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SYNTHESIS OF 6*Z*-PANDANAMINE BY REGIOSELECTIVE CYCLIZATION REACTION OF 2-EN-4-YNOIC ACID DERIVATIVES PROMOTED BY WEAK BASE

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This paper is dedicated to Professor Emeritus Keiichiro Fukumoto at Tohoku University on the occasion of his 75th birthday.

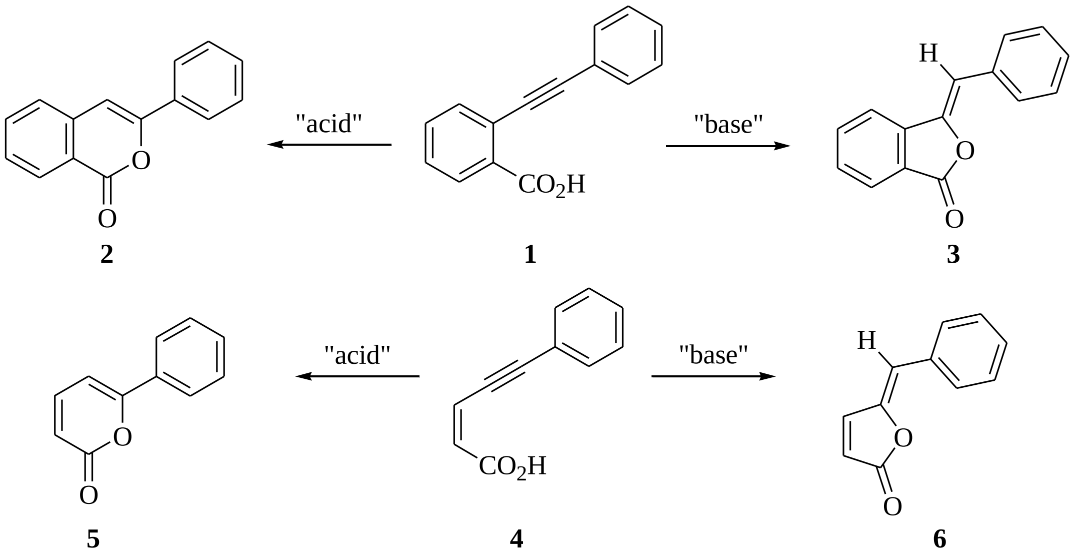
Abstract – The stereoselective synthesis of 6*Z*-pandanamine by base-promoted 5-*exo*-dig−selective cyclization reaction of bis-2-en-4-ynoic acid derivative as a key step is described

INTRODUCTION

The intramolecular cyclization reaction by nucleophilic addition to the carbon−carbon triple bond is a useful methodology for constructing heterocyclic compounds, and significant efforts have been made to develop reagents that promote such reactions.[1] We have previously reported effective methods for the synthesis of substituted heterocyclic compounds catalyzed by Cu(II) salts,[2] Pd(PPh_3)$_4$-methyl propiolate complex,[3] or $PtCl_4$ in ethanol.[4]

We have also reported regiocontrolled intramolecular annulation reactions between carbon−carbon triple bonds and carboxylic acid, promoted by acid or base.[5,6] Acid- and base-promoted cyclization gave isocoumarin **2** and phthalide **3**, respectively, from carboxylic acid **1** (Figure 1). This method was also successfully applied to aliphatic (*Z*)-5-phenylpent-2-en-4-ynoic acid (**4**), which gave pyran-2(2*H*)-one **5** and furan-2(2*H*)-one **6**, respectively. In this paper, we present the total synthesis of 6*Z*-pandanamine (**11**) using base-promoted cyclization as a key step.

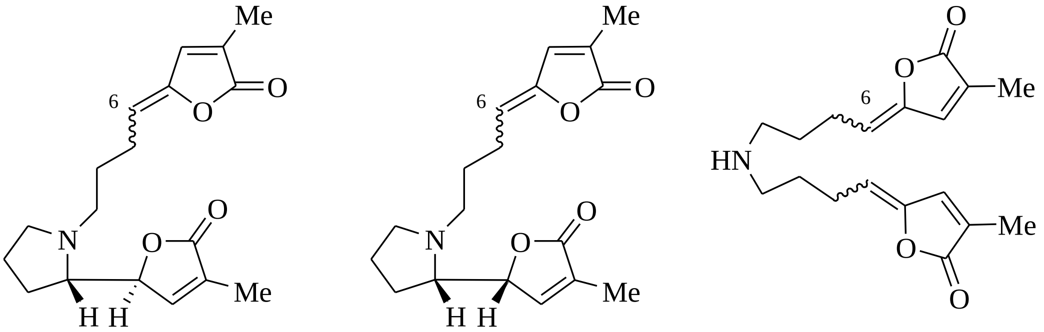
Figure 1. Regio-controlled intramolecular annulation reactions of 1 and 4



