CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Total Synthesis of Lajollamycin B

Authors: Tatsuya Nishimaru, Kohei Eto, Keita Komine, Jun Ishihara, and Susumi Hatakeyama

To be cited as: *Chem. Eur. J.* 10.1002/chem.201901069

Link to VoR: http://dx.doi.org/10.1002/chem.201901069

Supported by
ACES

WILEY-VCH

10.1002/chem.201901069

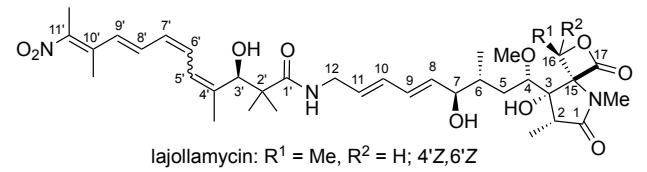
WILEY-VCH

Total Synthesis of Lajollamycin B

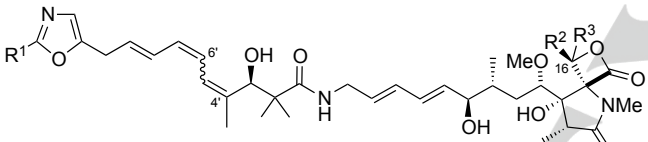
Tatsuya Nishimaru,[a] Kohei Eto,[a] Keita Komine,[a] Jun Ishihara,*[a] and Susumi Hatakeyama*[b]

Abstract: The first total synthesis of lajollamycin B, a structurally novel nitro-tetraene spiro-β-lactone/γ-lactone antibiotic, is described. The convergent synthesis involves the construction of the C8'-C11' nitrodienylstannane and its coupling with the segment prepared from the C1'-C7' ω-iodoheptadienoic acid and the right-hand heterocyclic fragment which have been utilized for our previous syntheses of oxazolomycin A. The revision of the geometry of the terminal $\Delta^{10',11'}$-double bond from *E* to *Z* is also described for the structure of natural lajollamycin B.

Introduction



lajollamycin: R^1 = Me, R^2 = H; 4'*Z*,6'*Z*
lajollamycin B: R^1 = R^2 = H; 4'*E*,6'*E*
lajollamycin C: R^1 = Me, R^2 = H; 4'*E*,6'*E*
lajollamycin D: R^1 = Me, R^2 = H; 4'*Z*,6'*E*



oxazolomycin A: R^1 = R^2 = R^3 = H; 4'*Z*,6'*Z*
oxazolomycin B: R^1 = R^2 = R^3 = H; 4'*E*,6'*E*
oxazolomycin C: R^1 = R^2 = R^3 = H; 4'*Z*,6'*E*
16-methyloxazolomycin: R^1 = R^2 = H, R^3 = Me; 4'*Z*,6'*Z*
curromycin A: R^1 = Me, R^2 = H, R^3 = CH_2OMe; 4'*Z*,6'*Z*
curromycin B: R^1 = Me, R^2 = H, R^3 = Me; 4*Z*,6'*Z*
KSM-2690 B: R^1 = H, R^2 = Me, R^3 = H; 4'*Z*,6'*Z*
KSM-2690 C: R^1 = H, R^2 = Me, R^3 = H; 4'*Z*,6'*E*

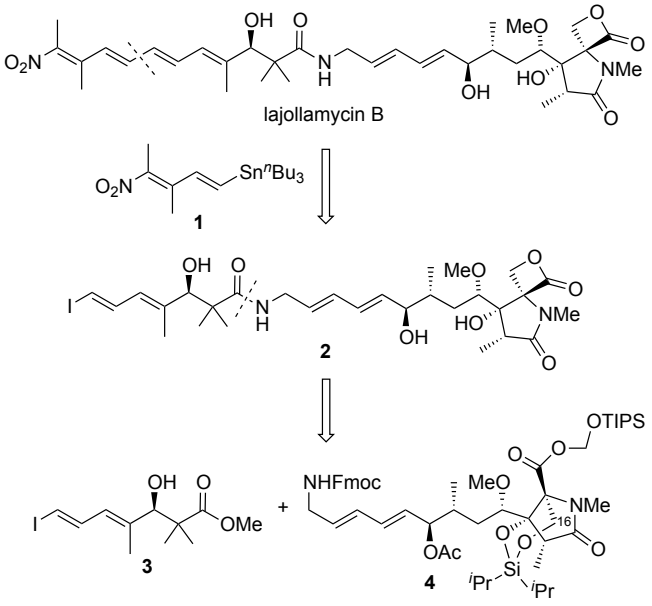
Figure 1. Lajollamycins and oxazolomycins.

