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ORIGINAL ARTICLE

Improved total synthesis of incednam

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An alternative and improved total synthesis of incednam, the aglycon of the 24-membered macrolactam glycoside antibiotic incednine, was accomplished. The synthesis was realized *via* construction of the 24-membered macrocycle using intramolecular ring-closing olefin metathesis reaction as a key step.
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INTRODUCTION

Incednam (**1**) is the aglycon of the 24-membered macrolactam glycoside antibiotic incednine (**2**), which was isolated by Imoto *et al.*[1] in 2008. Compound **2** exhibits significant inhibitory activity against the anti-apoptotic oncoproteins Bcl-2 and Bcl-xL, with a mode of action distinctly different from those of other agents that inhibit the binding capacity of Bcl-xL to the pro-apoptotic protein Bax. Furthermore, these proteins are overexpressed in many cancer cells, resulting in the expansion of a transformed population and promotion of the multidrug-resistant stage.[2–4] Therefore, **2** is expected to be a lead compound in the development of novel antitumor drugs. In addition, **2** is likely to be a useful tool for the further study of Bcl-2 and Bcl-xL functions. The identification of its target protein could provide insight into the anti-apoptotic mechanism of the Bcl-2 family proteins. From a chemical structural perspective, **1** and **2** contain unique features: an α-methoxy-α,β-unsaturated amide moiety and two independent conjugated polyene systems embedded in the 24-membered macrolactam ring. Due to the nature of the highly conjugated polyene subunits, **1** and **2** are light- and acid-sensitive. Although **1** was also isolated from *Streptomyces* sp.,[1] its semi-synthesis from **2** has not been realized, in part due to its inherent chemical instabilities. However, their important biological activities and novel molecular architecture make **1** and **2** prime targets for chemical synthesis. The first total synthesis of **1** involved preparation of the C1–C13 subunit **3** and the C14–C23 subunit **4,** and construction of the novel 24-membered macrocycle through Stille coupling between **3** and **4**, followed by macrolactamization as shown in Figure 1.[5] The present report describes an alternative and improved synthesis of **1** *via* construction of the 24-membered macrocycle by intramolecular ring-closing olefin metathesis reaction as a key step.

RESULTS AND DISCUSSION

The initial total synthesis of **1** was accomplished by preparation of the C14–C23 subunit **4**, which could not be stored and was used immediately for the next step due to the instability.[5] To circumvent this issue for the practical synthesis of **1**, the retrosynthesis of **1** was redesigned *via* precursor **5** or **6** for intramolecular ring-closing olefin metathesis reaction[6–8] to construct the 24-membered macrocycle concomitant with the labile C14-C21 tetraene unit at a later stage in the synthesis. The new retrosynthetic analysis of **1** is depicted in Figure 1. The convergent strategy applied to the construction of the 24-membered macrocycle is based on coupling of three domains: the C1–C13 subunit **3** containing the vinyl iodide moiety,[5] the C14–C18 subunit **7** containing the vinyl stannane moiety, and the C19–C23 subunit **8** containing the amino group. This union was produced by application of intermolecular Stille coupling and amidation, followed by intramolecular ring-closing olefin metathesis reaction.

The synthesis of the triene subunit **7**, corresponding to the C14–C18 in **1**, is summarized in Scheme 1. The known aldehyde **10** was prepared from ethyl 2-butynoate (**9**) in 5 steps by a procedure previously reported.[9,10] Wittig reaction of **10** with $Ph_3P=CH_2$ in CH_2Cl_2 provided the triene **7** in 88% yield. Next, the synthesis of the C19–C23 subunit **8** was accomplished starting from the alcohol **12**, which was prepared as in the initial total synthesis of **1**,[5] as shown in Scheme 2. The secondary alcohol **12** was converted into the mesylate **13** utilizing methanesulfonyl chloride (MsCl) in pyridine (Py), which was subsequently transformed into the azide **14** using NaN_3 in DMF at 110 °C with stereochemical inversion in 88% overall yield. Deprotection of the *tert*-butyldiphenylsilyl (TBDPS) ether of **14** with tetrabutylammonium fluoride (TBAF) in THF, and subsequent oxidation of the resulting allyl alcohol **15** using MnO_2 in CH_2Cl_2 provided the aldehyde **16** in 89% overall yield. Wittig reaction of **16** using $Ph_3P=CH_2$ gave the diene **17** in 72% yield. Finally, reduction of the azide group of **17** using PPh_3 under Staudinger's conditions[11,12] furnished the amine **8** in 98% yield.

