.4, 68.3, 69.6, 73.9, 77.2, 79.6, 101.1, 113.8, 127.47, 127.52, 130.2, 131.8, 160.2, 172.7; HRMS (ESI), calcd for $C_{19}H_{24}O_7Na$ 387.1414 ($M+Na^+$), found 387.1415.

Benzoate 20. To a mixture of **19** (2.19 g, 6.00 mmol), Ph_3P (4.75 g, 18.1 mmol) and benzoic acid (1.47 g, 12.0 mmol) in toluene (20 mL) at 0 °C was added DEAD (2.2 M in toluene, 8.2 mL, 18.1 mmol). After being stirred for 1 h at rt, the mixture was quenched with pH 7 phosphate buffer. The organic layer was washed with brine, and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 30:1-10:1) gave benzoate **20** (2.80 g, 5.99 mmol) in 100% yield: colorless solid; $[\alpha]_D^{27}$ = 92.0 (*c* 1.08, $CHCl_3$); IR (film) ν 3212, 2982, 1758, 1719, 1252, 1104, 1060, 715 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 2.33 (1H, ddd, *J* = 14.0, 7.0, 2.0 Hz, H19), 2.45 (1H, dd, *J* = 15.5, 9.5 Hz, H14), 2.55 (1H, dd, *J* = 15.5, 4.0 Hz, H14), 2.71 (1H, dddd, *J* = 14.0, 9.5, 4.5, 1.0 Hz, H19), 3.26 (3H, s, MeO), 3.28 (3H, s, MeO), 3.47 (1H, dd, *J* = 10.5, 10.0 Hz, H22), 3.52 (1H, ddd, *J* = 9.5, 4.5, 2.0 Hz, H20), 3.80 (1H, ddd, *J* = 10.5, 9.5, 5.0 Hz, H21), 4.12 (1H, ddd, *J* = 9.5, 8.5, 4.0 Hz, H15), 4.34 (1H, dd, *J* = 10.0, 5.0 Hz, H22), 5.27 (1H, s, MP), 5.20 (1H, ddd, *J* = 11.0, 6.0, 1.0 Hz, H17), 5.68 (1H, ddd, *J* = 8.5, 6.0, 2.0 Hz, H16), 5.71 (1H, dddd, *J* = 11.0, 9.5, 7.0, 2.0 Hz, H18), 6.83 (2H, d, *J* = 8.5 Hz, MP), 7.02-7.04 (2H, m, Bz), 7.13 (1H, m, Bz), 7.55 (2H, d, *J* = 8.5 Hz, MP), 8.03 (1H, m, Bz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.6, 38.4, 51.8, 55.4, 69.2, 73.1, 73.8, 79.3, 81.7, 101.8, 113.8, 127.6, 128.7, 129.7, 129.8, 130.2, 130.3, 132.8, 133.6, 160.2, 165.3, 171.4; HRMS (ESI), calcd for $C_{26}H_{28}O_8Na$ 491.1676 ($M+Na^+$), found 491.1680.

Eight-membered E-ring 22. To a mixture of **20** (2.80 g, 6.00 mmol) and anisaldehyde dimethyl acetal (4.0 mL, 24.0 mmol) in EtOH (30 mL) at rt was added $RuH(CO)Cl(PPh_3)_3$ (290 mg, 0.300 mmol). The mixture was stirred for 6 h at 100 °C. After being cooled to rt, the mixture was concentrated. The residue was subjected to flash column chromatography (hexane/EtOAc 16:1-10:1) to afford benzoate (**21**:**20**=7.6:1), which was inseparable from anisaldehyde. The mixture was used in the next reaction without further purification: colorless solid; ^1H NMR (500 MHz, C_6D_6) δ 2.34 (1H, dd, *J* = 16.0, 10.0 Hz, H14), 2.39 (1H, ddd, *J* = 13.5, 7.0, 3.0 Hz, H17), 2.40 (1H, dd, *J* = 16.0, 3.0 Hz, H14), 2.63 (1H, ddd, *J* =

13.5, 10.5, 3.0 Hz, H17), 3.22 (3H, s, MeO), 3.27 (3H, s, MeO), 3.50 (1H, dd, *J* = 10.5, 10.0 Hz, H22), 3.96 (1H, ddd, *J* = 10.5, 9.5, 5.5 Hz, H21), 4.23 (1H, ddd, *J* = 9.5, 5.0, 2.0 Hz, H20), 4.34 (1H, ddd, *J* = 10.0, 10.0, 3.0 Hz, H15), 4.36 (1H, ddd, *J* = 10.0, 5.5 Hz, H22), 5.18 (1H, ddd, *J* = 10.0, 3.0, 3.0 Hz, H16), 5.31 (1H, s, Me), 5.47 (1H, dddd, *J* = 11.0, 10.5, 7.0, 2.0 Hz, H18), 6.02 (1H, dd, *J* = 11.0, 5.0 Hz, H19), 6.83 (2H, d, *J* = 8.5 Hz, MP), 7.02-7.06 (2H, m, Bz), 7.11-7.15 (1H, m, Bz), 7.55 (2H, d, *J* = 8.5 Hz, MP), 8.02-8.05 (1H, m, Bz); HRMS (ESI), calcd for $C_{26}H_{28}O_8Na$ 491.1676 ($M+Na^+$), found 491.1678.

To a solution of **21** in MeOH/THF (3:1, 40 mL) at rt was added K_2CO_3 (362 mg, 2.63 mmol). After being stirred for 6 h at rt, the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc(x2), and dried over Na_2SO_4. Concentration and open column chromatography (hexane/EtOAc 15:1-2:1) gave eight-membered E-ring **21** (1.27 g, 3.49 mmol) in 58% over 2 steps: colorless solid; $[\alpha]_D^{21}$ = -111.7 (*c* 1.09, $CHCl_3$); IR (film) ν 3468, 2930, 1730, 1615, 1518, 1250, 1102, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60 (1H, d, *J* = 6.0 Hz, OH), 2.32 (1H, ddd, *J* = 14.0, 6.5, 2.5 Hz, H17), 2.44 (1H, dd, *J* = 16.0, 9.5 Hz, H14), 2.79 (1H, ddd, *J* = 14.0, 10.5, 3.5 Hz, H17), 2.82 (1H, dd, *J* = 16.0, 3.0 Hz, H14), 3.53 (1H, dd, *J* = 10.5, 9.5 Hz, H22), 3.64 (1H, ddd, *J* = 9.5, 9.5, 5.0 Hz, H21), 3.71 (3H, s, MeO), 3.76 (1H, dddd, *J* = 9.0, 6.0, 3.5, 2.5 Hz, H16), 3.80 (1H, s, MeO), 3.87 (1H, ddd, *J* = 9.5, 9.0, 3.0 Hz, H15), 4.14 (1H, dd, *J* = 10.5, 5.0 Hz, H22), 4.40 (1H, ddd, *J* = 9.5, 5.5, 2.0 Hz, H20), 5.40 (1H, s, MP), 5.81 (1H, dddd, *J* = 11.5, 10.5, 6.5, 2.0 Hz, H18), 5.95 (1H, dd, *J* = 11.5, 5.5 Hz, H19), 6.87-6.91 (2H, m, MP), 7.39-7.43 (2H, m, MP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.2, 39.4, 51.9, 55.5, 69.6, 75.7, 76.0, 79.1, 79.7, 100.9, 113.8, 125.2, 127.6, 130.2, 134.9, 160.2, 172.4; HRMS (ESI), calcd for $C_{19}H_{24}O_7Na$ 387.1414 ($M+Na^+$), found 387.1416.

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