Marine actinomycetes are an attractive source of diverse secondary metabolites useful for drug discovery.[1] In the course of research to discover drug candidates from marine microorganisms, in 2005, Potts et al. isolated lajollamycin from a marine *Streptomyces nodosus* and determined the planar structure.[2] Lajollamycin was found to show antimicrobial activity against both drug-sensitive and drug-resistant bacteria and to inhibit the growth of murine melanoma cell line B16-F10 (EC_{50} = 9.6 μM). Nine years later, Oh et al. further isolated lajollamycins B-D together with lajollamycin from another marine-derived *Streptomyces* strain (SMC72) and disclosed their absolute structures as well as their moderate inhibitory activities against *Candida albicans* isocitrate lyase.[3] These natural products exhibit close structural similarity with oxazolomycin antibiotics[4] in the C1-C17 right-hand segment involving a spiro-β-lactone/γ-lactone structure, whereas the C1'-C11' left-hand segment featuring a nitrotetraene structure differs from that of the oxazolomycin family. In connection with our research for developing a general comprehensive method for the synthesis of the oxazolomycins,[5] we became interested in the synthesis of lajollamycins. Herein we report the first synthesis of lajollamycin B in naturally occurring form.

Results and Discussion

Retrosynthetic analysis

Taking into account the labile nature of the left-hand part of the molecule with an aldol-nitrotetraene structure under various deprotection conditions, we focused on a strategy wherein the final step is Stille coupling of nitrodienylstannane **1** and the protecting group-free dienyl iodide **2** (Scheme 1). Based on the methodology developed in our synthesis of oxazolomycin A,[5b] we envisioned that compound **2** could be accessed from intermediates **3** and **4**, which have been utilized in our total syntheses of inthomycin C[6] and oxazolomycin A,[5b] respectively. Since we have already reported the syntheses of *Z*,*Z*- and *Z*,*E*-isomers of **3**[6a] as well as the 16*R*-methylated derivative of **4**,[5d] this approach is expected to be applicable to the syntheses of other lajollamycins.



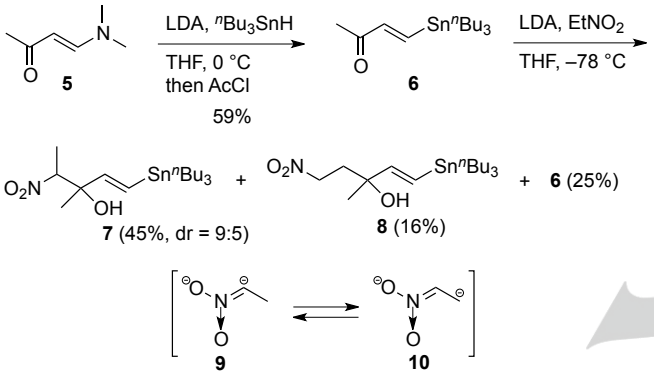
Scheme 1. Retrosynthesis of lajollamycin B.

[a] Dr. T. Nishimaru, Dr. K. Eto, Dr. K. Komine, Prof. Dr. J. Ishihara
Graduate School of Biomedical Sciences
Nagasaki University
Bunkyo-machi, Nagasaki 852-8521 (Japan)
[b] Prof. Dr. S. Hatakeyama
Medical Innovation Center
Nagasaki University
Bunkyo-machi, Nagasaki 852-8521 (Japan)
E-mail: susumi@nagasaki-u.ac.jp

Supporting information for this article is given via a link at the end of the document.