With the key fragments **7** and **8** in hand, attention turned to the total synthesis of **1** using **3**. Completion of the synthesis of **1** is

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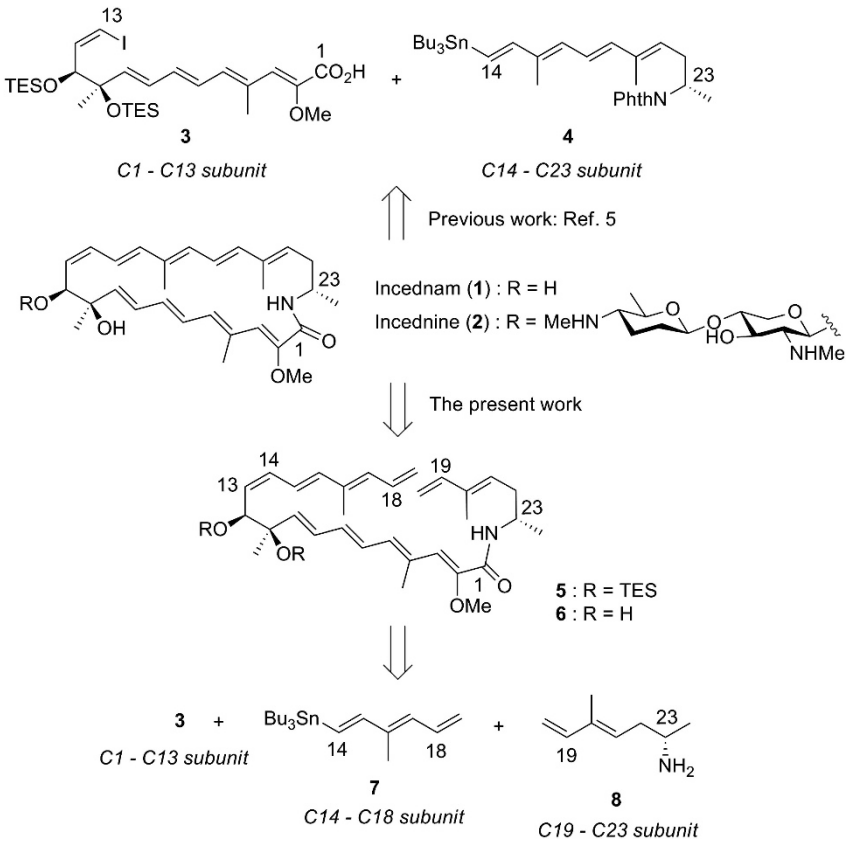
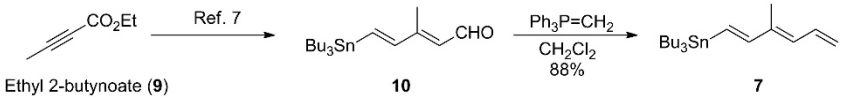
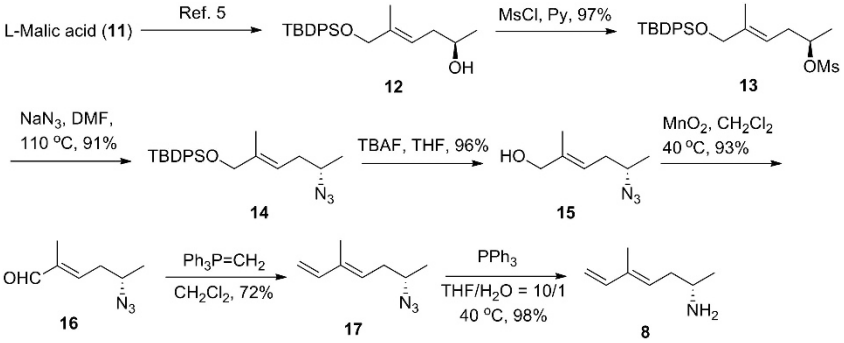


Figure 1 Retrosynthetic analysis of incednam (**1**).

