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A TRANSANNULAR DIELS-ALDER STRATEGY TO THE CONSTRUCTION OF THE CDE RING SYSTEM OF NAKITERPIOSIN

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Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Abstract – The transannular Diels-Alder (TADA) reaction was applied to the synthesis of the CDE ring system of nakiterpiosin (**1**). TADA product **28** is a key intermediate toward the total synthesis of **1**.

INTRODUCTION

Coral reefs are good sources of medicines such as antimicrobial and anticancer agents.[1,2] However, many reefs are now increasingly threatened due to overfishing, pollution, typhoons, and global warming. In addition, the overgrowth of other organisms in coral reefs has been recognized as another factor of their destruction.[3] One of the authors (D. U.) previously reported the isolation and structural determination of nakiterpiosin (**1**) and nakiterpiosinone (**2**) from the marine sponge *Terpios hosinota*, which overgrew coral communities in waters off the Ryukyu Islands (Figure 1).[4] Compounds **1** and **2** exhibit potent cytotoxicity against mouse lymphocytic leukemia cells (P388). However, the limited availability of **1** and **2** (**1** of 0.4 mg and **2** of 0.1 mg isolated from *Terpios hosinota* of 30 kg) has hampered further biological studies. Thus, supply of these compounds from chemical syntheses is strongly demanded. We describe herein the results of our study toward the synthesis of **1** by a transannular Diels-Alder (TADA) strategy

which is the most useful method for the construction of the fused carbocyclic compounds.[5,6]

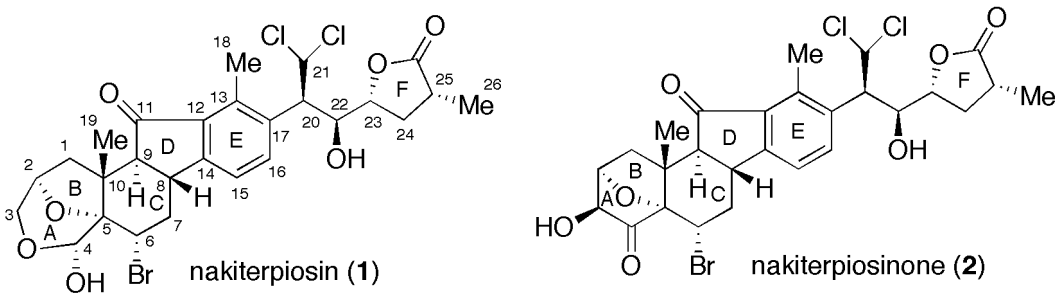
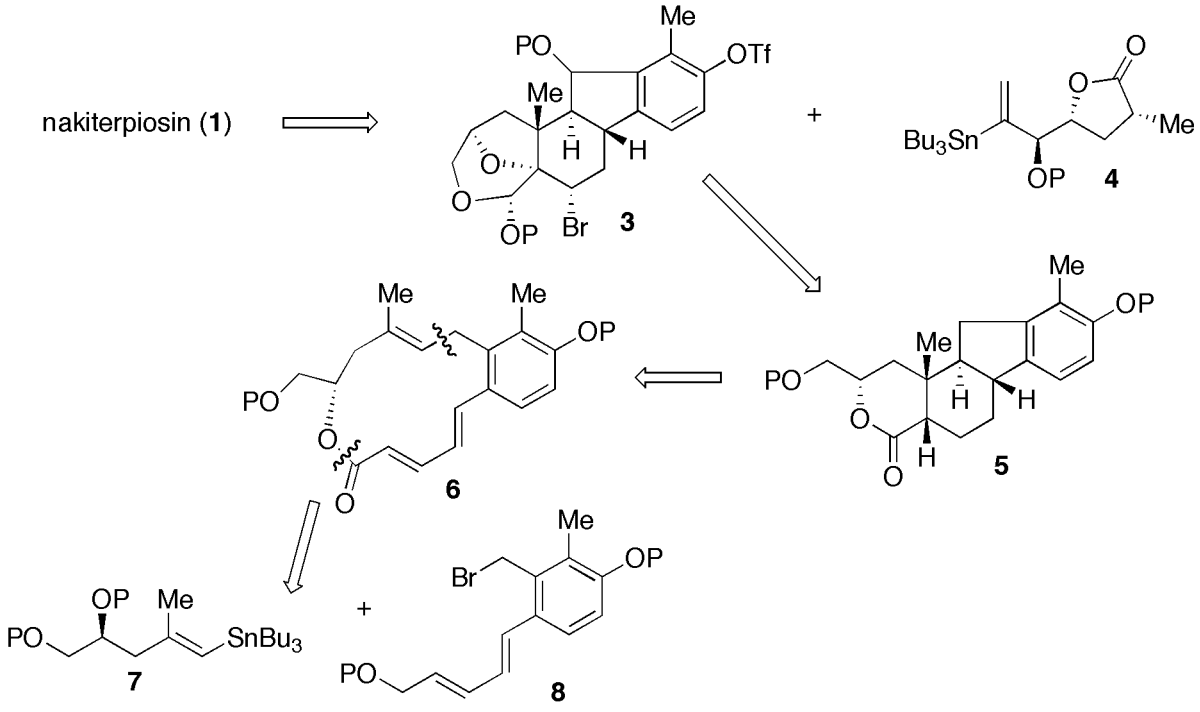


Figure 1

RESULTS AND DISCUSSION

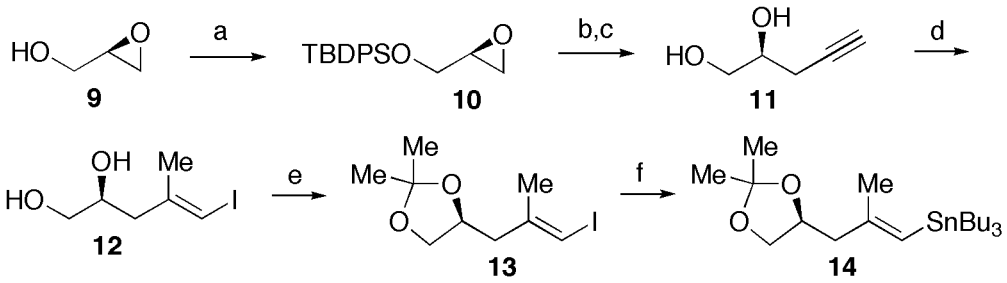
Scheme 1 shows the retrosynthetic analysis of **1**. The carbon framework of **1** can be broken down into the pentacyclic core **3** and C20-C26 fragment **4**. Compound **3** can be synthesized from **5** through oxidative functionalization. Rings C and D of **5** can be constructed by a TADA reaction of **6**. Lactone **6** would be synthesized via a Stille coupling reaction of the vinyl stannane **7** and the benzyl bromide **8**.



