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Studies toward the total synthesis of nakiterpiosin: construction of the CDE ring system by a transannular Diels–Alder strategy

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Abstract—The transannular Diels–Alder (TADA) reaction was applied to the synthesis of the CDE ring system of nakiterpiosin (**1**). Tetracyclic compound **25** may be a key intermediate in the total synthesis of **1**.

Coral communities are good sources of medicines such as antimicrobial and anticancer agents.[1,2] However, many reefs around the world are now increasingly threatened due to overfishing, pollution, typhoons, global warming and coral predators such as the crown-of-thorns starfish *Acanthaster planci*.[3] In addition, the overgrowth of other organisms in coral communities has been recognized as another factor that contributes to their destruction.[4] It has been reported that these organisms produce toxic compounds; for example, the steroidal alkaloids plakinamines A and B were isolated from the marine sponge *Plakina* sp., which overgrows coral heads.[5] We previously reported the isolation and structural determination of nakiterpiosin (**1**), a novel cytotoxic C-nor-D-homosteroid[6] from the marine sponge *Terpios hosinota*, which overgrew coral communities in waters off the Ryukyu Islands (Scheme 1).[7] The limited availability of **1** from natural sources (0.4 mg isolated from 30 kg of *Terpios hosinota*) has hampered biological studies. Therefore, a method for the chemical synthesis of this compound is needed. We report here the results of our study toward the synthesis of **1** by a transannular Diels–Alder (TADA) strategy.[8,9]

A retrosynthetic analysis of **1** is described in Scheme 1. The carbon framework of **1** could be broken into pentacyclic core **2** and the C20–C26 unit **3**. Compound **2** can be prepared from **4** through oxidative functionalization. Rings C and D of **4** can be constructed via a TADA reaction. Lactone **5** could be synthesized via a Stille coupling reaction of vinyl stannane **6** and benzyl bromide **7**.

Vinyl stannane **6** was synthesized as shown in Scheme 2. Treatment of (*R*)-(+)-glycidol (**8**) with *tert*-butyldiphenylsilyl (TBDPS) chloride and imidazole gave TBDPS ether **9**. After two-carbon elongation with trimethylsilylacetylene, the silyl protecting groups were removed with TBAF to afford diol **10** in 72% yield from **9**. Diol **10** was transformed into vinyl iodide **11** using Negishi's carbometalation.[10] The reaction was unsuccessful when the hydroxy groups of **10** were protected with acetonide. The 1,2-diol moiety of **11** was protected with 2,2-dimethoxypropane, and the resulting acetal was converted to vinyl stannane **6**, which is the coupling precursor of the Stille reaction.

Next, we investigated the construction of the aromatic part (Scheme 3). Treatment of 2-methyl-3-nitrobenzoic acid (**12**) with sulfuric acid under reflux conditions in methanol provided ester **13**. Hydrogenation of the nitro group in **13** followed by a Sandmeyer reaction gave phenol **14** in 78% yield from **13**. Bromination of phenol **14** proceeded smoothly in the presence of Br_2 to exclusively