In 2000, Takayama and co-workers reported the isolation of pandamarilactonine A (**7**) and B (**8**) (Figure 2) from the leaves of *Pandanus amaryllifolius* Roxb. from the Philippines, Thailand, and Indonesia, where it is used as a traditional medicine for toothache, heart problems and other conditions.[7] Subsequently, pandamarilactonine C (**9**) and D (**10**), isomers of **7** and **8**, respectively, were isolated from the plant,[8] and the structure for the other congeners that contained 6*E*-pandanamine (**12**) were also determined.[9] The biomimetic total synthesis of racemic **7** and **8** was reported by Takayama's research group,[7,8] and synthetic attempts at optically active forms were also reported.[10] The first asymmetric total synthesis and determination of absolute configuration of **7** was achieved by Takayama and co-workers in 2005.[11]

6*Z*-Pandanamine (**11**) was isolated from the same plant in 2001,[12] although the secondary amine **11** was a nameless precursor molecule for the total synthesis of **7** and **8** in 2000.[7] Takayama reported that the optical purity of the isolated **7** was low (26% e.e.), and **8** was isolated as racemate. Later, Craik and co-workers suggested that both **7** and **8**, which were not isolated using a solvent partitioned method, were artifacts formed during the acid-base extraction.[9] Meanwhile, Takayama concluded that **7** was formed enzymatically with high optical purity and racemized during the isolation process, and that **8** was an artifact from **11**, which were demonstrated by NMR experiments using **7** synthesized as an optically active form.[11]

Figure 2. The *Pandanus* alkaloids

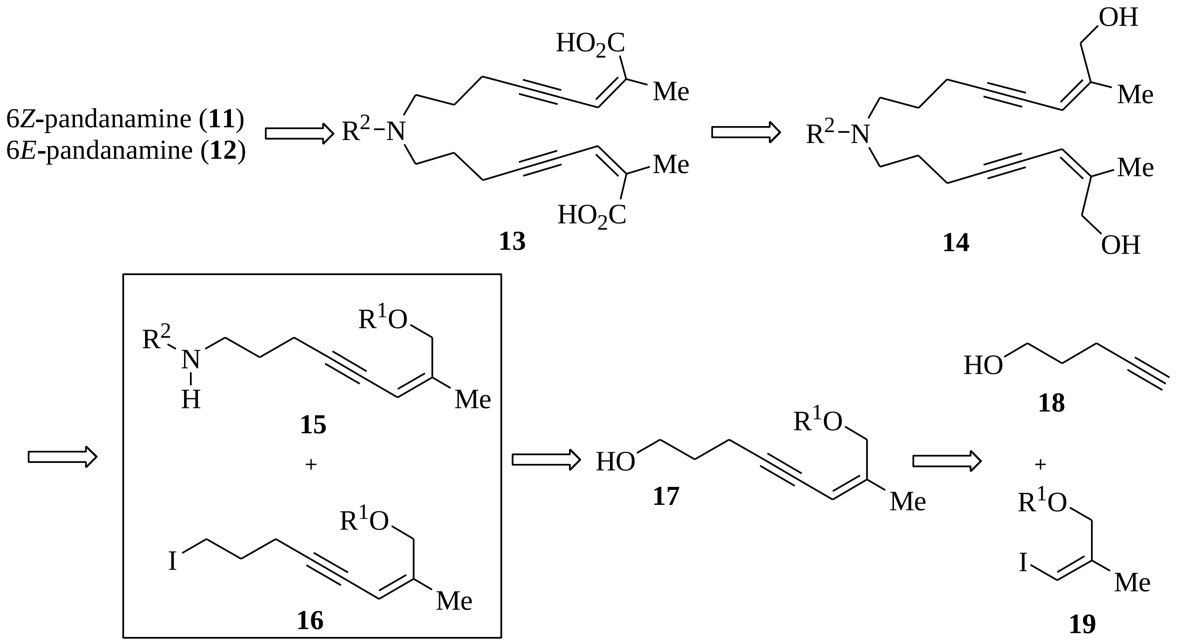


6*Z*-pandamarilactonine-A (**7**) 6*Z*-pandamarilactonine-B (**8**) 6*Z*-pandanamine (**11**)
6*E*-pandamarilactonine-C (**9**) 6*E*-pandamarilactonine-D (**10**) 6*E*-pandanamine (**12**)