Scheme 1

Scheme 2 describes the preparation of the vinyl stannane **14**. Treatment of (*R*)-(+)-glycidol (**9**) with TBDPSCl/imidazole gave the TBDPS ether **10**. Two-carbon was elongated with (trimethylsilyl)acetylene,[7] followed by removal of silyl protecting groups with TBAF to afford the diol **11**.

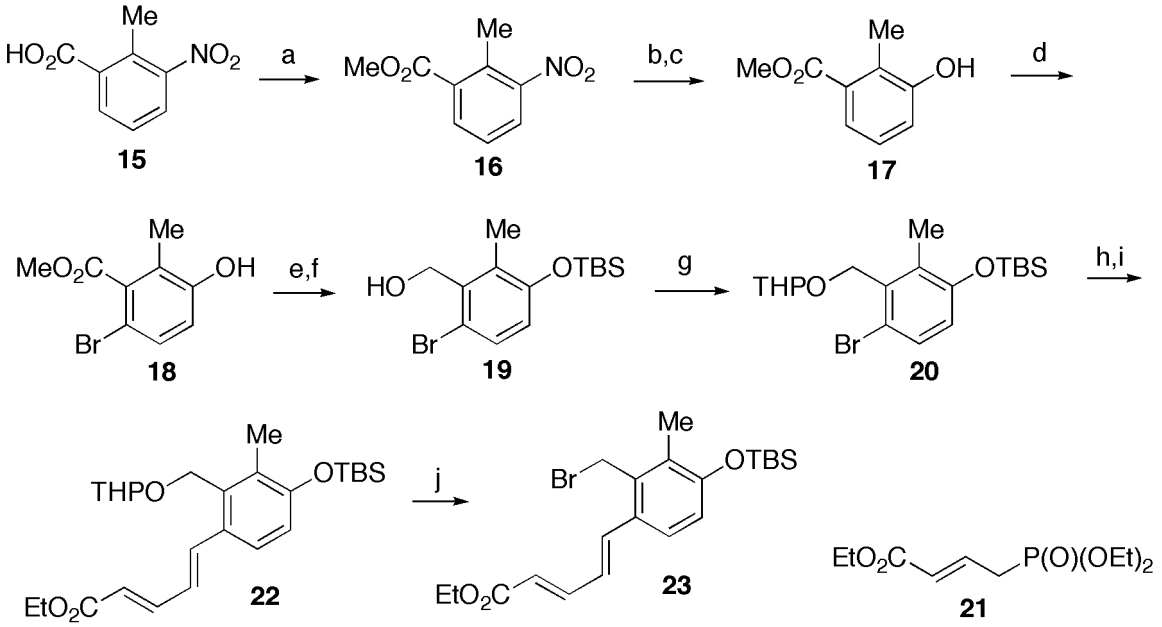
The alkyne **11** was subjected to Negishi's carbometalation conditions[8] to provide the vinyl iodide **12**. The vicinal diol moiety of **12** was protected with 2,2-dimethoxypropane to give the acetonide **13**. Treatment of **13** with *t*-BuLi, and subsequent trapping of the resulting vinyl lithium with Bu_3SnCl gave the vinyl stannane **14**.



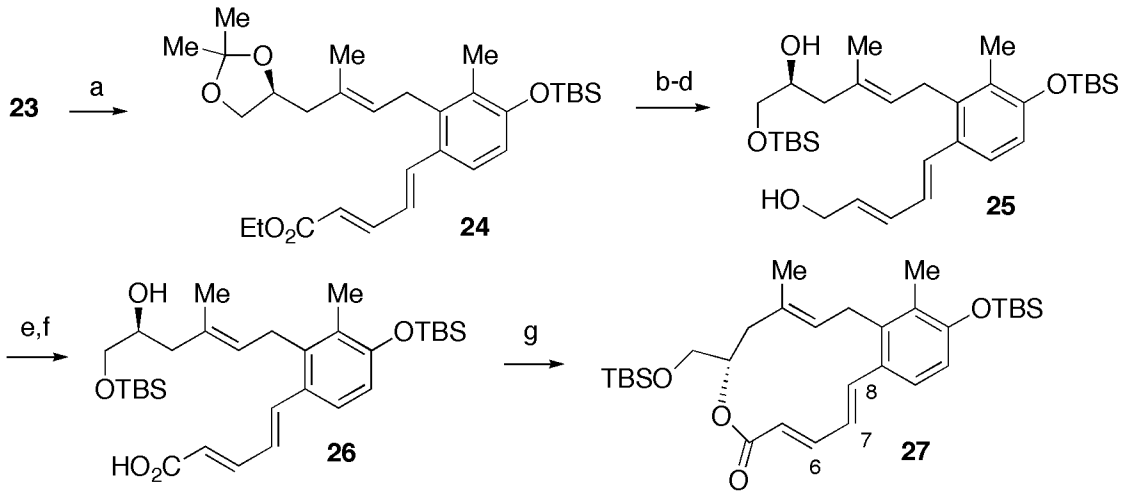
Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C, 94%; (b) trimethylsilylacetylene, *n*-BuLi, THF, -78 °C then $BF_3{\cdot}OEt_2$, **10**, -78 °C; (c) TBAF, THF, 0 °C, 72% (2 steps); (d) $AlMe_3$, Cp_2ZrCl_2, $Cl(CH_2)_2Cl$, 50 °C, then I_2, THF, -30 °C, 55%; (e) 2,2-dimethoxypropane, $TsOH{\cdot}H_2O$, rt, 99%; (f) *t*-BuLi, Et_2O, -78 °C, then Bu_3SnCl, -78 °C to 0 °C, 77%.

Next, we examined the synthesis of the aromatic part (Scheme 3). 2-Methyl-3-nitrobenzoic acid (**15**) was esterified with sulfuric acid in methanol to give the methyl ester **16**. Hydrogenation of the nitro functional group of **16** followed by Sandmeyer reaction with sodium nitrite and sulfuric acid provided the phenol **17**. **17** was brominated with Br_2 to exclusively give the 6-bromo isomer **18**.[9] Hydroxy group was protected with TBSCl/imidazole, then ester moiety was reduced with DIBALH to afford the benzyl alcohol **19**. Protection of the alcohol **19** with DHP/PPTS gave the THP ether **20** in 70% yield from **17**. After formyl moiety was introduced, subsequent four-carbon elongation was performed by the Horner-Wadsworth-Emmons reaction of **20** and triethyl 4-phosphonocrotonate **21** to provide the coupling product **22**, which possesses an *E,E*-diene moiety. THP ether **22** was converted to the benzyl bromide **23** with CBr_4/PPh_3 in CH_2Cl_2 at 40 °C.[10]

With coupling precursors **14** and **23** in hand, next task was preparing the precursor of the TADA reaction. Vinyl stannane **14** and benzyl bromide **23** were connected by Stille coupling reaction to give the desired product **24** in 80% yield (Scheme 4). After the acetonide protecting group was removed with 1,3-propanedithiol and $BF_3{\cdot}OEt_2$, the resulting primary hydroxy group was selectively protected with TBSCl/imidazole, and the ester moiety was reduced to give the diol **25**. Chemoselective oxidation of the allylic alcohol moiety of **25** with MnO_2, and subsequent Pinnic oxidation[11] gave the seco-acid **26**. As a result of our investigation in macrolactonization of **26**, Shiina's protocol[12] was found to be suitable for the synthesis of **27**. Thus, treatment of **27** with 2-methyl-6-nitrobenzoic anhydride (MNBA) and DMAP gave the desired lactone **27**, which is the precursor of the TADA reaction, in 56% yield from **25**.