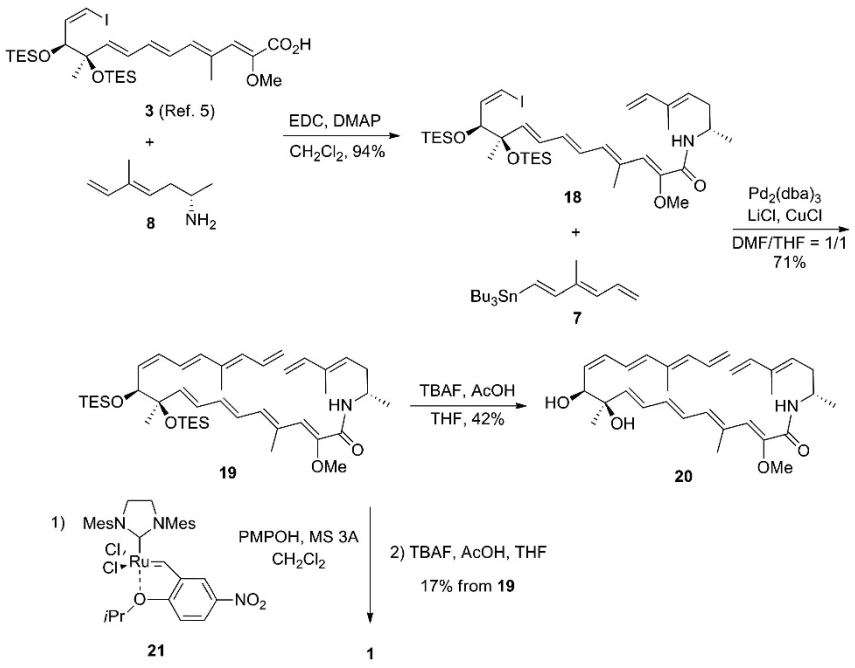


Scheme 1 Synthesis of the C14–C18 subunit **7**.



Scheme 2 Synthesis of the C19–C23 subunit **8**.

summarized in Scheme 3. Amidation of **3** and **8** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 proceeded smoothly to give the amide **18** in 94% yield. Subsequently, Stille coupling of **18** and **7** using $Pd_2(dba)_3$ in the presence of LiCl and CuCl in DMF/THF[13] gave the best result, providing the desired coupling product **19** in 71% yield. Removal of the triethylsilyl (TES) groups of **19** using TBAF and AcOH in THF furnished the diol **20** in 42% yield. Conditions for the intramolecular ring-closing olefin metathesis of **19** or **20** were rigorously explored using Grubbs first-generation,[14] Grubbs second-generation,[15] Hoveyda–Grubbs first-generation,[16] Hoveyda–Grubbs second-generation,[17] and Grela[18,19] catalysts. Experimentation revealed that the best conditions were those using **19** and Grela catalyst **21** in the presence of *P*-methoxyphenol (PMPOH) and MS 3A in CH_2Cl_2 to give



Scheme 3 Total synthesis of incednam (**1**).

incednam (**1**) in 17% overall yield after deprotection of the TES groups in the resulting cyclic product. ^{1}H-NMR, ^{13}C-NMR, HRMS (ESI-TOF), and optical rotation data obtained for a sample of the synthetic incednam matched those of an authentic sample[1] and of a sample from the initial synthesis of **1**.[5]

In conclusion, a novel convergent synthetic route was developed for incednam (**1**), which is the aglycon of the 24-membered macrolactam glycoside antibiotic incednine (**2**), using intramolecular ring-closing olefin metathesis reaction as a key step. Although the yield of the intramolecular ring-closing olefin metathesis reaction was not extremely high, the present synthetic route avoids the use of unstable fragments, such as **4**, in the total synthesis of **1**. Furthermore, this approach shows potential for intramolecular ring-closing olefin metathesis even in a complex structure possessing polyene units. Additional studies related to the total synthesis of incednine (**2**) from **1** are currently underway.[20]

With great respect, we dedicate this work to Professor Kuniaki Tatsuta as a memorial to his total synthesis of 101 antibiotics. This research was supported in part by the MEXT-supported Program for the Strategic Research Foundation at Private Universities, 2012–2016, Scientific Research on Innovative Areas 'Chemical Biology of Natural Products' and JSPS Fellow 22 · 5820 from MEXT.