RESULTS AND DISCUSSION

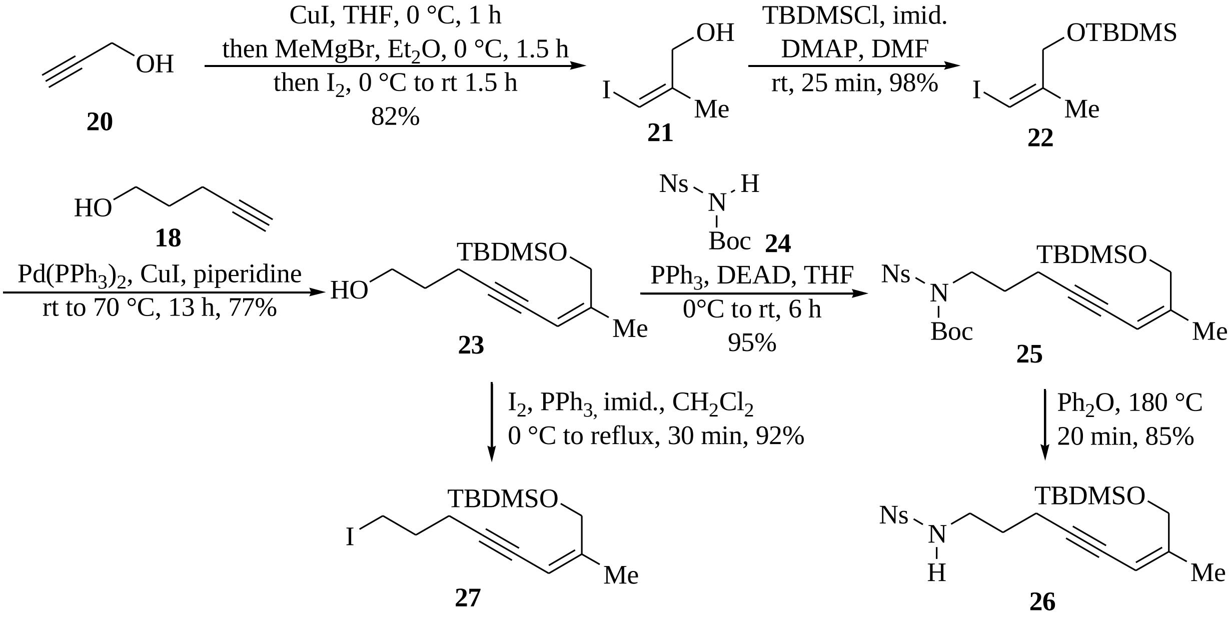
The synthetic strategy for **11** is shown in Figure 3. Briefly, the enol-lactone moieties of **11** are constructed from the symmetrical bis-carboxylic acid **13** by the base-promoted cyclization reaction. The stereochemistry of the enol moiety can be expected as "Z" from our previous results.[5] Since **14**, which is the precursor of the target natural product(s), has a symmetrical structure, it can be synthesized from the amide **15** and the iodide **16**. Both **15** and **16** will be synthesized from the common intermediate **17**, which will be synthesized by Pd-catalyzed coupling reaction between 4-hexyn-1-ol (**18**) and the vinyl iodide **19**.

Figure 3. Synthetic strategy for 6*Z*-pandanamine (11) and/or 6*E*-pandanamine (12)



Along with the strategy shown above, we started synthesizing the common intermediate **17**. The vinyl iodide **21** was selectively synthesized from propargyl alcohol (**20**) according to the literature,[13] and it was converted to the TBDMS ether **22** by standard reaction conditions (Scheme 1). The Sonogashira coupling reaction between **22** and **18** was carried out in the presence of $Pd(PPh_3)_4$ and CuI in piperidine, which afforded the desired alcohol **23** in good yield. Treatment of **23** with *N*-*tert*-butoxycarbonyl-2-nitorobenzensulfonamide (**24**) under Mitsunobu reaction condition gave **25** in 95% yield.[14] Attempts at selective removal of the Boc group of **25** using either Lewis acid or protonic acid were unsuccessful. However, the amide **26** was successfully obtained under thermal condition (diphenyl ether at 180 ˚C, 85%).[15] On the other hand, the iodide **27** was synthesized from **23** by standard reaction conditions (I_2, PPh_3, imidazole, 92%).

Scheme 1. Synthesis of the fragments 26 and 27



As we could establish an efficient pathway to synthesize both fragments **26** and **27**, the next task was the coupling reaction of them. The sodium salt of **26**, which was prepared from **26** with NaH, was reacted with the iodide **27** in DMF at 80 ˚C, affording the desired alkylated product **28** in 90% yield. Next, **28** was converted to the bis-carboxylic acid **29**, which is the substrate for the key reaction, by removal of the TBDMS group (TBAF) and oxidation of the allylic alcohol (Dess-Martin periodinane; DMP), followed by oxidation of the formyl group with $NaClO_2$ in the presence of $NaH_2PO_4 \cdot H_2O$ (Pinnick oxidation). The cyclization reaction of the bis-carboxylic acid **29** was carried out by refluxing with the excess amount of DMAP in toluene to afford the expected bis-lactone **30** as a sole product, in 9% overall yield from **28**.