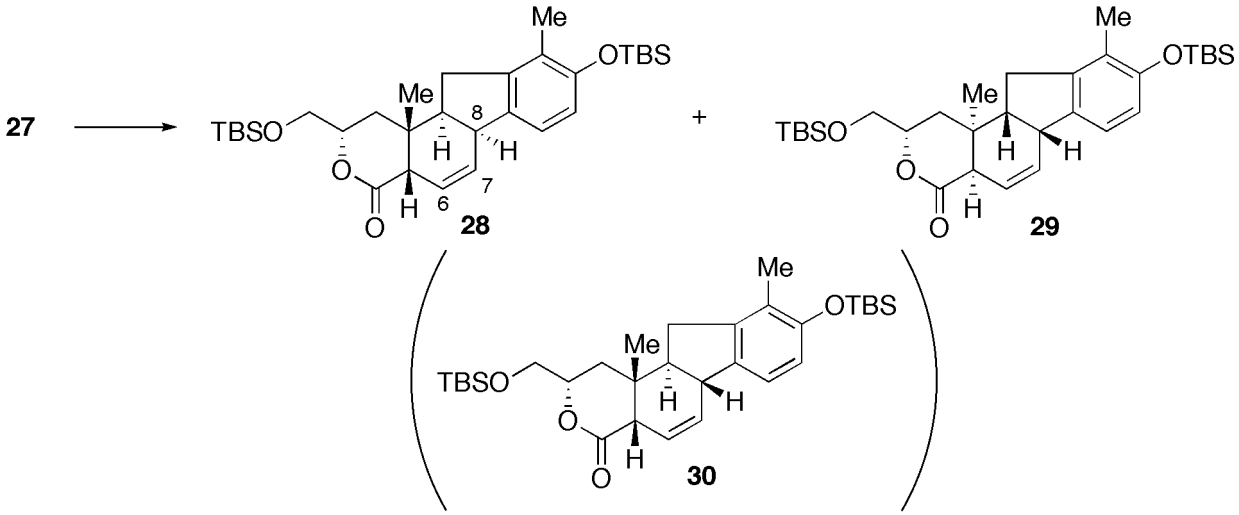


Scheme 3. Reagents and conditions: (a) H_2SO_4, MeOH, reflux; (b) H_2, Pd/C, EtOH, rt; (c) $NaNO_2$, H_2SO_4, reflux, 47% (3 steps); (d) Br_2, CH_2Cl_2, -45 °C; (e) TBSCl, imidazole, DMF, rt; (f) DIBALH, CH_2Cl_2, -78 °C; (g) DHP, PPTS, CH_2Cl_2, rt, 70% (4 steps); (h) *n*-BuLi, THF, -78 °C, then DMF, -78 °C; (i) **21**, NaH, THF, rt, 78% (2 steps); (j) CBr_4, PPh_3, CH_2Cl_2, 40 °C, 86%.



Scheme 4. Reagents and conditions: (a) **14** (1.2 equiv.), $Pd(dba)_2$, PPh_3, DMF, 30 °C, 80%; (b) 1,3-propanedithiol, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C, 85%; (c) TBSCl, imidazole, DMF, 0 °C; (d) DIBALH, CH_2Cl_2, -78 °C, 70% (2 steps); (e) MnO_2, CH_2Cl_2, rt; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*-BuOH/H_2O (3:3:1), rt; (g) MNBA, DMAP, CH_2Cl_2, rt, 56% (3 steps).

Next, investigation of the TADA reaction of **27** was carried out (Table 1). Cyclization did not proceed, either in refluxing toluene (entry 1) or under the conditions of 5.0 M $LiClO_4$ in diethyl ether, reported by Grieco et al.[13] (entry 2). Finally, heating in 1,2,4-trichlorobenzene at 160 °C gave the TADA products **28** and **29** in respective yields of 50% and 35%. Unfortunately, the TADA product **30**, which possesses the desired stereochemistries, was not obtained.



entry	conditions	yield (%)	
		28	**29**
1	toluene, reflux	0[a]	0
2	5.0 M $LiClO_4$/Et_2O, reflux	0[a]	0
3	1,2,4-trichlorobenzene, 160 °C	50	35

[a]No reaction was observed.

Table 1. TADA reaction of **27**.

The stereostructures of **28** and **29** were determined by ^1H-^1H coupling constants and NOE experiments (Figure 2). Concerning the TADA product **28**, H_a-1 and H_b-1 were assigned by coupling constants ($J_{1a,2}$ = 3.6 Hz and $J_{1b,2}$ = 12.6 Hz). The observation of NOEs for 19-Me/H_a-1, 19-Me/H-2, and 19-Me/H-5 indicated that 19-Me, H_a-1, H-2, and H-5 were in *syn* orientation to each other. Based on the NOE observations for H_b-1/H-8 and H-8/H-9, these three protons were considered to be in *syn* relationships. Thus, the stereochemistries of **28** were determined as shown in Figure 2. The stereostructure of **29** was examined in a similar way. Based on the NOEs observed for H_a-1/H-2, H_a-1/H-8, and H-8/H-9, these protons were found to be in *syn* relationships. Furthermore, NOEs for 19-Me/H_b-1 and 19-Me/H-5

suggested that 19-Me, H_b-1, and H-5 were oriented in a *syn* arrangement. Therefore, the stereochemistries of **29** were elucidated to be as shown in Figure 2.