EXPERIMENTAL PROCEDURE

Melting points were determined on a micro hot-stage (Yanako MP-S3) and were uncorrected. Optical rotations were measured on a JASCO P-2200 polarimeter. ^{1}H-NMR spectra were recorded on a JEOL ECA-500 (500 MHz) spectrometer. ^{13}C-NMR spectra were taken on a JEOL ECA-500 (125 MHz) spectrometer in $CDCl_3$ at room temperature, unless otherwise noted. ^{1}H-NMR data were reported as follows: chemical shift in parts par million (p.p.m.) downfield or upfield from tetramethylsilane (δ 0.00), $CHCl_3$ (δ 7.26), integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants (Hz). ^{13}C chemical shifts were reported in p.p.m. downfield or upfield from $CDCl_3$ (δ 77.36) or acetone-d_6 (δ 30.60). ESI-TOF Mass spectra and APCI-TOF Mass spectra were measured on a Waters LCT premier XE. Silica-gel TLC and column chromatography were performed on Merck TLC 60F-254 (0.25 mm) and Kanto Chemical Co., Inc. (Tokyo, Japan) Silica-Gel 60 N (spherical, neutral), respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon using oven-dried glassware. In general, organic solvents were purified and dried using an appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

(1*E*,3*E*,5*E*)-3-Methylhex-1,3,5-trien-1-tributylstannane (7)

To a solution of **10** (56.6 mg, 146 μmol) in dry CH_2Cl_2 (1.12 ml) was added $Ph_3P=CH_2$ (202 mg, 731 μmol) under Ar atmosphere at room temperature. The reaction mixture was stirred for 15 h at the temperature, the mixture was quenched by addition of a saturated NH_4Cl aq. (1 ml). The resulting mixture was extracted with $CHCl_3$ (2 ml × 3). The combined organic layer was washed with brine (1 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane) on aluminum oxide activated, basic, Brockmann I gave **7** (49.0 mg, 128 μmol, 88% yield). Pale yellow syrup; R_f 0.72 (10/1 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, TMS) δ 6.71 (1H, ddd, J = 10.0, 11.2, 16.9 Hz), 6.57 (1H, d, J = 19.2 Hz), 6.30 (1H, d, J = 19.2 Hz), 6.06 (1H, d, J = 11.2 Hz), 5.26 (1H, d, J = 16.9 Hz), 5.13 (1H, d, J = 10.0 Hz), 1.87 (3H, s), 1.50 (6H, m), 1.31 (6H, m), 0.90 (15H, m); ^{13}C-NMR ($CDCl_3$) δ 150.7, 137.2, 133.6, 131.4, 128.0, 117.8, 29.3, 27.5, 13.9, 12.2, 9.7; HRMS (ESI-TOF) *m/z* 385.19 (385.1921 calcd for $C_{19}H_{37}Sn$, $[M+Na]^+$).

(2*E*,5*R*)-1-*tert*-Butyldiphenylsilyloxy-5-methanesulfonyloxy-2-methylhex-2-ene (13)

To a solution of **12** (1.30 g, 3.53 mmol) in dry pyridine (19.5 ml) was added MsCl (410 μl, 5.30 mmol) under Ar atmosphere at 0 °C. After the mixture was stirred for 3 h at room temperature, the reaction was quenched by addition of water (20 ml). The resulting mixture was extracted with EtOAc (10 ml × 3). The combined organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 4/1) gave **13** (1.53 g, 3.42 mmol, 97% yield). Colorless syrup; R_f 0.60 (2/1 hexane/EtOAc); $[\alpha]_D^{26}$ +2.4° (*c* 0.28, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 7.65 (4H, dd, J = 1.5, 7.7 Hz), 7.39 (6H, m), 5.51 (1H, dt, J = 1.7, 7.5 Hz), 4.79 (1H, ddq, J = 6.3, 6.3, 6.6 Hz), 4.06 (2H, s), 2.94 (3H, s), 2.52 (1H, ddd, J = 6.6, 7.5, 14.0 Hz), 2.38 (1H, ddd, J = 6.3, 7.5, 14.0 Hz), 1.61 (3H, s), 1.41 (3H, d, J = 6.3 Hz) 1.06

(9H, s); ^{13}C-NMR ($CDCl_3$) δ 138.2, 135.6, 133.7, 129.8, 127.8, 117.4, 80.0, 68.4, 38.6, 34.8, 26.9, 21.1, 19.4, 13.9; Anal. calcd for $C_{24}H_{34}O_4SSi$: C, 64.53; H, 7.67; S, 7.18. Found: C, 64.37; H, 7.85; S, 7.46.