The stereochemistry of the cyclized product was determined as "*Z*" by comparing the chemical shift of the olefinic protons with those of **11** and **12**[9,12] (Table 1). Consequently, *5-exo*-dig reaction was far superior to *6-endo*-dig mode in base-promoted cyclization reaction for this substrate, which is identical to our previous observation (Figure 1).[5] We encountered trouble with the last stage, removal of the 2-nitorobenzensulfonamide (Ns) group. The lactone moiety decomposed before elimination of the Ns group due to instability of the vinylogous lactone, even under mild reaction condition [(A) PhSH, Cs_2CO_3, DMF, rt or (B) 2-mercaptoethanol, DBU, MeCN, rt] (Scheme 2).[14]

Scheme 2. Synthesis of the bis-lactone 30

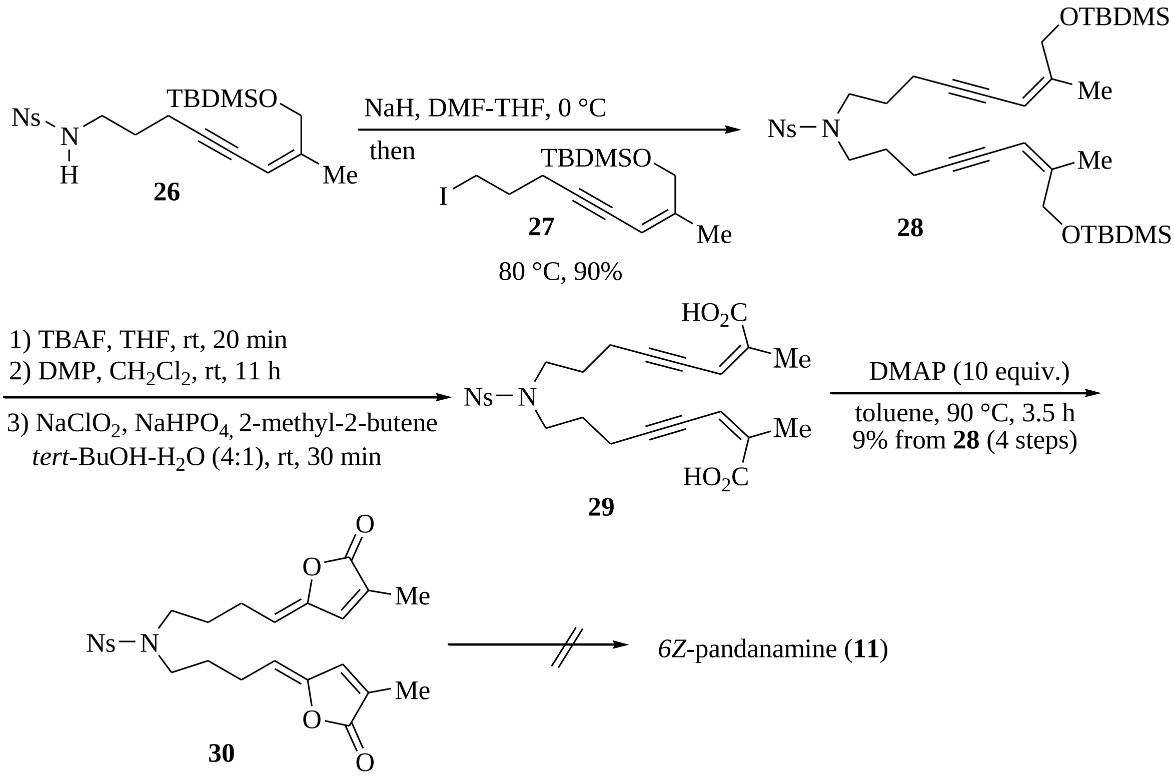
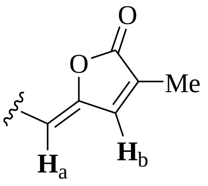
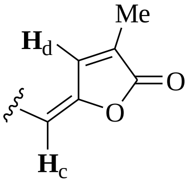
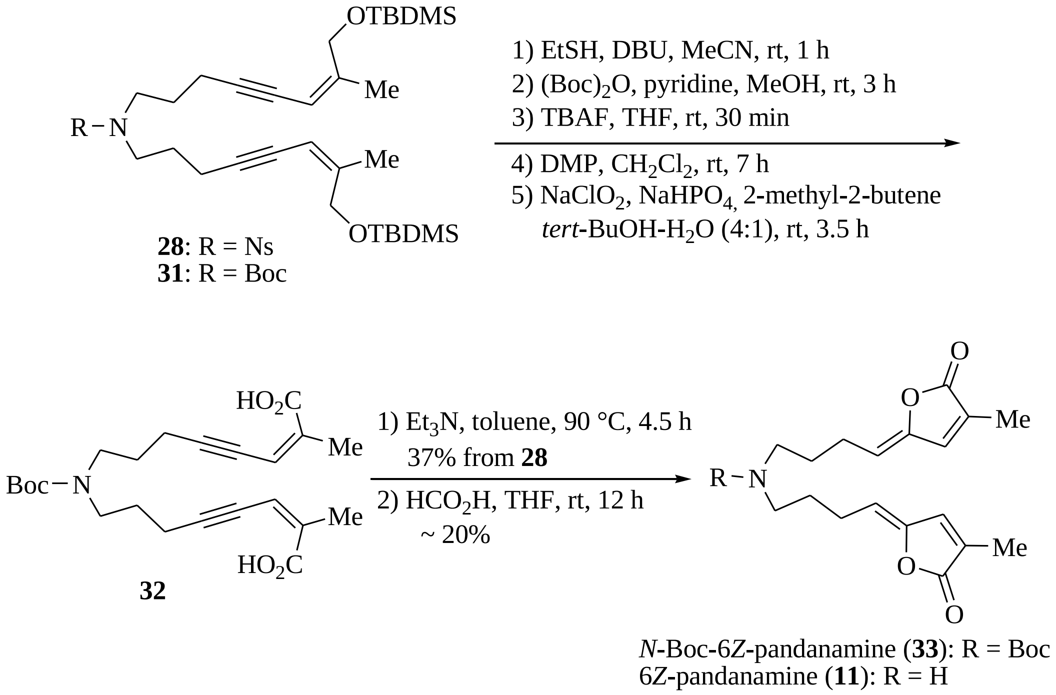