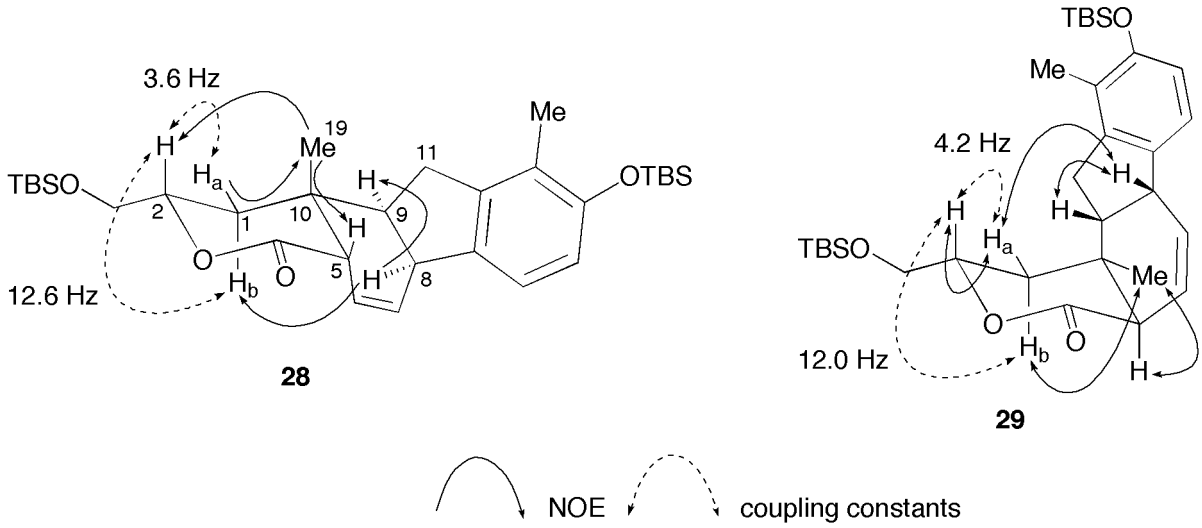
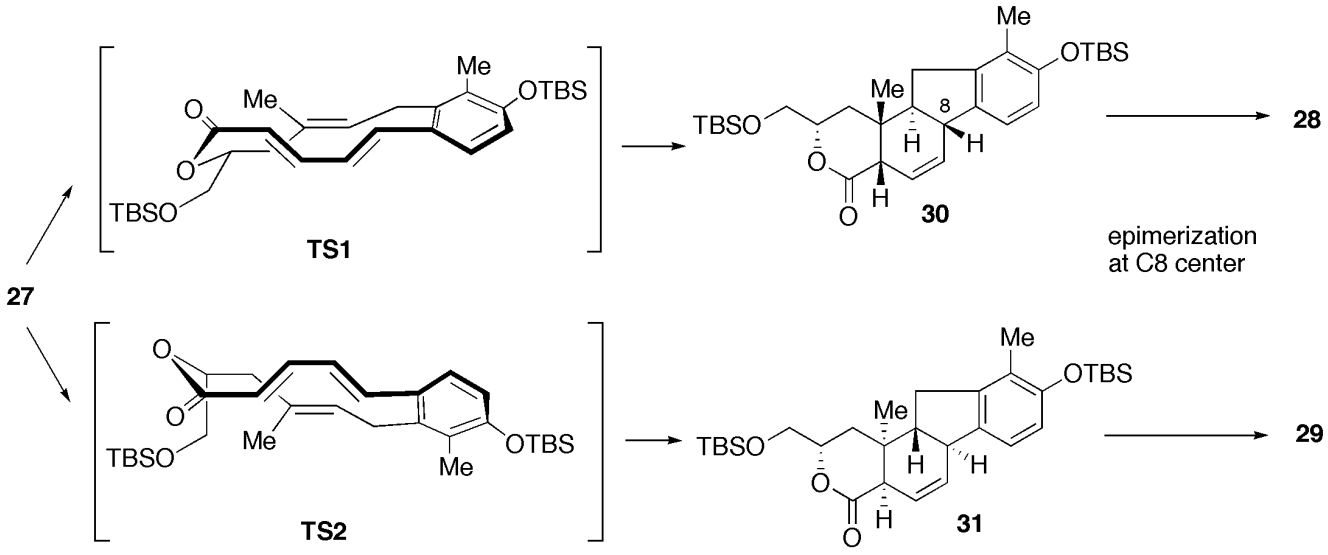


Figure 2

There is a possibility that compounds **28** and **29** could be formed by the isomerization of the C7-C8 (*E*)-alkene of **27** to the (*Z*)-alkene, followed by the TADA reaction. However, when the (*Z*)-alkene compound at C7-C8[14] was subjected to heating in 1,2,4-trichlorobenzene at 160 °C (conditions of entry 3 in Table 1), the TADA products were not obtained. Thus, reaction pathways to **28** and **29** are thought to be as described in Scheme 5. The TADA reaction of **27** proceeded through the transition states **TS1** and **TS2** to form the cyclized products **30** and **31**. The epimerization at C8 center under the heating reaction conditions occurred to give **28** and **29**.[15] We are planning to convert **28** to nakiterpiosin (**1**) by the epimerization of C8 center.



Scheme 5

In conclusion, we constructed the CDE ring framework of nakiterpiosin by the TADA reaction. Further studies toward the total synthesis of nakiterpiosin are underway in our laboratory.

EXPERIMENTAL

General Method. Reagents and starting materials were obtained from commercial suppliers and used without further purification. Reactions requiring anhydrous conditions were performed under an argon atmosphere. The melting point was measured with YAZAWA BY-2. The NMR spectra were recorded on JEOL JNM-EX270, JEOL JNM-AL400, and JEOL JNM-A600 (^{1}H, ^{13}C NMR). Chemical shifts were reported in delta units (δ) relative to chloroform (7.24), benzene (7.15). IR spectra were recorded on a JASCO FT/IR-460 plus. Optical rotations were measured by a JASCO DIP-1000. Mass spectra were measured by JEOL JMS-LG2000 (FAB) and Micromass LCT (ESI). Thin layer chromatography (TLC) was performed on Merck silica gel 60F-254 plates. Column chromatography was performed with Kanto Chemical silica gel 60N (40-100 μm, spherical, neutral) and Fuji Silysia silica gel BW-820MH.

TBDPS Ether 10. To a solution of (*R*)-(+)-glycidol (**9**) (5.00 g, 67.5 mmol) in CH_2Cl_2 (200 mL) were added imidazole (9.20 g, 0.14 mol) and TBDPSCl (18.4 mL, 74.3 mmol) at 0 °C. After stirring at the same temperature, the mixture was diluted with EtOAc. The organic layer was washed by satd aq. NH_4Cl, H_2O, and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc, 8:1) gave the TBDPS ether **10** (19.8 g, 94%): colorless oil; R_f = 0.65 (hexane/EtOAc, 3:1); $[\alpha]^{22}_D$ +4.8° (c 1.55, CH_2Cl_2); IR (neat) 2959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.73 (m, 4 H), 7.49-7.41 (m, 6 H), 3.90 (dd, J = 11.8, 3.1 Hz, 1 H), 3.76 (dd, J = 11.8, 4.7 Hz, 1 H), 3.18-3.14 (m, 1 H), 2.77 (t, J = 4.3 Hz, 1 H), 2.66-2.63 (m, 1 H), 1.12 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.0, 129.8, 102.6, 87.1, 70.2, 66.4, 26.8, 19.3.