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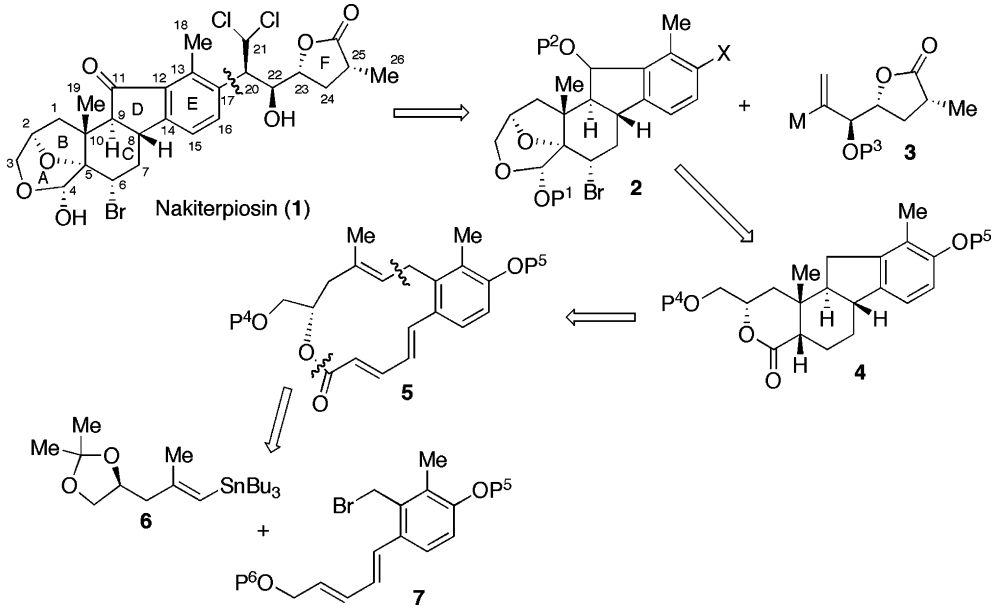
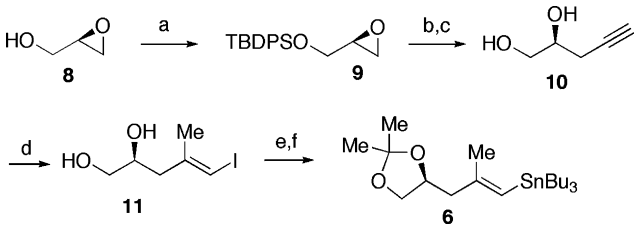
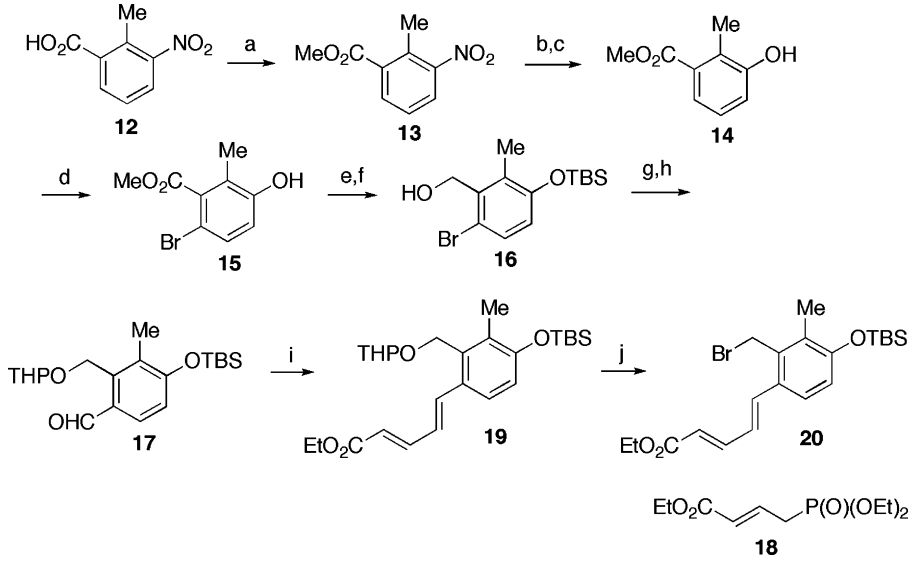


Scheme 1. Retrosynthetic analysis of nakiterpiosin (**1**).

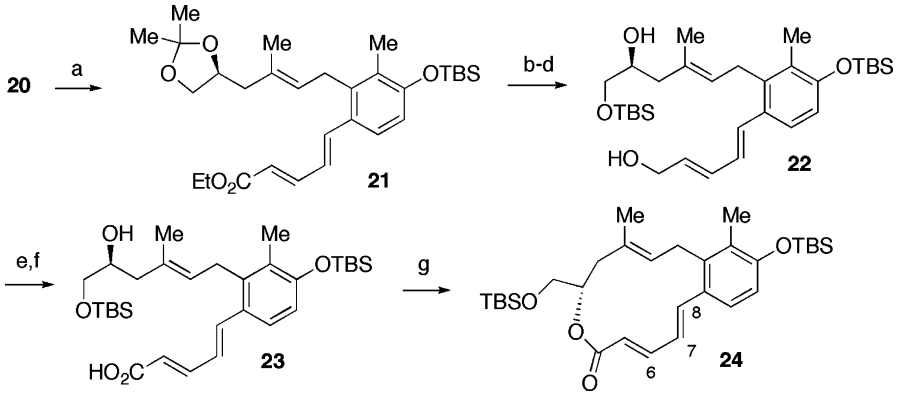


Scheme 2. Synthesis of vinyl stannane **6**. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C, 94%; (b) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (c) TBAF, THF, 0 °C, 72% (2 steps); (d) $AlMe_3$, Cp_2ZrCl_2, $Cl(CH_2)_2Cl$, 50 °C, then I_2, THF, −30 °C, 55%; (e) 2,2-dimethoxypropane, TsOH, DMF, rt, 96%; (f) *t*-BuLi, Et_2O, −78 °C, then Bu_3SnCl, −78 °C, 88%.