(2*E*,5*S*)-5-Azido-1-*tert*-butyldiphenylsilyloxy-2-methylhex-2-ene (14)

To a solution of **13** (1.53 g, 3.41 mmol) in dry DMF (20.0 ml) was added NaN_3 (333 mg, 5.12 mmol) under Ar atmosphere at room temperature. After the mixture was stirred for 1.5 h at 110 °C, the reaction was quenched by addition of water (20 ml). The resulting mixture was extracted with hexane/EtOAc = 1/1 (10 ml × 3). The combined organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 20/1) gave **14** (1.22 g, 3.10 mmol, 91% yield). Colorless syrup; R_f 0.61 (5/1 hexane/EtOAc); $[\alpha]_D^{26}$ +6.6° (*c* 0.28, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 7.67 (4H, d, J = 6.6 Hz), 7.39 (6H, m), 5.50 (1H, t, J = 7.5 Hz), 4.07 (2H, s), 3.48 (1H, tq, J = 6.6, 6.9 Hz), 2.31 (1H, ddd, J = 6.9, 7.5, 14.1 Hz), 2.22 (1H, ddd, J = 6.9, 7.5, 14.1 Hz), 1.61 (3H, s), 1.23 (3H, d, J = 6.6 Hz), 1.07 (9H, s); ^{13}C-NMR ($CDCl_3$) δ 137.3, 135.6, 133.9, 129.7, 127.7, 119.1, 77.4, 77.1, 76.9, 68.7, 58.0, 34.3, 26.9, 19.4, 19.2, 13.8; Anal. Calcd for $C_{23}H_{31}N_3OSi$: C, 70.18; H, 7.94. Found: C, 69.85; H, 8.00.

(2*E*,5*S*)-5-Azido-2-methylhex-2-en-1-ol (15)

To a solution of **14** (1.91 g, 4.85 mmol) in dry THF (38.0 ml) was added 1.0 M TBAF in THF (7.27 ml, 7.27 mmol) under Ar atmosphere at 0 °C. After the mixture was stirred for 3 h at room temperature, the reaction was quenched by addition of H_2O (10 ml). The resulting mixture was extracted with EtOAc (20 ml × 3). The combined organic layer was washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 2/1, 1% Et_3N) gave **15** (726 mg, 4.68 mmol, 96% yield). Colorless syrup; R_f 0.18 (5/1 hexane/EtOAc); $[\alpha]_D^{25}$ +11.9° (*c* 0.49, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 5.45 (1H, dt, J = 1.6, 7.2 Hz), 4.03 (2H, s), 3.51 (1H, m), 2.27 (2H, m), 1.69 (3H, s), 1.26 (3H, d, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 138.1, 120.7, 68.5, 34.5, 19.3, 14.0; HRMS (ESI-TOF) *m/z* 128.1077 (128.1075 calcd for $C_7H_{14}NO$, $[MH\text{-}N_2]^+$).

(2*E*,5*S*)-5-Azido-2-methylhex-2-en-1-al (16)

To a solution of **15** (726 mg, 4.68 mmol) in dry CH_2Cl_2 (46.8 ml) was added MnO_2 (4.07 g, 46.8 mmol) under Ar atmosphere at the room temperature. After the mixture was stirred for 15 h at 40 °C, the mixture was filtered through a pad of Celite. The combined filtrates were concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 2/1) gave **16** (663 mg, 4.33 mmol, 93% yield). Colorless syrup; R_f 0.33 (5/1 hexane/EtOAc); $[\alpha]_D^{24}$ +24.3° (*c* 0.68, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 9.45 (1H, s), 6.51 (1H, dt, J = 1.4, 7.2 Hz), 3.71 (1H, m), 2.55 (2H, dd, J = 6.6, 7.0 Hz), 1.78 (3H, s), 1.35 (3H, d, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 194.9, 148.5, 141.5, 56.8, 35.5, 19.5, 9.6; HRMS (ESI-TOF) *m/z* 126.0917 (126.0919 calcd for $C_7H_{12}NO$, $[MH\text{-}N_2]^+$).