Diol 11. To a solution of trimethylsilylacetylene in THF (150 mL) was added *n*-BuLi (83 mL, 0.14 mol, 1.6 M in hexane) at –78 °C. After stirring at the same temperature for 30 min, $BF_3{\cdot}OEt_2$ (16.9 mL, 0.13 mol) and a solution of **10** (19.8 g, 63.5 mmol) in THF (50 mL) were added to the mixture. The mixture was stirred at the same temperature for 2 h, then diluted with EtOAc. The organic layer was washed with satd aq. NH_4Cl, H_2O, and brine. Dried over $MgSO_4$, concentration gave the corresponding crude alcohol (23.5 g). This crude alcohol was used for next reaction without further purification. To a solution of the alcohol (23.5 g) obtained above in THF (200 mL) was added TBAF (158 mL, 0.158 mol, 1.0 M in THF) at 0 °C. After stirring at the same temperature for 1 h, the mixture was diluted with EtOAc. The organic layer was washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography

(hexane/EtOAc, 4:1 to 1:1) gave the diol **11** (4.60 g, 72% in 2 steps): colorless oil; R_f = 0.10 (hexane/EtOAc, 1:1); $[\alpha]^{21}_D$ +7.2° (c 1.01, CH_2Cl_2); IR ($CHCl_3$) 3366, 3291, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (ddd, J = 6.4, 6.4, 3.5 Hz, 1 H), 3.75 (dd, J = 11.3, 3.5 Hz, 1 H), 3.60 (dd, J = 11.3, 6.4 Hz, 1 H), 2.51 (brs, 2 H), 2.44 (dd, J = 2.7, 1.0 Hz, 1 H), 2.43 (dd, J = 2.7, 1.0 Hz, 1 H), 2.07 (t, J = 2.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1, 71.0, 70.1, 65.4, 23.4.

Vinyl Iodide 12. To a solution of Cp_2ZrCl_2 (5.84 g, 20 mmol) in CH_2Cl_2 (200 mL) were added $AlMe_3$ (85 mL, 0.12 mol, 1.4 M in hexane) and a solution of **11** (4.00 g, 40.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 50 °C for 20 h. To the mixture a solution of I_2 (35.0 g, 0.14 mol) in THF (70 mL) was added at –35 °C. After stirring at the same temperature for 30 min, the mixture was diluted with EtOAc. The organic layer was washed with satd aq. potassium sodium tartrate, H_2O, and brine. Dried over $MgSO_4$, concentration and column chromatography (EtOAc) gave the vinyl iodide **12** (5.32 g, 55%): colorless oil; R_f = 0.45 (hexane/EtOAc, 1:2); $[\alpha]^{22}_D$ –45.4° (c 1.00, $CHCl_3$); IR (neat) 3366, 2928, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (t, J = 1.2 Hz, 1 H), 3.89-3.83 (m, 1 H), 3.65 (dd, J = 11.2, 3.6 Hz, 1 H), 3.45 (dd, J = 11.2, 6.8 Hz, 1 H), 2.43-2.32 (m, 2 H), 1.88 (d, J = 1.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 70.0, 66.6, 43.7, 24.6.

Acetonide 13. To a solution of **12** (40.9 mg, 0.169 mmol) in 2,2-dimethoxypropane (1.6 mL) was added $TsOH \cdot H_2O$ (3.2 mg, 16.9 μmol). The mixture was stirred at rt before the reaction was quenched with Et_3N. Concentration and column chromatography (hexane to hexane/EtOAc, 20:1) gave the acetonide **13** (47.1 mg, 99%): colorless oil; R_f = 0.55 (hexane/EtOAc, 4:1); $[\alpha]^{24}_D$ +2.3° (c 1.00, $CHCl_3$); IR (neat) 2985, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00-5.99 (m, 1 H), 4.24-4.17 (m, 1 H), 4.00 (dd, J = 8.1, 6.0 Hz, 1 H), 3.53 (dd, J = 8.1, 6.8 Hz, 1 H), 2.52 (ddd, J = 14.1, 6.8, 1.2 Hz, 1 H), 2.37 (ddd, J = 14.1, 6.0, 1.2 Hz, 1 H), 1.86 (d, J = 0.80 Hz, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 109.2, 74.0, 69.0, 43.5, 27.0, 25.7, 24.6.

Vinyl Stannane 14. To a solution of **13** (37.8 mg, 0.134 mmol) in Et_2O (1.0 mL) was added *t*-BuLi (0.17 mL, 0.268 mmol, 1.58 M in pentane) at –78 °C. After stirring at the same temperature for 1 h, Bu_3SnCl (0.11 mL, 0.402 mmol) was added. The reaction temperature was gradually raised to 0 °C for 1 h. The reaction was quenched with satd aq. NH_4Cl, and the mixture was diluted with Et_2O. The organic layer was separated and washed with H_2O and brine. Dried over Na_2SO_4, concentration and column chromatography (hexane including 0.5% Et_3N) gave the vinyl stannane **14** (45.8 mg, 77%): colorless oil; R_f = 0.60 (hexane/EtOAc, 10:1); $[\alpha]^{23}_D$ +5.6° (c 1.00, $CHCl_3$); IR (neat) 2926, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (d, J = 0.8 Hz, 1 H), 4.21-4.15 (m, 1 H), 3.87 (dd, J = 7.8, 5.9 Hz, 1 H), 3.50 (dd, J = 7.8,

7.8 Hz, 1 H), 2.51 (dd, J = 13.5, 6.6 Hz, 1 H), 2.24 (ddd, J = 13.5, 7.8, 0.8 Hz, 1 H), 1.79 (s, 3 H), 1.70-1.50 (m, 6 H), 1.45-1.30 (m, 6 H), 1.44 (s, 3 H), 1.35 (s, 3 H), 1.09-0.85 (m, 15 H); HRMS (ESI) calcd for $C_{21}H_{42}O_2SnNa$ $(M+Na)^+$ 469.2108, found 469.2112.

Phenol 17. To a solution of 2-Methyl-3-nitrobenzoic acid (**15**) (10.0 g, 55.2 mmol) in MeOH (50 mL) was added H_2SO_4 (1.0 mL). The mixture was stirred at reflux for 20 h, then concentrated. To the residue was added EtOAc, the organic layer was washed with H_2O and brine. Dried over Na_2SO_4, concentration gave the crude methyl ester **16** (10.5 g) as a pale yellow solid. This methyl ester was used for next reaction without further purification. To a solution of the above ester (10.5 g) and Pd/C (500 mg, 10%wt) in EtOH (78 mL) was stirred under H_2 atmosphere at room temperature for 3 h. The catalyst was filtered off, and the filtrate was concentrated to give the crude amino ester (9.52 g) as a black oil. This amino ester was used for next reaction without further purification. To a solution of the above amino ester (9.52 g) in 5% H_2SO_4 (150 mL) was gradually added $NaNO_2$ (4.19 g, 60.7 mmol) in H_2O (10 mL) at 0 °C. The mixture was stirred at rt for 1 h. After stirring at reflux for 1 h, the mixture was cooled to rt. The mixture was diluted with EtOAc, then organic layer was separated and washed with brine. Dried over Na_2SO_4, concentration and column chromatography (hexane/EtOAc, 20:1 to 10:1 to 5:1) gave the phenol **17** (4.27 g, 47% in 3 steps): yellow crystal; mp 66-67 °C (hexane); R_f = 0.62 (hexane/EtOAc, 2:1); IR (neat) 3293, 2978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.8 Hz, 1 H), 7.09 (t, J = 7.8 Hz, 1 H), 6.92 (d, J = 7.8 Hz, 1 H), 5.00 (s, 1 H), 3.87 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.2, 131.8, 126.1, 125.3, 122.7, 118.3, 52.0, 12.6.