Table 1. Comparison of the chemical shifts of the olefinic protons

Compound	 6*Z*-pandanamine (**11**)	 6*E*-pandanamine (**12**)
Natural product	$\mathbf{H_a}$ = 5.14 $\mathbf{H_b}$ = 7.03	$\mathbf{H_c}$ = 5.51 $\mathbf{H_d}$ = 7.43
Synthesized **30**	$\mathbf{H_a}$ = 5.15 $\mathbf{H_b}$ = 7.00	– –
Synthesized **33**	$\mathbf{H_a}$ = 5.16 $\mathbf{H_b}$ = 6.99	– –

Having learned that the Ns group has to be removed before cyclization reaction, we decided to replace the protecting group before cyclization. Removal of the Ns group was carried out with ethanethiol and DBU in MeCN at room temperature, and the resulting secondary amine was treated with $(Boc)_2O$ in the presence of pyridine to afford the carbamate **31**. The following three-step sequence was carried out as described above. Desilylation of **31** with TBAF, DMP oxidation, and Pinnick oxidation gave bis-2-en-4-ynoic acid derivative **32**. Et_3N was a much better base than DMAP for the stereoselective cyclization reaction of **32**, and **33** was obtained as a single isomer in 37% overall yield from **28**. The stereochemistry of **33** was confirmed as "*Z*" by comparing with **11** and **30** as described before (Table 1). The synthesis was completed by removal of the Boc group with formic acid in THF, which provided **11** (Scheme 3).

Scheme 3. Synthesis of 6*Z*-pandanamine (11)



In summary, we demonstrated the application of base-promoted 5-*exo*-dig–selective cyclization reaction of bis-2-en-4-ynoic acid derivatives **29** and **32** to the enol-lactones **30** and **33**. Although the bis-lactone **30** could not be converted to the target natural product, the synthesis of 6*Z*-pandanamine (**11**) was achieved from **33**.

EXPERIMENTAL

(*Z*)-3-Iodo-2-methylprop-2-en-1-ol (21).[13] Under Ar atmosphere, propargyl alcohol (**20**) (2.66 mL, 45.0 mmol) was added to a suspension of CuI (857 mg, 4.5 mmol) in anhydrous THF (50 mL) at 0 °C and stirred for 1 h, then a solution of MeMgBr (3.0 M solution in Et_2O, 30 mL, 90 mmol) was added to a reaction mixture over 10 min and the stirring was continued for 90 min at the same temperature. A solution of I_2 (17.1 g, 67.5 mmol) in anhydrous Et_2O (80 mL) was added to a reaction mixture over 10 min, then stirred at rt for 90 min. The reaction mixture was treated with saturated aqueous NH_4Cl solution and the aqueous solution was extracted with Et_2O (40 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (3:1)] to afford **21** (7.27 g, 82%) as a yellow oil: IR (neat) cm^{-1} 3329, 3053, 1435, 1013; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 3.40 (1H, br), 4.21 (2H, s), 5.96 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 67.8, 74.6, 145.9; MS *m/z* (relative intensity) 198 (100, M$^+$), 149 (84), 71 (86); HRMS Calcd for C_4H_7IO: 197.9542. Found: 197.9536.