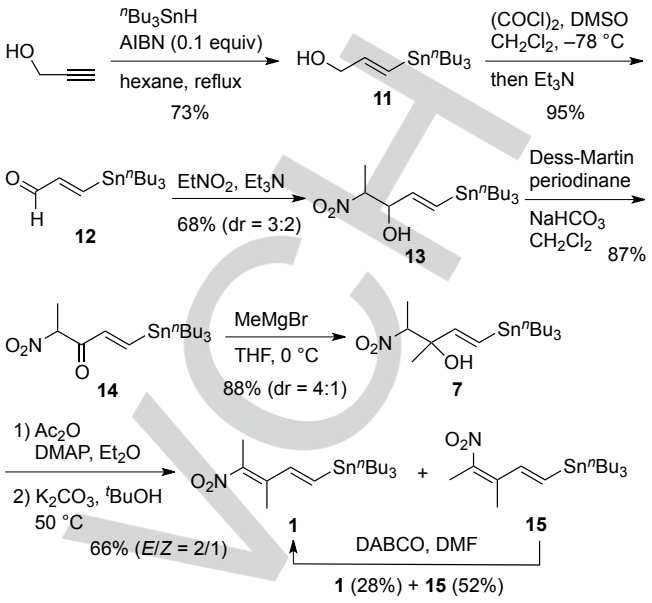
Synthesis of nitrodienylstannanes

We first planned to synthesize stannane **1** by Henry reaction of ketone **6** with nitroethane followed by dehydration of adduct **7** (Scheme 2). Thus, ketone **6**, prepared from commercially available **5** by the addition of (tributylstannyl)lithium,[7] was reacted with nitroethane using LDA as a base in THF at –78 °C to give adduct **7** as a 9:5 diastereoisomeric mixture and the structural isomer **8** in 45% and 16% yields, respectively (Scheme 2). In this reaction, two dianions **9** and **10** were generated under equilibrium[8] and each dianion added to ketone **6** giving rise to **7** and **8**. The ratio of **7** and **8** was found to vary in large extent depending on the reaction scale, resulting in the poor reproducibility of this reaction. To improve the yield of **7**, we examined this reaction using various solvents and bases in the presence or absence of DMPU; however, we could not obtain encouraging results.



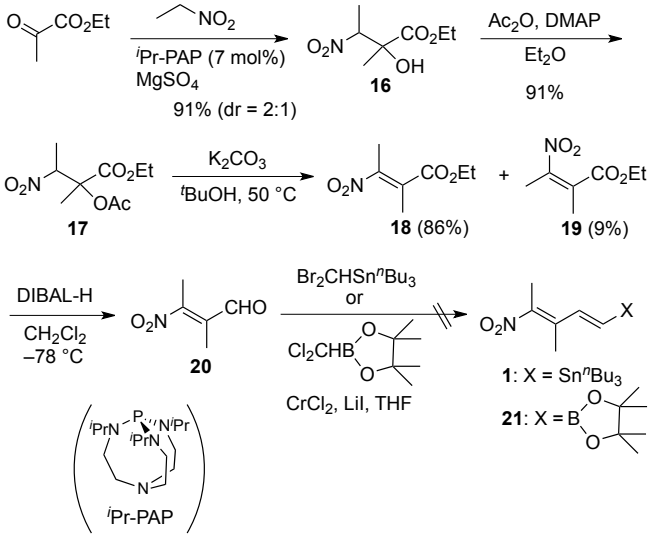
Scheme 2. Reaction of **6** with nitroethane.

Alternatively, we examined the synthesis of **7** starting from propargyl alcohol (Scheme 3). According to the literature procedure,[9] propargyl alcohol was converted to *E*-vinylstannane **11** in 73% yield by heating under reflux with tributylstannane in the presence of AIBN in hexane. After Swern oxidation of **11**, aldehyde **12** was subjected to Henry reaction with nitroethane using triethylamine as a base to produce alcohol **13** as a 3:2 diastereoisomeric mixture in 65% yield. Dess-Martin oxidation of **13** gave **14** which, upon Grignard methylation, afforded **7** as a 4:1 diastereoisomeric mixture in 77% yield. Compound **14** was then dehydrated[10] via the acetate to afford *E*-isomer **1** and *Z*-isomer **15** in a ratio of 2:1 in 66% yield. It is important to note that direct dehydration of **7** totally failed under the conditions using MsCl/Et$_3$N and SOCl$_2$/pyridine as well as various acidic conditions. The geometries of nitrodienylstannanes **1** and **15** were unambiguously determined by their NOESY spectra. After separation of this *E*/*Z*-mixture, treatment of *Z*-isomer **15** with DABCO in DMF at room temperature was found to provide *E*-isomer **1** and *Z*-isomer **15** in 28% and 52% yields, respectively. When this isomerization was carried out at higher temperature, both of **1** and **15** were largely decomposed.



Scheme 3. Synthesis of nitrodienylstannanes.

Furthermore, we also attempted the synthesis of stannane **1** starting from ethyl pyruvate (Scheme 4). Henry reaction of ethyl pyruvate with niroethane proceeded smoothly using a catalytic amount of 2,8,9-triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (^{i}Pr-PAP)[11] in the presence of MgSO$_4$ to give adduct **16** as a 2:1 diastereoisomeric mixture in 91% yield. Compound **16** was then subjected to dehydration via acetate **17** to afford *E*-isomer **18** and *Z*-isomer **19**[12] in 86% and 9% yields, respectively. However, DIBAL-H reduction of **18** to aldehyde **20** followed by Takai-Utimoto olefination[13,14] did not deliver stannane **1** at all. The preparation[15] of boronate **21** also met with failure.