(2*E*,4*E*,6*E*)-2-Azido-5-methylhepta-4,6-diene (17)

To a solution of **16** (175 mg, 1.14 mmol) in dry Et_2O (11.4 ml) was added $Ph_3P{=}CH_2$ (450 mg, 1.60 mmol) under Ar atmosphere at 0 °C. The reaction mixture was stirred for 1 h at the room temperature, the mixture was quenched by addition of a saturated NH_4Cl aq. (5 ml). The resulting mixture was extracted with Et_2O (5 ml × 3). The combined organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/Et_2O = 30/1, 1% Et_3N) gave **17** (124 mg, 822 µmol, 72% yield). Pale yellow syrup; R_f 0.71 (10/1 hexane/EtOAc); $[\alpha]_D^{25}$ +12.1° (*c* 0.52, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 6.38 (1H, dd, J = 10.6, 17.5 Hz), 5.48 (1H, t, J = 7.2 Hz), 5.14 (1H, d, J = 17.5 Hz), 4.99 (1H, d, J = 10.6 Hz), 3.52 (1H, m), 2.35 (2H, m), 1.77 (3H, s), 1.26 (3H, d, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 141.2, 136.8, 127.5, 111.9, 57.9, 35.0, 19.3, 12.1; HRMS (ESI-TOF) *m/z* 124.1127 (124.1126 calcd for $C_8H_{14}N$, $[MH-N_2]^+$).

(2*E*,4*E*,6*E*)-2-Amino-5-methylhepta-4,6-diene (8)

To a solution of **17** (124 mg, 822 µmol) in THF/H_2O (10/1, v/v, 11.7 ml) was added PPh_3 (431 mg, 1.64 mmol) under Ar atmosphere at room temperature. After the mixture was stirred for 15 h at 40 °C, the mixture was quenched by addition of H_2O (5 ml). The resulting mixture was extracted with Et_2O (5 ml × 3). The combined organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography ($CHCl_3$/MeOH = 10/1–5/1, 1% NH_3 aq.) gave **8** (101 mg, 806 µmol, 98% yield). Pale yellow syrup; R_f 0.23 (5/1 $CHCl_3$/MeOH); $[\alpha]_D^{24}$ +8.21° (*c* 0.84, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 6.39 (1H, dd, J = 10.6, 17.5 Hz), 5.51 (1H, t, J = 7.5 Hz), 5.11 (1H, d, J = 17.5 Hz), 4.95 (1H, d, J = 10.6 Hz), 2.99 (1H, m), 2.19 (2H, dd, J = 7.2, 7.5 Hz), 1.74 (3H, s), 1.42 (2H, s), 1.09 (3H, d, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 141.5, 136.0, 129.9, 111.1, 47.4, 38.9, 23.7, 12.0; HRMS (ESI-TOF) *m/z* 126.1283 (126.1283 calcd for $C_8H_{16}N$, $[M+H]^+$).

(2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*)-1-((2*E*,4*E*,6*E*)-5-Methylhepta-4,6-diene)amide-10,11-bis(triethylsilyloxy)-13-iodo-2-methoxy-4,10,16-trimethyltrideca-2,4,6,8,12-pentaene (18)