***tert*-Butyl-[(*Z*)-3-iodo-2-methylallyloxy]dimethylsilane (22).** Imidazole (210 mg, 3.1 mmol), DMAP (12 mg, 0.15 mmol), and TBDMSCl (465 mg, 3.1 mmol) were added to a solution of (*Z*)-3-iodo-2-methylprop-2-en-1-ol (**21**) (309 mg, 1.5 mmol) in DMF (10 mL) and the mixture was allowed to react at rt for 25 min. The reaction mixture was extracted with Et_2O (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (1:1)] to afford **22** (472 mg, 98%) as a colorless oil: IR (neat) cm^{-1} 2955, 2930, 2856, 1472, 1097, 839; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.91 (9H, s), 1.91 (3H, s), 4.24 (2H, s), 5.85 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −5.1, 18.3, 21.5, 25.9, 68.7, 72.4, 146.6; FAB-MS *m/z* 311 (M$^+$). *Anal.* Calcd for $C_{10}H_{21}IOSi$: C, 38.46; H, 6.78. Found: C, 38.30; H, 6.60.

(*Z*)-8-(*tert*-Butyldimethylsilanyloxy)-7-methyloct-6-en-4-yn-1-ol (23). Under Ar atmosphere, CuI (10 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) were added to a solution of *tert*-butyl-[(*Z*)-3-iodo-2-methylallyloxy]dimethylsilane (**22**) (312 mg, 1.0 mmol) in anhydrous piperidine (5 mL) and the mixture was stirred at 80 °C. After being stirred for 1 h, pentyn-1-ol (**18**) (138 mg, 1.5 mmol) was added to a reaction mixture and stirring was continued for 13 h. The reaction mixture was extracted with AcOEt (5 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography [hexane-AcOEt (9:1)] to afford **23** (207 mg, 77%) as a brown oil: IR (neat) cm^{-1} 3354, 2953, 2930, 2856, 2361, 1251, 1074, 837; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.91 (9H, s), 1.79 (2H, quint, J = 6.6 Hz), 1.82 (3H, s), 2.46 (2H, td, J = 6.6, 2.2 Hz), 3.77 (2H, t, J = 6.6 Hz), 4.36 (2H, s), 5.28 (1H, brs); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −5.2, 16.1, 18.3, 19.7, 25.9, 31.6, 61.6, 63.9, 77.6, 92.6, 105.5, 149.2; MS *m*/*z*: (relative intensity) 268 (4, M$^+$), 211 (68), 183 (64), 75 (100); HRMS Calcd for $C_{15}H_{28}O_2Si$: 268.1859. Found: 268.1844.

***N*-[(*Z*)-8-(*tert*-Butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-*N*-(*tert*-butoxycarbonyl)-2-nitrobenzenesulfonamide (25).** Under Ar atmosphere, a solution of (*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-yn-1-ol (**23**) (1.34 g, 5.0 mmol) in anhydrous THF (5 mL) was added to a mixture of PPh_3 (1.44 g, 5.5 mmol) and *N*-*tert*-butoxycarbonyl-2-nitrobenzenesulfonamide (**24**) (2.27 g, 7.5 mmol) in anhydrous THF (10 mL). Diethyl azodicarboxylate (40 w/v% toluene solution, 2.42 mL, 5.5 mmol) was added to a reaction mixture at 0 °C. After being stirred for 6 h, the reaction mixture was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (5:1)] to afford **25** (2.62 g, 95%) as a yellow oil: IR (neat) cm^{-1} 2928, 2856, 2361, 1732, 1545, 1367, 1153; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.91 (9H, s), 1.37 (9H, s), 1.82 (3H, s), 1.99 (2H, quint, *J* = 7.2 Hz), 2.44 (2H, td, *J* = 7.2, 1.8 Hz), 3.86 (2H, t, *J* = 7.2 Hz), 4.38 (2H, s), 5.29 (1H, brs), 7.73-7.76 (3H, m), 8.30-8.32 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −5.2, 17.2, 18.4, 19.8, 26.0, 27.4, 27.9, 29.5, 30.9, 47.4, 63.9, 77.7, 85.0, 91.9, 105.4, 124.2, 131.6, 133.2, 134.0, 149.4, 150.2; MS *m*/*z* (relative intensity) 552 (0.5, M$^+$), 439 (24), 395 (46), 253 (64), 209 (100); HRMS Calcd for $C_{26}H_{40}N_2O_7SSi$: 552.2326. Found: 552.2323.