give 6-bromo isomer **15** in 83% yield.[11] Protection of phenol **15** with *tert*-butyldimethylsilyl (TBS) chloride and subsequent reduction of the ester moiety with diisobutylaluminum hydride (DIBALH) gave benzyl alcohol **16**. Treatment of benzyl alcohol **16** with dihydropyran (DHP) followed by formylation of the resulting tetrahydropyranyl (THP) ether gave aldehyde **17**. The Horner–Wadsworth–Emmons reaction of **17** and triethyl 4-phosphonocrotonate **18** proceeded smoothly to give the desired coupling product **19**, which possesses an *E*,*E*-diene moiety. THP ether **19** was directly converted to benzyl bromide **20**, which is the coupling partner of vinyl stannane **6**, in the presence of CBr_4 and PPh_3 in CH_2Cl_2 at 40 °C.[12]



Scheme 3. Synthesis of benzyl bromide **20**. Reagents and conditions: (a) H_2SO_4, MeOH, reflux, 92%; (b) H_2, Pd/C, EtOH, rt; (c) $NaNO_2$, H_2SO_4, reflux, 78% (2 steps); (d) Br_2, CH_2Cl_2, −45 °C, 83%; (e) TBSCl, imidazole, DMF, rt, 92%; (f) DIBALH, CH_2Cl_2, −78 °C, 95%; (g) DHP, PPTS, CH_2Cl_2, rt, 90%; (h) *n*-BuLi, THF, −78 °C, then DMF, −78 °C; (i) **18**, NaH, THF, rt, 83% (2 steps); (j) CBr_4, PPh_3, CH_2Cl_2, 40 °C, 73%.



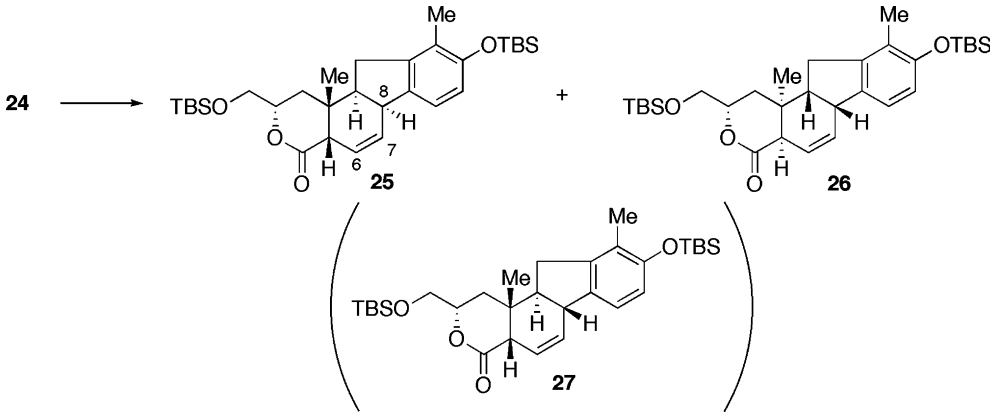
Scheme 4. Synthesis of lactone **24**. Reagents and conditions: (a) **6** (1.2 equiv.), $Pd_2(dba)_3$, PPh_3, DMF, 30 °C, 80%; (b) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 85%; (c) TBSCl, imidazole, DMF, 0 °C; (d) DIBALH, CH_2Cl_2, −78 °C, 70% (2 steps); (e) MnO_2, CH_2Cl_2, rt; (f) $NaClO_2$, 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).

Scheme 4 shows the method for preparing the precursor in the TADA reaction, lactone **24**. Vinyl iodide **6** and benzyl bromide **20** were coupled by a Stille reaction to give the desired product **21** in 80% yield. After removal of the acetonide moiety in the presence of 1,3-propanedithiol and $BF_3{\cdot}OEt_2$, selective protection of the resulting primary alcohol with TBSCl and subsequent reduction of the α,β-unsaturated ester moiety provided diol **22**. Chemoselective oxidation of the allylic alcohol moiety of **22** with MnO_2, followed by Pinnic oxidation, gave seco-acid **23**.[13] After an extensive survey of known macrolactonization methods, Shiina's protocol[14] was found to be suitable for the synthesis of **24**. Thus, treatment of **23** with 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethylamino)pyridine (DMAP) gave the desired lactone **24**, which is the precursor in the TADA reaction, in 56% yield from **22**.