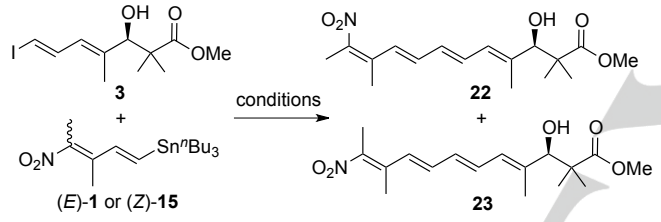


Scheme 4. Attempted synthesis of **1** from ethyl pyruvate.

Model study for the final Stille coupling

As a model study for the final step, Stille coupling reactions of dienyl iodide **3**[6a] with *E* and *Z*-nitrodienylstannanes **1** and **15** were examined under Baldwin's conditions,[16] which had been found to cause no isomerization of the similar conjugated triene systems during the Stille coupling.[5b,17] However, as seen in entry 1 in Table 1, isomerization of the tetra-substituted terminal double bond took place to produce a 4:5 mixture of **22** and **23** in 38% yield. It was found that the decrease of amounts of $Pd(PPh_3)_4$ and CsF led to the vast improvement of the yield (73%) although the isomerization of the terminal double bond was not suppressed (**22**:**23** = 1:2) (entry 2). Under the same conditions, the reaction using (*Z*)-**15** in place of (*E*)-**1** turned out to afford **22** and **23** in a ratio of 1 to 2.5 in 71% yield (entry 3). When the 2:3 mixture of **1** and **15** was used, the similar result was obtained (entry 4). Since this isomeric mixture was not chromatographically separable, the double bond geometries of **22** and **23** were determined by the direct examination of COSY, HSQC, HMBC, and NOESY spectra of the mixture (see Supporting Information).

Table 1. Stille Coupling Reactions of **3** with **1** or **15**.

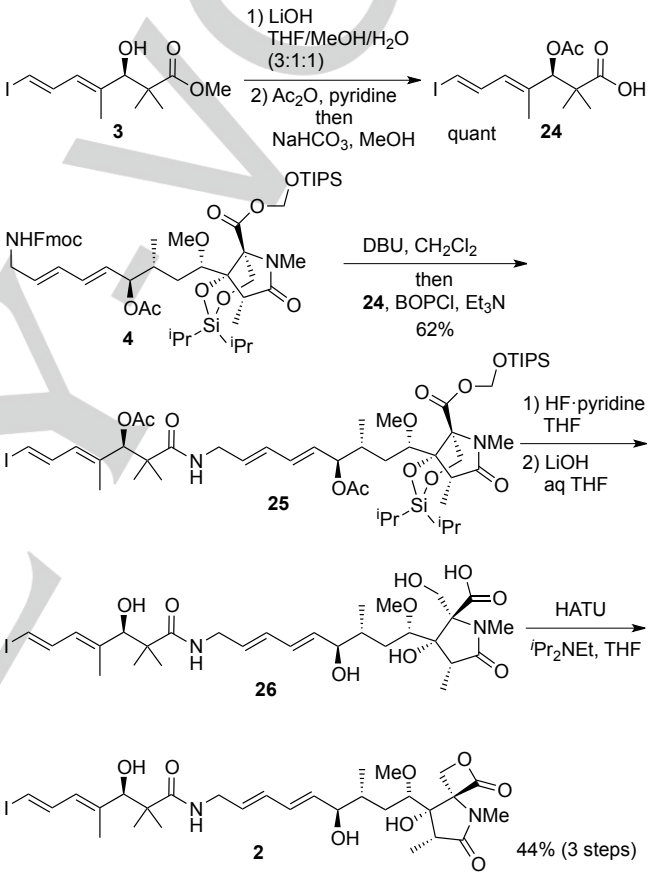


Entry	Conditions	Yield [%][a]	22:23[b]
1	**1** (1.1 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (10 mol %), CsF (2 equiv), DMF, RT, 1.5 h	38	4:5
2	**1** (1.1 equiv), $Pd(PPh_3)_4$ (2 mol %), CuI (10 mol %), CsF (20 mol %), DMF, RT, 26 h	73	1:2
3	**15** (1.1 equiv), $Pd(PPh_3)_4$ (1 mol %), CuI (10 mol %), CsF (20 mol %), DMF, RT, 5 h	71	1:2.5
4	2:3 mixture of **1** and **15** (1.1 equiv), $Pd(PPh_3)_4$ (2 mol %), CuI (10 mol %), CsF (20 mol %), DMF, RT, 71 h	76	1:2

[a] Yield of the *E*/*Z*-mixture. [b] Determined by ^{1}H NMR.