***N*-[(*Z*)-8-(*tert*-Butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-2-nitrobenzenesulfonamide (26).** A solution of *N*-[(*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-*N*-(*tert*-butoxycarbonyl)-2-nitrobenzenesulfonamide (**25**) (1.35 g, 2.45 mmol) in diphenyl ether (5 mL) was stirred at 180 °C for 20 min. The reaction mixture was subjected to silica gel column chromatography [hexane-AcOEt (3:1)] to afford **26** (937 mg, 85%) as a yellow oil: IR (neat) cm^{-1} 3344, 2930, 2856, 2359, 1541, 1361, 1167, 1084; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.77 (2H, quint, *J* = 6.6 Hz), 1.81 (3H, s), 2.40 (2H, td, *J* = 6.6, 2.0 Hz), 3.23 (2H, q, *J* = 6.6 Hz), 4.32 (2H, s), 5.24 (1H, brs), 5.40 (1H, t, *J* = 6.6 Hz), 7.73-7.76 (2H, m), 7.86-7.88 (1H, m), 8.14-8.15 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −5.2, 16.8, 18.4, 19.8, 25.9, 28.8, 42.8, 63.9, 78.3, 91.2, 105.2, 125.3, 131.0, 132.7, 133.5, 133.6, 147.9, 149.7; MS *m*/*z* (relative intensity) 452 (0.7, M$^+$), 395 (69), 209 (100); HRMS Calcd for $C_{21}H_{32}N_2O_5SSi$: 452.1801. Found: 452.1807.

***tert*-Butyl-[(*Z*)-8-iodo-2-methyloct-2-en-4-ynyloxy]dimethylsilane (27).** Imidazole (544 mg, 8.0 mmol), PPh_3 (1.57 g, 6.0 mmol), and I_2 (1.52 g, 6.0 mmol) were successively added to a solution of (*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-yn-1-ol (**23**) (1.08 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was refluxed for 30 min and extracted with $CHCl_3$ (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (9:1)] to afford **27** (1.39 g, 92%) as a yellow oil: IR (neat) cm^{-1} 2955, 2928, 2856, 2360, 1252, 1086, 837; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.91 (9H, s), 1.82 (3H, s), 2.00 (2H, quint, *J* = 6.5 Hz), 2.48 (2H, td, *J* = 6.5, 2.2 Hz), 3.31 (2H, t, *J* = 6.5 Hz), 4.34 (2H, s), 5.28 (1H, brs); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −5.1, 5.5, 18.4, 19.8, 20.6, 26.0, 32.3, 63.9, 78.3, 91.0, 105.3, 149.7; FAB-MS *m/z* 377 (M^+-1).

***N,N*-Bis-[(*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-2-nitrobenzenesulfonamide (28).** Under Ar atmosphere, a solution of *N*-[(*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-2-nitrobenzenesulfonamide (**26**) (804 mg, 1.77 mmol) in anhydrous DMF (6 mL) was added to a suspension of NaH (85 mg, 2.12 mmol) in anhydrous THF (5 mL) at 0 °C. After being stirred for 1 h, a solution of *tert*-butyl-[(*Z*)-8-iodo-2-methyloct-2-en-4-ynyloxy]dimethylsilane (**27**) (1.34 g, 3.54 mmol) in anhydrous DMF (6 mL) was added to the reaction mixture. After being stirred for another 3 h at 80 °C, the reaction mixture was extracted with Et_2O (30 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (9:1)] to afford **28** (1.12 g, 90%) as a brown oil: IR (neat) cm^{-1} 2930, 2856, 1547, 1360, 1252, 1163, 1084, 837, 775; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.90 (18H, s), 1.79 (4H, quint, *J* = 7.2 Hz), 1.82 (6H, s), 2.33 (4H, td, *J* = 7.2, 1.8 Hz), 4.00 (4H, t, *J* = 7.2 Hz), 4.33 (4H, s), 5.25 (2H, s), 7.62 (1H, dd, *J* = 7.7, 1.8 Hz), 7.64-7.72 (2H, m), 8.03 (1H, dd, *J* = 7.7, 1.8 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ −5.2, 16.9, 18.3, 19.8, 25.9, 27.6, 46.8, 63.8, 78.0, 91.6, 105.3, 124.1, 130.9, 131.5, 133.2, 133.3, 147.9, 150.0; MS *m/z* (relative intensity) 702 (3, M^+), 645 (68), 459 (100); HRMS Calcd for $C_{36}H_{58}N_2O_6SSi_2$: 702.3554. Found: 702.3562.

***N*-Ns-Pandanamine (30).** TBAF (1.0 M solution in THF, 11.4 mL, 11.4 mmol) was added to a solution of *N,N*-bis-[(*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-2-nitrobenzenesulfonamide (**28**) (1.0 g, 1.43 mmol) in THF (5 mL) at rt. After being stirred for 20 min, the reaction mixture was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude alcohol, which was used to the next reaction without further purification.

Dess-Martin periodinane (DMP) (705 mg, 1.66 mmol) was added to a solution of the crude alcohol in CH_2Cl_2 (7 mL) at rt. After being stirred for 11 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous solution was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude α,β-unsaturated aldehyde, which was used to the next reaction without further purification.

$NaClO_2$ (360 mg, 3.32 mmol), $NaH_2PO_4 \cdot H_2O$ (518 mg, 3.32 mmol), and 2-methyl-2-butene (2 M solution in THF, 3.3 mL, 6.64 mmol) were added to a solution of the crude α,β-unsaturated aldehyde (156 mg) in a mixture of *tert*-BuOH-H_2O (4:1, 5 mL) at rt. After being stirred for 30 min, 3N HCl was added and the aqueous solution was extracted with AcOEt (10 mL x 3) and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude carboxylic acid (**29**), which was used to the next reaction with out further purification.