Our examination of the TADA reaction of **24** is summarized in Table 1. Cyclization did not proceed, either in refluxing toluene (entry 1) or under the conditions reported by Grieco et al.[15] (entry 2). Finally, heating in 1,2,4-trichlorobenzene at 160 °C gave the TADA products **25** and **26** in respective yields of 50% and 35% (entry 3). Unfortunately, the desired TADA product **27** was not obtained.

The stereochemistries of **25** and **26** were determined based on ^1H–^1H coupling constants and NOE experiments (Fig. 1). With regard to TADA product **25**, H_a and H_b at C1 were assigned by ^1H–^1H 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* relationships 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 structure of **25** was determined to be as depicted in Figure 1. The stereochemistry of **26** was examined in a similar manner. Based on the NOEs observed for

Table 1. TADA reaction of **24**



Entry	Conditions	Yield (%)	
		25	**26**
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.

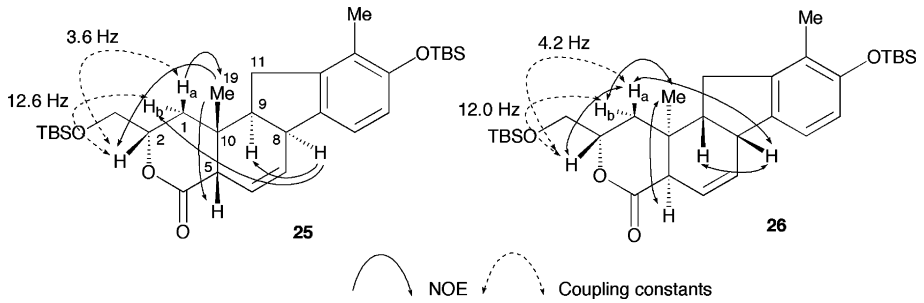
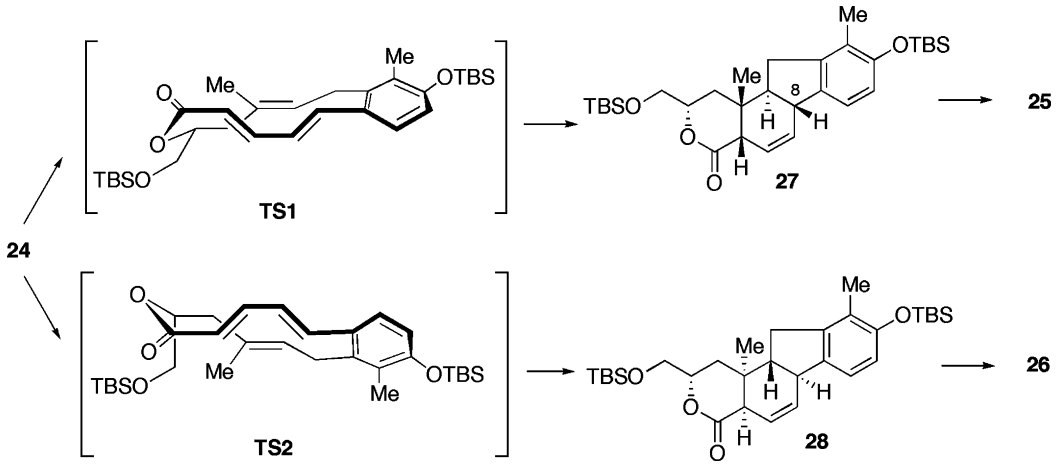


Figure 1. Structural determination of **25** and **26**.



Scheme 5. Reaction pathways to **25** and **26**.

H_a-1/H-2, H_a-1/H-8, and H-8/H-9, these protons were established 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 stereochemistry of **26** was elucidated to be as shown in Figure 1.

Compounds **25** and **26** could be formed by the prior isomerization of the C7–C8 (*E*)-alkene of **24** to a (*Z*)-alkene. However, when the C7–C8 (*Z*)-alkene compound was subjected to the conditions of entry 3 in Table 1, the formation of TADA products was not observed. Thus, reaction pathways to **25** and **26** are thought to be as shown in Scheme 5. TADA reaction of **24** proceeded via the transition states **TS1** or **TS2** to give **27** or **28**, and epimerization at the C8 center occurred to form **25** or **26**. We are planning to convert **25** to nakiterpiosin (**1**) via epimerization at the C8 center.

In conclusion, we synthesized **25**, which possesses the CDE ring framework of nakiterpiosin (**1**) by a TADA reaction. Further studies toward the total synthesis of nakiterpiosin are in progress.

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