To a solution of **3** (114 mg, 176 µmol) in CH_2Cl_2 (1.50 ml) were added DMAP (43.0 mg, 352 µmol) and EDC (67.4 mg, 352 µmol) under Ar atmosphere at 0 °C. After the mixture was stirred for 20 min at the temperature, a solution of **8** (88.1 mg, 704 µmol) in CH_2Cl_2 (2.00 ml) was added and stirring was continued for another 13 h at room temperature. The reaction was quenched by addition of H_2O (2 ml). The resulting mixture was extracted with EtOAc (2 ml × 3). The combined organic layer was washed with brine (2 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 10/1 to 4/1, 1% Et_3N) gave **18** (115 mg, 152 µmol, 94% yield). Pale yellow syrup; R_f 0.30 (5/1 hexane/EtOAc); $[\alpha]_D^{26}$ +23.7° (*c* 0.89, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 6.67 (1H, s), 6.51 (1H, dd, J = 11.5, 14.0 Hz), 6.40 (1H, d, J = 11.5 Hz), 6.38 (1H, dd, J = 10.9, 17.5 Hz), 6.33 (1H, dd, J = 10.9, 14 Hz), 6.32 (1H, d, J = 7.7 Hz), 6.24 (1H, dd, J = 10.9, 15.2 Hz), 6.15 (1H, dd, J = 7.7, 8.3 Hz), 5.86 (1H, d, J = 15.2 Hz), 5.50 (1H, t, J = 7.5 Hz), 5.12 (1H, d, J = 17.5 Hz), 4.97 (1H, d, J = 10.9 Hz), 4.14 (1H, m), 4.12 (1H, d, J = 8.3 Hz), 3.57 (3H, s), 2.38 (2H, dd, J = 6.9, 7.5 Hz), 2.09 (3H, s), 1.77 (3H, s), 1.35 (3H, s), 1.20 (3H, d, J = 6.6 Hz), 0.93 (18H, m), 0.59 (12H, m); ^{13}C-NMR ($CDCl_3$) δ 163.7, 147.3, 141.3 × 2, 140.8, 136.7, 135.9, 135.4, 131.8, 129.6, 128.4, 128.1, 124.8, 111.6, 83.6, 81.3, 78.3, 61.1, 45.5, 35.2, 22.9, 20.6, 15.0, 12.1, 7.3, 7.0, 6.8, 5.2; HRMS (ESI-TOF) *m/z* 756.3340 (756.3340 calcd for $C_{36}H_{63}NO_4Si_2I$, $[M+H]^+$).

(2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*,14*E*,16*E*,18*E*)-1-((2*E*,4*E*,6*E*)-5-Methylhepta-4,6-diene)amide-10,11-bis(triethylsilyloxy)-13-iodo-2-methoxy-4,10,16-trimethylnonadeca-2,4,6,8,12,14,16-heptaene (19)

To a solution of **18** (25.8 mg, 34.1 µmol) and **7** (78.5 mg, 205 µmol) in dry THF/DMF (1/1, v/v, 683 µl) were added LiCl (11.6 mg, 273 µmol), CuCl (20.3 mg, 205 µmol) and $Pd_2(dba)_3$ (6.3 mg, 6.83 µmol) under Ar atmosphere at room temperature. After the mixture was stirred for 4 h, the reaction was quenched by addition of saturated $NaHCO_3$ aq. (1 ml). The resulting mixture was extracted with hexane/EtOAc (1/1, v/v, 1 ml × 3). The combined organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography (hexane/EtOAc = 10/1 to 8/1, 1% Et_3N) gave **19** (16.5 mg, 22.8 µmol, 71% yield). Pale yellow syrup: R_f 0.31 (5/1 hexane/EtOAc); $[\alpha]_D^{26}$ −86.8° (*c* 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, TMS) δ 6.72 (1H, ddd, J = 10.0, 11.2, 16.6 Hz), 6.56 (1H, dd, J = 11.2, 15.2 Hz), 6.51 (1H, dd, J = 11.5, 14.1 Hz), 6.41 (1H, d, J = 11.5 Hz), 6.37 (1H, dd, J = 11.2, 17.5 Hz), 6.32 (1H, dd, J = 11.8, 14.1 Hz), 6.26 (1H, d, J = 15.2 Hz), 6.25 (1H, dd, J = 11.8, 14.9 Hz), 6.12 (1H, d, J = 11.2 Hz), 6.11 (1H, dd, J = 10.3, 11.2 Hz), 5.91 (1H, d, J = 14.9 Hz), 5.50 (1H, t, J = 7.2 Hz), 5.37 (1H, dd, J = 9.2, 10.3 Hz), 5.26 (1H, d, J = 16.6 Hz), 5.15 (1H, d, J = 10.0 Hz), 5.12 (1H, d, J = 17.5 Hz), 4.97 (1H, d, J = 11.2 Hz), 4.32 (1H, d, J = 9.2 Hz), 4.14 (1H, m), 3.57 (3H, s), 2.38 (2H, dd, J = 6.9, 7.2 Hz), 2.09 (3H, s), 1.90 (3H, s), 1.77 (3H, s), 1.31 (3H, s), 1.20 (3H, d, J = 6.6 Hz), 0.91 (18H, m), 0.59 (12H, m); ^{13}C-NMR ($CDCl_3$) δ 163.7, 147.3, 142.1, 141.3, 138.3, 136.7, 136.0, 135.9, 135.6, 133.3, 132.3, 131.7, 131.6, 130.8, 129.2, 128.2, 128.1 × 2, 125.0, 124.8, 117.8, 111.6, 61.1, 45.5, 35.2,