Synthesis of lajollamycin B and revision of the structure

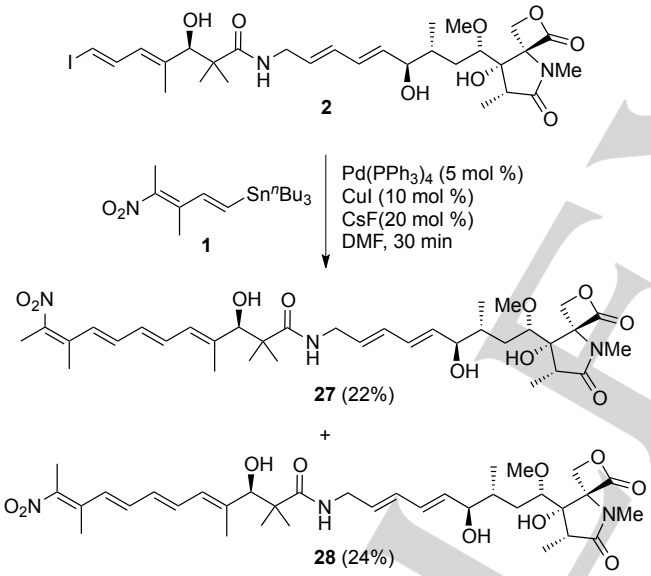
Since the Stille coupling was found to proceed in a good yield though poor *E*/*Z*-ratio regarding the geometry of the terminal double bond, we next attempted to synthesize lajollamycin B under the conditions optimized in the model study. To this end, the required coupling precursor **2** was synthesized from intermediates **3**[6a] and **4**[5b] using the preparation methods which we previously established (Scheme 5). Thus, compound **3** was converted to carboxylic acid **24** by saponification followed by acetylation, quantitatively. In the meantime, compound **4** was converted to the corresponding free amine by treatment with DBU, which was directly condensed with **24** using BOPCl and triethylamine to give amide **25** in 62% yield. Upon desilylation and deacetylation, amide **25** afforded tetrahydroxy acid **26**, which was then treated with HATU[18] in the presence of Hünig's base in THF at room temperature to deliver the key precursor **2** in 44% yield over 3 steps.



Scheme 5. Synthesis of the key precursor **2**.

With the required precursor **2** in hand, we then investigated the final Stille coupling with stannane **1** (Scheme 6). Thus, upon **2** was reacted with 2 equiv of stannane **1** in the presence of 5 mol % of $Pd(Ph_3P)_4$, 10 mol % CuI, and 20 mol % of CsF in DMF at room temperature, two coupling products **27** and **28** were obtained in 22% and 24% yields, respectively. From the spectroscopic comparison (^{1}H and ^{13}C NMR), compound **27** but not **28** was found to be identical with natural lajollamycin B (see Supporting information).[3] It was indicated that the originally assigned two protons 7'-H [6.73 (dd, *J* = 15.0, 11.0 Hz)] and 9'-H [6.42 (d, *J* = 15.0 Hz)] should be corrected to 7'-H [6.30 (dd, *J* =

15.0, 11.0 Hz)] and 9'-H [6.73 (d, *J* = 15.0 Hz)], respectively.[19] With such corrections, we carefully reinvestigated Oh's COSY, HSQC, HMBC, and ROESY spectra of lajollamycin B.[3] Surprisingly, the ROESY correlation between 9'-H and 11'-Me was not observed, on the basis of which Oh et al. had assigned for the configuration of $\Delta^{10',11'}$-double bond to be *E*.[3] The stereostructures of **27** and **28** were unambiguously assigned by their NOESY spectra as shown in Figure 2. Furthermore, the ^{1}H and ^{13}C NMR spectra of the nitro-tetraene portion of **27** and **28** exhibited close similarity with those of **22** and **23**, respectively (see Supporting Information). As a consequence, these findings allowed us to revise the initially assigned geometry of the terminal $\Delta^{10',11'}$-double bond of lajollamycin B from *E* to *Z*. Strangely, it was found that the specific rotation of the synthetic substance, $[\alpha]_D^{24}$ –14.4 (*c* 0.10, MeOH), was not identical with that reported for natural lajollamycin B, $[\alpha]_D^{24}$ +70 (*c* 0.10, MeOH). However, lajollamycin B was proved to have the same absolute configuration as that of oxazolomycin A by Oh et al[3] and our synthesis was achieved from **4** which was previously employed for our synthesis of oxazolomycin A.[5b] Thus, it is clear that we have synthesized lajollamycin B in naturally occurring form.[20]



Scheme 6. Synthesis of lajollamycin B and its isomer.