THP Ether 20. To a solution of **17** (1.70g, 10.2 mmol) in CH_2Cl_2 was added Br_2 solution (14.9 mL, 11.2 mmol, 0.75 M in CH_2Cl_2) at -45 °C. After stirring at the same temperature for 2 h, the mixture was quenched with satd aq. $Na_2S_2O_3$. The mixture was diluted with EtOAc, then the organic layer was separated and washed with satd aq. $NaHCO_3$, H_2O, and brine. Dried over Na_2SO_4, concentration gave the crude bromobenzene **18** (2.61 g) as a light brown solid. This compound was used for next reaction without further purification. To a solution of the above crude **18** (2.61 g) in DMF (50 mL) were added imidazole (1.39 g, 20.4 mmol) and TBSCl (2.31 g, 15.3 mmol) at 0 °C. The mixture was stirred at rt for 1 h. The mixture was diluted with EtOAc, then the organic layer was washed with satd aq. NH_4Cl, H_2O and brine. Dried over Na_2SO_4, concentration gave the corresponding TBS ether (3.59 g). This TBS ether was used for next reaction without further purification. To a solution of the above TBS ether (3.59 g) in CH_2Cl_2 (50 mL) was added DIBALH (30.0 mL, 30.6 mmol, 1.02 M in hexane) at –78 °C. After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with MeOH. The mixture was diluted with EtOAc, then the gel residue was removed with a Celite pad and washed with EtOAc.

The filtrate was concentrated to give the crude alcohol **19** (3.21 g) as a pale yellow oil. This alcohol was used for next reaction without further purification. To a solution of crude **19** (3.21 g) in CH_2Cl_2 (50 mL) were added 3,4-dihydro-2*H*-pyran (1.9 mL, 20.4 mmol) and PPTS (256 mg, 1.02 mmol) at 0 °C. The mixture was stirred at rt for 2 h before the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, and the organic layer was separated and washed with satd aq. $NaHCO_3$, H_2O, and brine. Dried over Na_2SO_4, concentration and column chromatography (hexane to hexane/EtOAc, 100:1 to 20:1) gave the THP ether **20** (2.98 g, 70% in 4 steps): pale yellow oil; R_f = 0.64 (hexane/EtOAc, 4:1); IR (neat) 2932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 4.93 (d, J = 11.0 Hz, 1 H), 4.74 (t, J = 3.7 Hz, 1 H), 4.61 (d, J = 11.0 Hz, 1 H), 4.01-3.94 (m, 1 H), 3.63-3.52 (m, 1 H), 2.29 (s, 3 H), 1.86-1.43 (m, 6 H), 1.03-0.95 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 136.3, 131.7, 130.0, 119.8, 117.3, 98.6, 67.3, 62.2, 30.6, 25.8, 25.5, 19.4, 18.3, 13.3, -4.1; HRMS (ESI) calcd for $C_{19}H_{31}BrO_3SiNa$ $(M+Na)^+$ 437.1124, found 437.1136.

Unsaturated Ester 22. To a solution of **20** (20.5 g, 49.5 mmol) in THF (200 mL) was added *n*-BuLi (38.0 mL, 59.4 mmol, 1.57 M in hexane) at –78 °C. The mixture was stirred at the same temperature for 30 min before DMF (5.74 mL, 74.3 mmol) was added. After stirring at –78 °C for 1 h, the reaction was quenched with satd aq. NH_4Cl. The aqueous layer was separated and washed with Et_2O. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$. Concentration gave the crude aldehyde (25.1 g) as a colorless oil. This aldehyde was used for next reaction without further purification. To a suspension of NaH (2.40 g, 59.4 mmol, 60% dispersion in mineral oil) was added triethy 4-phosphonocrotonate **21** (13.1 mL, 59.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min before the solution of above aldehyde (25.1 g) in THF (100 mL and 20 mL rinse) was added. The mixture was stirred at 0 °C for 2 h, then the reaction was quenched with satd aq. NH_4Cl. The aqueous phase was separated and washed with EtOAc. The combined organic layer was washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc, 19:1 to 9:1 to 6:1) gave the unsaturated ester **22** (17.8 g, 78% in 2 steps): pale yellow oil; R_f = 0.51 (hexane/EtOAc, 4:1); IR (C_6H_6) 2929, 1713, 1623 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.81 (dd, J = 15.0, 11.7 Hz, 1 H), 7.45 (d, J = 15.0 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.61 (dd, J = 15.0, 11.7 Hz, 1 H), 6.08 (d, J = 15.0 Hz, 1 H), 4.82 (d, J = 11.4 Hz, 1 H), 4.54 (d, J = 11.4 Hz, 1 H), 4.53 (t, J = 3.0 Hz, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 3.82-3.80 (m, 1 H), 3.37-3.35 (m, 1 H), 2.39 (s, 3 H), 1.59-1.19 (m, 6 H), 1.02 (t, J = 7.2 Hz, 3 H), 1.00 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (150 MHz, C_6D_6) δ 166.7, 154.8, 145,5, 139.1, 136.7, 130.9, 131.1, 127.8, 124.9, 118.9, 97.7, 62.8, 62.1, 60.1, 30.9, 25.9, 25.8, 19.6, 14.4, 12.7, -4.2; HRMS (FAB) calcd for $C_{26}H_{40}O_5SiNa$ $(M+Na)^+$ 483.2543, found 483.2522.

Benzyl Bromide 23. To a solution of **22** (1.10 g, 2.39 mmol) in CH_2Cl_2 (20 mL) were added CBr_4 (950 mg, 2.87 mmol) and PPh_3 (1.50 g, 5.74 mmol) at 0 °C. The mixture was stirred at reflux for 15 h before the reaction was quenched with satd aq. $NaHCO_3$. The aqueous layer was separated and washed with Et_2O. The combined organic layer was washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc, 20:1) gave the benzyl bromide **23** (930 mg, 86%): colorless oil; R_f = 0.58 (hexane/EtOAc, 4:1); IR (neat) 2930, 1710, 1625 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.68 (ddd, J = 15.2, 11.2, 0.7 Hz, 1 H), 7.00 (d, J = 15.2 Hz, 1 H), 6.98 (d, J = 8.5 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 6.50 (ddd, J = 15.2, 11.2, 0.5 Hz, 1 H), 6.04 (d, J = 15.2 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 4.11 (s, 2 H), 2.17 (s, 3 H), 1.5 (t, J = 7.1 Hz, 3 H), 0.98 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.5, 154.8, 144.9, 136.9, 135.9, 129.5, 128.8, 127.9, 125.3,, 121.8, 119.4, 60.3, 28.6, 26.0, 18.5, 14.6, 12.2, -4.1; HRMS (ESI) calcd for $C_{42}H_{62}Br_2O_6Si_2Na$ $(2M+Na)^+$ 901.2335, found 901.2327.