21.8, 20.6, 15.0, 12.8, 12.1, 7.4, 7.3, 7.0, 6.8, 5.1; HRMS (ESI-TOF) *m/z* 722.4979 (722.5000 calcd for $C_{43}H_{72}NO_4Si_2$, $[M+H]^+$).

Incednam (1)

To a stirred solution of **19** (16.6 mg, 23.0 μmol) in deaerated CH_2Cl_2 (12.0 ml) was added molecular sieves 3A (16.6 mg), *p*-methoxyphenol (5.7 mg, 46.0 μmol) and Grela catalyst **21** (6.2 mg, 9.20 μmol) at room temperature. After stirring at the temperature for 6.5 h, the solution was passed through silica-gel column chromatography ($CHCl_3$, 1% Et_3N), and concentrated *in vacuo*. The crude product (3.9 mg) was used for the next reaction without further purification. To a solution of crude product (3.9 mg) in dry THF (562 μl) were added the mixture of 1.0 M TBAF in THF (33.7 μl, 33.7 μmol) and AcOH (1.6 μl, 28.1 μmol) under Ar atmosphere. The reaction mixture was stirred for 16 h at room temperature, and then the mixture of 1.0 M TBAF in THF (67.4 μl, 67.4 μmol) and AcOH (3.2 μl, 56.2 μmol) was added at the same temperature. After the mixture was stirred for 8 h at the temperature, the reaction was quenched by addition of saturated $NaHCO_3$ aq. (2 ml). The resulting mixture was extracted with EtOAc (2 ml × 3). The combined organic layer was washed with brine (2 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica-gel column chromatography ($CHCl_3$/MeOH = 40/1, 1% Et_3N) gave **1** (1.8 mg, 3.9 μmol, 17% yield in two steps). Data for an analytical sample of the synthetic incednam (**1**) obtained by ^{1}H-NMR, HRMS (ESI-TOF) and optical rotation matched those obtained for an authentic sample and a sample from the 1st generation synthesis.[1,5] Pale yellow powder; R_f 0.46 (10/1 $CHCl_3$/MeOH); $[\alpha]_D^{26}$ −1469.4° (*c* 0.10, $CHCl_3$), lit.[1] $[\alpha]_D^{20}$ −1616.7° (*c* 0.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$:CD_3OD = 1:1, TMS) δ 6.73 (1H, d, J = 10.6 Hz) 6.43 (1H, dd, J = 11.8, 14.4 Hz), 6.21 (1H, m), 6.21 (1H, m), 6.19 (1H, dd, J = 10.9, 15.8 Hz), 6.18 (1H, d, J = 15.4 Hz), 6.15 (2H, m), 6.10 (1H, m), 6.05 (1H, d, J = 10.6 Hz), 6.02 (1H, dd, J = 10.9, 14.4 Hz), 5.95 (1H, d, J = 11.5 Hz), 5.65 (1H, d, J = 15.8 Hz), 5.45 (1H, t, J = 9.2), 5.45 (1H, m), 4.22 (1H, d, J = 8.6 Hz), 4.17 (1H, m), 3.58 (3H, s), 2.28 (1H, m), 2.32 (1H, m), 2.09 (3H, s), 1.70 (3H, s), 1.66 (3H, s), 1.49 (3H, s), 1.32 (3H, d, J = 6.7 Hz Hz); ^{13}C-NMR ($CDCl_3$:CD_3OD = 1:1) δ 167.0, 147.4, 143.4, 138.0, 137.8 × 3, 137.4, 135.5, 132.4 × 2, 130.7, 130.6, 130.0, 129.1, 128.1, 127.1, 125.4, 124.6, 76.2, 76.0, 61.3, 47.2, 38.5, 22.8, 20.9, 14.3, 13.0, 12.8; HRMS (ESI-TOF) *m/z* 466.2948 (466.2957 calcd for $C_{29}H_{40}NO_4$, $[M+H]^+$).

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