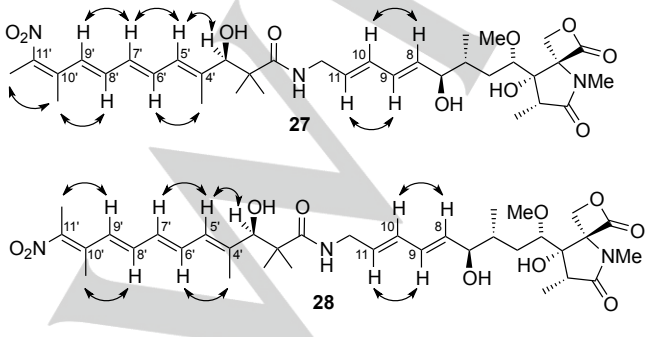


Figure 2. Key NOESY correlations for the determination of the double bond geometries.

Conclusions

Lajollamycin B and its 10'*E*-isomer **28** have been synthesized for the first time, thereby revising the stereostructure of lajollamycin B to be **27**. The developed convergent methodology is of general value in approaches to other lajollamycins. The present synthesis has been accomplished via the intermediates **3** and **4** developed for the oxazolomycins family.[5] We could therefore demonstrate a comprehensive synthetic methodology applicable to both lajollamycins and oxazolomycins.

Experimental Section

General. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), toluene, and dimethylsulfoxide (DMSO) were distilled over CaH_2. Methanol (MeOH) was distilled over Na. Thin-layer chromatography (TLC) was performed using precoated silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flash)). Optical rotations were recorded on a digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were measured using $CDCl_3$ or CD_3OD as solvent, and chemical shifts are reported as δ values in ppm based on solvent peak ($CHCl_3$, ^{1}H: 7.26 ppm, ^{13}C: 77.0 ppm; MeOH, ^{1}H: 3.30 ppm, ^{13}C: 49.0 ppm). High resolution mass spectra (HRMS) were taken in EI (dual focusing sector field) or FAB (dual focusing sector field) mode.

(*E*)-4-(Tributylstannyl)but-3-en-2-one (6). To an ice-cooled solution of diisopropylamine (1.61 mL, 11.49 mmol) in THF (38 mL) was added *n*-butyllithium (1.65 M in hexane, 6.42 mL, 10.60 mmol). After stirring at 0 °C for 10 min, tributylstannane (2.70 mL, 9.72 mmol) was added and, 10 min later, a solution of **5** (1.0 g, 8.84 mmol) in THF (6.0 mL) was added. The mixture was allowed to warm to room temperature and acetyl chloride (1.89 mL, 26.51 mmol) was added. After 5 min, saturated $NaHCO_3$ (80 mL) was added, and the mixture was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$, dried, and concentrated. The residue was purified by flash column chromatography (SiO_2 50 g, hexane:AcOEt = 100:1 to 10:1) to give **6** (1.88 g, 59%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (q, *J* = 16.7 Hz, $^2J_{Sn-H}$ = 55.6 Hz, 1H), 6.52 (d, *J* = 16.7 Hz, $^3J_{Sn-H}$ = 55.6 Hz, 1H), 2.26 (s, 3H), 1.66-1.40 (m, 6H), 1.40-1.20 (m, 6H), 1.01-0.80 (m, 15H). The ^{1}H NMR spectrum matched that reported.[7]

Reaction of 6 with nitroethane. To an ice-cooled solution of diisopropylamine (0.56 mL, 4.00 mmol) in THF (3 mL) was added *n*-butyllithium (2.69 M in hexane, 1.49 mL, 4.00 mmol), the mixture was stirred at 0 °C for 30 min. The mixture was cooled to –78 °C and nitroethane (0.14 mL, 1.95 mmol) was added. After stirring at –78 °C for 45 min, a solution of **6** (180 mg, 0.50 mmol) in THF (2 mL) was added, and the mixture was stirred at –78 °C for 3 h. The reaction was quenched

by the addition of AcOH (0.4 mL) at –78 °C, and the mixture was extracted with AcOEt, washed with H_2O and brine, dried, and concentrated. The residue was purified by flash column chromatography (SiO_2 12 g, hexane:AcOEt = 20:1 to 4:1) to give **7** (96.5 mg, 45%), **8** (35.5 mg, 16%), and recovered **6** (45 mg, 25%).