Stille Coupling Product 24. To a solution of **14** (97.5 mg, 0.218 mmol) and **23** (80.0 mg, 0.182 mmol) in DMF (5.0 mL) were added $Pd(dba)_2$ (110 mg, 0.191 mmol) and PPh_3 (112 mg, 0.427 mmol). The mixture was stirred at 30 °C for 2 h. Concentration and column chromatography (hexane/EtOAc, 19:1) gave the coupling product **24** (74.9 mg, 80%): colorless oil; R_f = 0.45 (hexane/EtOAc, 4:1); $[\alpha]^{23}_D$ –6.2° (c 0.50, $CHCl_3$); IR (neat) 2931, 1624 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.75 (dd, J = 15.1, 11.1 Hz, 1 H), 7.16 (d, J = 8.5 Hz, 1 H), 7.05 (d, J = 15.1 Hz, 1 H), 6.71 (d, J = 8.5 Hz, 1 H), 6.58 (dd, J = 15.1, 11.1 Hz, 1 H), 6.07 (d, J = 15.1 Hz, 1 H), 5.00 (t, J = 6.6 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.02-3.95 (m, 1 H), 3.72 (dd, J = 7.8, 6.0 Hz, 1 H), 3.32 (t, J = 7.8 Hz, 1 H), 3.25 (d, J = 6.0 Hz, 2 H), 2.22-2.12 (m, 1 H), 2.09 (s, 3 H), 1.90 (dd, J = 13.2, 5.6 Hz, 1 H), 1.62 (s, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.03 (t, J = 7.1 Hz, 3 H), 1.03 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.7, 155.0, 145.4, 140.8, 139.2, 132.7, 129.1, 127.9, 126.6, 125.2, 125.1, 120.8, 117.3, 109.0, 72.3, 69.5, 60.2, 43.9, 29.2, 27.4, 26.1, 18.6, 17.1, 14.6, 12.9, -4.0; HRMS (ESI) calcd for $C_{30}H_{46}O_5SiNa$ $(M+Na)^+$ 537.3012, found 537.3008.

Diol 25. To a solution of **24** (85.0 mg, 0.170 mmol) in CH_2Cl_2 (3.0 mL) were added 1,3-propanedithiol (0.02 mL, 0.181 mmol) and $BF_3 \cdot OEt_2$ (0.024 mL, 0.181 mmol) at –78 °C. The mixture was stirred at the same temperature for 2 h before the reaction was quenched with satd aq. $NaHCO_3$. To the mixture EtOAc was added, then organic layer was separated and washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc, 4:1) gave the corresponding diol (66.0 mg, 85%) : colorless oil; R_f = 0.25 (hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ +23.6° (c 0.01, CH_2Cl_2); IR (C_6H_6) 3587, 2928, 1712, 1625 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 8.01 (dd, J = 15.6, 12.0 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 1 H), 6.76 (d, J = 12.0 Hz, 1 H), 6.61 (d, J = 8.4 Hz, 1 H), 6.14 (d, J = 12.0 Hz, 1 H), 6.09 (d, J = 15.6 Hz, 1 H), 5.02-4.90 (m, 1 H), 4.00 (q, J = 7.2 Hz, 2 H), 3.55-3.50 (m, 1 H), 3.31-3.28 (m, 1 H), 3.21 (d, J = 6.6 Hz,

2 H), 3.14-3.08 (m, 1 H), 2.23 (s, 3 H), 1.91 (dd, J = 8.8, 5.6 Hz, 1 H), 1.85 (dd, J = 8.8, 3.4 Hz, 1 H), 1.57 (s, 3 H), 1.02 (s, 9 H), 0.94 (t, J = 7.2 Hz, 3 H), 0.10 (s, 6 H); HRMS (ESI) calcd for $C_{27}H_{42}O_5SiNa$ $(M+Na)^+$ 497.2699, found 497.2704. To a solution of the diol (50.0 mg, 0.109 mmol) in DMF (3.0 mL) were added imidazole (35.0 mg, 0.491 mmol) and TBSCl (48.0 mg, 0.490 mmol) at 0 °C. After stirring at 0 °C for 4 h, the mixture was diluted with EtOAc. The organic layer was washed with H_2O and brine. Dried over $MgSO_4$, concentration gave the crude mono-TBS ether (55.0 mg). This compound was used for next reaction without further purification. To a solution of the above TBS ether (55.0 mg) in CH_2Cl_2 (2.0 mL) was added DIBALH (0.36 mL, 0.354 mmol, 0.97 M in hexane) at –78 °C. The mixture was stirred at the same temperature for 3 h before the reaction was quenched with satd aq. sodium potassium tartrate. The aqueous layer was separated and washed with EtOAc. The combined organic layer was washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc. 5:1) gave the diol **25** (40.0 mg, 70% in 2 steps): colorless oil; R_f = 0.31 (hexane/EtOAc, 2:1); $[\alpha]^{20}_D$ +9.2° (c 0.05, CH_2Cl_2); IR (C_6H_6) 3215, 2976, 1716 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.79 (dd, J = 15.6, 11.6 Hz, 1 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.81 (d, J = 11.6 Hz, 1 H), 6.60 (d, J = 8.4 Hz, 1 H), 6.06 (t, J = 11.6 Hz, 1 H), 5.94 (d, J = 15.6 Hz, 1 H), 5.10 (t, J = 6.6 Hz, 1 H), 3.77-3.73 (m, 1 H), 3.45 (dd, J = 9.8, 3.6 Hz, 1 H), 3.36 (dd, J = 9.8, 6.6 Hz, 1 H), 3.27 (m, 2 H), 3.24 (m, 2 H), 2.24 (s, 3 H), 2.11 (m, 2 H), 1.69 (s, 3 H), 1.03 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 6 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

Carboxylic Acid 26. To a solution of **25** (40.0 mg, 0.075 mmol) in CH_2Cl_2 (3.0 mL) was added MnO_2 (65.0 mg, 0.750 mmol) at rt. After stirring for 12 h, the reaction residue was filtered off with a Celite pad, and washed with EtOAc. Concentration gave the crude aldehyde (38.0 mg). This aldehyde was used for next reaction without further purification. To a solution of the above aldehyde (38.0 mg) in THF (1.5 mL), *t*-BuOH (1.5 mL), and H_2O (0.5 mL) were added 2-methyl-2-butene (0.08 mL, 0.75 mmol), $NaH_2PO_4 \cdot 2H_2O$ (35.0 mg, 0.220 mmol), and $NaClO_2$ (20.0 mg, 0.220 mmol) at 0 °C. After stirring at rt for 7 h, the mixture was diluted with EtOAc. The organic layer was separated and washed with H_2O and brine. Dried over $MgSO_4$, concentration gave the crude carboxylic acid **26** (47.0 mg). This compound was used for next reaction without further purification.