DMAP (41 mg, 0.33 mmol) was added to a solution of the crude carboxylic acid (**29**) in toluene (5 mL) at 90 °C. After being stirred for 3.5 h, the reaction mixture was extracted with AcOEt (5 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (3:1)] to afford *N*-Ns-pandanamine (**30**) (65 mg, 9% overall yield from **28**) as a brown oil: IR (neat) cm^{-1}: 2926, 2855, 1767, 1543, 1346, 1161; ^1H-NMR (600 MHz, $CDCl_3$) δ 1.75 (4H, quint, *J* = 7.5 Hz), 2.00 (6H, s), 2.34 (4H, td, *J* = 7.8, 7.5 Hz), 3.31 (4H, t, *J* = 7.5 Hz), 5.15 (2H, t, *J* = 7.8 Hz), 7.00 (2H, s), 7.61 (1H, m), 7.69-7.70 (2H, m), 7.97-7.99 (1H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ −0.02, 10.5, 23.3, 28.0, 29.7, 47.4, 112.2, 124.2, 129.5, 130.6, 131.7, 133.6, 137.7, 149.0, 170.9; MS *m*/*z* (relative intensity) 502 (29, M^+), 180 (100); HRMS Calcd for $C_{24}H_{26}N_2O_8S$: 502.1410, Found: 502.1415.

***N*-Boc-Pandanamine (33).** DBU (0.55 mL, 3.65 mmol) and EtSH (0.27 mL, 3.65 mmol) were added to a solution of *N*,*N*-bis[(*Z*)-8-(*tert*-butyldimethylsilanyloxy)-7-methyloct-6-en-4-ynyl]-2-nitrobenzenesulfonamide (**28**) (512 mg, 0.73 mmol) in MeCN (5 mL) at rt. After being stirred for 1 h, the solvent was removed under reduced pressure to afford the crude amine, which was used to the next reaction without further purification.

Pyridine (0.29 mL, 3.65 mmol) and $(Boc)_2O$ (0.8 mg, 3.65 mmol) were added to a solution of the crude amine in MeOH (5 mL) at rt. After being stirred for 3 h, the reaction mixture was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude **31**, which was used to the next reaction without further purification.

TBAF (1 M solution in THF, 3.65 mL, 3.65 mmol) was added to a solution of the crude **31** in THF (5 mL) at rt. After being stirred for 30 min, the reaction mixture was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude alcohol, which was used to the next reaction without further purification.

DMP (2.5 g, 5.84 mmol) was added to a solution of the crude alcohol in CH_2Cl_2 (8 mL) at rt. After being stirred for 7 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous solution was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude α,β-unsaturated aldehyde, which was used to the next reaction without further purification.

$NaClO_2$ (528 mg, 5.84 mmol), $NaH_2PO_4 \cdot H_2O$ (911 mg, 5.84 mmol), and 2-methyl-2-butene (2 M solution in THF, 5.8 mL, 11.7 mmol) were added to a solution of the crude α,β-unsaturated aldehyde in *tert*-BuOH-H_2O (4:1, 5 mL) at rt. After being stirred for 3.5 h, 3N HCl was added and the aqueous solution was extracted with AcOEt (10 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude carboxylic acid **32**, which was used to the next reaction without further purification.

Et_3N (1.0 mL, 7.3 mmol) was added to a solution of the crude carboxylic acid **32** in toluene (5 mL) at 90 °C. After being stirred for 4.5 h, the reaction mixture was extracted with AcOEt (5 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel [hexane-AcOEt (3:1)] to give *N*-Boc-pandanamine (**33**) (109 mg, 37% overall yield from **28**) as a brown oil. Since **33** was decomposed on standing, the product was immediately used to the next reaction; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.70 (4H, t, J = 7.2 Hz), 2.00 (6H, s), 2.37 (4H, td, J = 7.5, 7.2 Hz), 3.20 (4H, brs), 5.16 (2H, brs), 6.99 (2H, s); MS *m*/*z* 317 (100).

6*Z*-Pandanamine (11). Formic acid (0.9 mL) was added to a solution of *N*-Boc-pandanamine (**33**) (2.4 mg, 0.06 mmol) in THF (0.3 mL) and stirred at rt for 12 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous solution was extracted with $CHCl_3$ (5 mL x 3). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford 6*Z*-Pandanamine (**11**); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.00 (6H, s), 2.00-2.06 (4H, m), 2.45 (4H, m), 2.85 (4H, m), 5.14 (2H, t, J = 7.8 Hz), 7.01 (2H, d, J = 1.8 Hz).

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