(*E*)-3-Methyl-4-nitro-1-(tributylstannyl)pent-1-en-3-ol (7), 9:5 diasteroisomeric mixture, a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 19.3 Hz, 0.64H), 6.32 (d, *J* = 19.3 Hz, 0.36H), 6.00 (d, *J* = 19.3 Hz, 0.36H), 5.86 (d, *J* = 19.3 Hz, 0.64H), 4.63 (q, *J* = 6.8 Hz, 0.36H), 4.59 (q, *J* = 6.8 Hz, 0.64H), 2.91 (s, 0.36H), 2.82 (s, 0.64H), 1.58 (d, *J* = 6.8 Hz, 3 x 0.36H), 1.53 (d, *J* = 6.8 Hz, 3 x 0.64H), 1.60-1.40 (m, 6H), 1.36 (s, 3 x 0.64H), 1.35-1.20 (m, 3 x 0.36H + 6H), 1.10-0.70 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8 (minor), 147.1, 130.0, 128.4 (minor), 90.2, 89.9 (minor), 74.7, 29.1, 27.3, 26.0, 23.9 (minor), 14.2, 13.8, 9.6; FTIR (neat) 3553, 2968, 1556, 1360, 1078 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{37}NO_3Sn$ (M^+) 435.1795, found 435.1791.

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 19.3 Hz, 1H), 5.86 (d, *J* = 19.3 Hz, 1H), 4.59 (q, *J* = 7.0 Hz, 1H), 2.80 (s, 1H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.60-1.40 (m, 6H), 1.36 (s, 3H), 1.35-1.20 (m, 6H), 1.10-0.75 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 130.0, 90.3, 74.8, 29.2, 27.3 ($^3J_{Sn-C}$ = 54.0 Hz), 26.1, 14.3, 13.8, 9.7 ($^1J_{Sn-C}$ = 344 Hz);

(E)-3-Methyl-5-nitro-1-(tributylstannyl)pent-1-en-3-ol (8), a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 19.0 Hz, $^2J_{Sn-H}$ = 67.6 Hz, 1H), 5.97 (d, *J* = 19.0 Hz, $^3J_{Sn-H}$ = 63.7 Hz, 1H), 4.45 (m, 1H), 4.38 (m, 1H), 2.31 (m, 1H), 2.22 (m, 1H), 1.60-1.40 (m, 6H), 1.34 (s, 3H), 1.40-1.25 (m, 6H), 1.03-0.75 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 126.0, 73.2, 71.8, 38.0, 29.1, 29.0, 27.2 ($^3J_{Sn-C}$ = 59.0 Hz), 13.7, 9.5 ($^1J_{Sn-C}$ = 344 Hz); FTIR (neat) 3452, 2957, 2925, 1553, 1458, 1379, 1265, 1121, 996 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{28}NO_3Sn$ [(M-Bu)$^+$] 378.1091, found 378.1098.

(*E*)-3-(Tributylstannyl)prop-2-en-1-ol (11). To a solution of 2-propyn-1-ol (11.3 g, 200 mmol) in hexane (500 mL) were added tributylstannane (59 mL, 220 mmol) and AIBN (3.28 g, 20 mmol) at room temperature. After being heated under reflux for 24 h, the mixture was cooled in an ice bath, diluted with H_2O (200 mL), and extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 250 g, hexane:AcOEt = 3:1 to 2:1) to give **11** (50.7 g, 73%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 19.2 Hz, 1H), 6.14 (dt, *J* = 19.2, 3.6 Hz, 1H), 4.16 (m, 2H), 1.52-1.42 (m, 6H), 1.33-1.23 (m, 6H), 0.90-0.82 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 128.2 ($^1J_{Sn-C}$ = 367 Hz), 66.3 ($^3J_{Sn-C}$ = 64.2 Hz), 29.0 ($^2J_{Sn-C}$ = 20.3 Hz), 27.0 ($^3J_{Sn-C}$ = 54.3 Hz), 9.4 ($^1J_{Sn-C}$ = 336 Hz); HRMS (EI) calcd for $C_{15}H_{32}OSn$ (M^+) 348.1475, found 348.1479. The ^{1}H and ^{13}C NMR spectra matched those reported.[9b]

(*E*)-3-(Tributylstannyl)acrylaldehyde (12). To a stirred solution of oxalyl chloride (0.66 mL, 6.89 mmol) in CH_2Cl_2 (24 mL) at –78 °C was added DMSO (1.0 mL, 13.79 mmol). After 30 min, a solution of **11** (2.0 g, 5.74 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred at –78 °C for 30 min. Then, triethylamine (2.9 mL, 20.68 mmol) was added, and the mixture was allowed to warm to room temperature. After 30 min, H_2O (20 mL) was added, and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 30 g, hexane:AcOEt = 20:1) to give **12** (1.89 g, 95%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 19.2 Hz, $^2J_{Sn-H}$ = 55.6 Hz 1H), 6.62, (d, *J* = 7.2, 19.2 Hz, $^3J_{Sn-H}$ = 44.4 Hz 1H), 1.55-1.45 (m, 6H), 1.35-1.25 (m, 6H), 1.00 (t, *J* = 8.0 Hz, 6H), 0.89 (t, *J* = 7.6 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 163.2, 147.6, 28.9 ($^2J_{Sn-C}$ = 21.4 Hz), 27.2 ($^3J_{Sn-C}$ = 54.3 Hz), 13.6, 9.8 ($^1J_{Sn-C}$ = 331 Hz); FTIR (neat) 2957, 2695, 1694, 1463, 1376, 1278, 1190, 1073 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{30}OSn$ (M^+) 346.1318, found 346.1328. The ^{1}H and ^{13}C NMR spectra matched those reported.[9b]