Lactone 27. To a solution of **26** obtained above (47.0 mg) in CH_2Cl_2 (10 mL) were added DMAP (360 mg, 0.300 mmol) and MNBA (1.03 g, 0.300 mmol) at 0 °C. The mixture was stirred at rt for 15 h before the reaction was quenched with satd aq. NH_4Cl. The mixture was diluted with EtOAc, then the organic layer was separated and washed with H_2O and brine. Dried over $MgSO_4$, concentration and column chromatography (hexane/EtOAc, 9:1 to 4:1) gave the lactone **27** (23.0 mg, 56% in 3 steps): colorless solid; R_f = 0.52 (hexane/EtOAc, 7:1); $[\alpha]^{20}_D$ –52.6° (c 0.25, CH_2Cl_2); IR (C_6H_6) 2928, 1755 cm^{-1}; ^1H NMR

(600 MHz, C_6D_6) δ 7.86 (dd, J = 15.0, 12.1 Hz, 1 H), 6.82 (d, J = 9.0 Hz, 1 H), 6.74 (d, J = 9.0 Hz, 1 H), 6.45 (d, J = 12.1 Hz, 1 H), 6.00 (t, J = 12.1 Hz, 1 H), 5.84 (d, J = 15.0 Hz, 1 H), 5.21 (m, 1 H), 5.14-5.10 (m, 1 H), 3.82 (dd, J = 10.5, 5.1 Hz, 1 H), 3.62 (dd, J = 10.5, 6.0 Hz, 1 H), 3.28-3.24 (m, 1 H), 3.21-3.16 (m, 1 H), 2.37 (m, 1 H), 2.27 (s, 3 H), 2.20-2.17 (m, 1 H), 1.39 (s, 3 H), 1.03 (s, 9 H), 0.94 (s, 9 H), 0.14 (s, 6 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 167.7, 154.3, 143.0, 140.3, 138.0, 132.8, 130.7, 129.2, 128.9, 128.8, 127.4, 122.7, 116.9, 72.1, 65.9, 43.1, 30.5, 30.4, 30.2, 26.0, 25.9, 18.4, 15.6, -4.2, -5.2, -5.3; HRMS (ESI) calcd for $C_{31}H_{50}O_4Si_2Na$ $(M+Na)^+$ 565.3145, found 565.3148.

TADA Reaction of 27. A solution of **27** (5.2 mg, 9.59 μmol) in 1,2,4-trichlorobenzene (1.0 mL) was stirred at 160 °C for 10 h. Concentration and purification with PTLC (hexane/EtOAc, 8:1) gave **28** (2.7 mg, 50%) and **29** (1.9 mg, 35%). For **28**: colorless solid; R_f = 0.23 (hexane/EtOAc, 7:1); $[\alpha]^{20}_D$ +69.7° (c 0.14, CH_2Cl_2); IR ($CHCl_3$) 2930, 1717, 1601 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.81 (d, J = 7.2 Hz, 1 H), 6.73 (d, J = 7.2 Hz, 1 H), 5.69 (dt, J = 9.6, 2.4 Hz, 1 H), 5.58 (dt, J = 9.6, 2.4 Hz, 1 H), 4.18-4.14 (m, 1 H), 3.62 (dd, J = 11.4, 4.2 Hz, 1 H), 3.46 (dd, J = 11.4, 3.6 Hz, 1 H), 3.38-3.35 (m, 1 H), 2.99-2.97 (m, 1 H), 2.42 (dd, J = 15.6, 7.8 Hz, 1 H), 2.27 (dd, J = 15.6, 10.8 Hz, 1 H), 2.16 (s, 3 H), 2.11-1.97 (m, 2 H), 1.07 (s, 9 H), 0.99 (s, 9 H), 0.96-0.92 (m, 1 H), 0.70 (s, 3 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.13 (s, 6 H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.0, 153.1, 142.6, 137.2, 130.8, 128.4, 123.5, 121.4, 117.6, 76.8, 65.8, 48.8, 46.1, 43.4, 32.6, 32.5, 31.5, 30.2, 26.0, 25.9, 23.7, 18.5, 13.4, -4.2, -5.1, -5.3; HRMS (ESI) calcd for $C_{31}H_{50}O_4Si_2Na$ $(M+Na)^+$ 565.3145, found 565.3130. For **29**: colorless solid; R_f = 0.41 (hexane/EtOAc, 7:1); $[\alpha]^{20}_D$ –43.7° (c 0.10, CH_2Cl_2); IR ($CHCl_3$) 2928, 1729, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 7.8 Hz, 1 H), 6.62 (d, J = 7.8 Hz, 1 H), 5.89 (dt, J = 10.2, 3.0 Hz, 1 H), 5.59 (dt, J = 10.2, 2.4 Hz, 1 H), 4.64-4.60 (m, 1 H), 3.75-3.71 (m, 2 H), 3.69 (dd, J = 10.8, 4.8 Hz, 1 H), 3.13 (dd, J = 5.4, 3.0 Hz, 1 H), 2.82 (dd, J = 15.0, 7.8 Hz, 1 H), 2.67-2.50 (m, 1 H), 2.09 (s, 3 H), 1.95 (dd, J = 14.4, 4.2 Hz, 1 H), 1.71-1.65 (m, 1 H), 1.15 (s, 3 H), 1.02-0.95 (m, 1 H), 1.01 (s, 9 H), 0.91 (s, 9 H), 0.20 (s, 3 H), 0.19 (s, 3 H), 0.09 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 158.9, 152.9, 142.3, 136.4, 132.9, 127.8, 120.8, 117.8, 77.1, 65.0, 48.5, 47.0, 43.5, 37.4, 37.0, 33.0, 32.0, 29.7, 29.5, 25.8, 25.7, 13.1, 0.0, -4.1, -5.3; HRMS (ESI) calcd for $C_{31}H_{50}O_4Si_2Na$ $(M+Na)^+$ 565.3145, found 565.3132.

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14. Treatment of the benzaldehyde, which was prepared from **20** by the formylation, with $(PhO)_2P(O)CH_2CO_2Et$/NaH gave the corresponding unsaturated ester possessing the (*Z*)-alkene moiety at C7-C8. The ester group was reduced to the corresponding aldehyde followed by Wittig reaction with $Ph_3P{=}CHCO_2Et$ to give the unsaturated ester, which possesses the *Z,E*-diene moiety. Further transformation to the TADA precursor was performed according to the synthetic route in Scheme 4.
15. The epimerization at C8 was thought to be proceeded via the radical pathway. Thus, we carried out the TADA reaction of **27** in the presence of Bu_3SnD to catch the C8-deuterated TADA products. However, we couldn't obtain such expected products. So far, reaction mechanism of the epimerization is unclear.