(*E*)-1-(Tributylstannyl)-4-nitropent-1-en-3-ol (13). To a solution of **12** (850 mg, 2.46 mmol) in nitroethane (2 mL) was added triethylamine (2 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water (10 mL), and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 10 g, hexane:AcOEt = 13:1) to give **13** (704 mg, 68%, 3:2 diastereoisomeric mixture) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 19.2, 1.6 Hz, $^2J_{Sn-H}$ = 66.7 Hz, 1 x 0.6H), 6.40 (dd, *J* = 19.2, 1.6 Hz, $^2J_{Sn-H}$ = 66.7 Hz, 1 x 0.4H), 5.91 (dd, *J* = 19.2, 6.4 Hz, 1 x 0.6H), 5.90 (dd, *J* = 19.2, 5.6 Hz, 1 x 0.4H), 4.66 (m, 1 x 0.4H), 4.62-4.50 (m, 1H), 4.40 (m, 1 x 0.6H), 2.44 (d, *J* = 5.6 Hz, 1 x 0.4H), 2.34 (d, *J* = 5.6 Hz, 1H), 1.54-1.45 (m, 9H), 1.35-1.25 (m, 6H), 0.95-0.83 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.2 (minor), 135.4, 133.5 (minor), 86.9, 85.9 (minor), 76.9, 75.2 (minor), 29.0, 27.2 ($^3J_{Sn-C}$ = 34.6 Hz), 16.0, 13.6, 12.5 (minor), 9.8 ($^1J_{Sn-C}$ = 338 Hz); FTIR (neat) 3448, 2964, 1560, 1457, 1359, 1182 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{35}NO_3Sn$ (M^+) 421.1639, found 421.1633.

(*E*)-1-(Tributylstannyl)-4-nitropent-1-en-3-one (14). To a solution of **13** (3.07 g, 7.29 mmol) in CH_2Cl_2 (73 mL) were added Dess-Martin periodinane (4.64 g, 10.9 mmol) and $NaHCO_3$ (1.84 g, 21.9 mmol), and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched with saturated $Na_2S_2O_3$ (20 mL) at 0 °C, and the mixture was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, dried, and concentrated. The residue was purified by column chromatography (SiO_2 120 g, hexane:AcOEt = 20:1) to give ketone **14** (2.67 g, 87%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 19.2 Hz, $^2J_{Sn-H}$ = 55.6 Hz 1H), 6.65 (d, *J* = 19.2 Hz, $^3J_{Sn-H}$ = 55.6 Hz 1H), 5.64 (q, *J* = 7.2 Hz, 1H), 1.72 (d, *J* = 7.2 Hz, 3H), 1.55-1.45 (m, 6H), 1.35-1.25 (m, 6H), 1.00 (t, *J* = 8.0 Hz, 6H), 0.89 (t, *J* = 8.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 158.1, 139.9, 85.9, 28.9, 27.1 ($^3J_{Sn-C}$ = 24.5 Hz), 15.4, 13.6, 9.8 ($^1J_{Sn-C}$ = 335 Hz); FTIR (neat) 2964, 1688, 1567, 1455, 1385, 1186, 1048 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{33}NO_3Sn$ (M^+) 419.1482, found 419.1479.

(*E*)-1-(Tributylstannyl)-3-methyl-4-nitropent-1-en-3-ol (7). To a solution of **14** (12.2 g, 29.1 mmol) in THF (291 mL) was added MeMgBr (29.1 mL, 1 M THF solution, 87.3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 min. The reaction was quenched with saturated NH_4Cl (20 mL) at 0 °C, and the mixture was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, dried, and concentrated. The residue was purified by column chromatography (SiO_2 300 g, hexane:AcOEt = 20:1) to give **7** (11.1 g, 88%, 4:1 diastereoisomeric mixture) as a colorless oil. Except the diastereoisomeric ratio, the ^{1}H and ^{13}C NMR spectra were identical with those of compound **7** obtained from **6** (vide supra).

Dehydration of 7 giving 1 and 15. To a solution of **7** (11.1 g, 25.5 mmol) in Et_2O (350 mL) were added DMAP (37.3 g, 305 mmol) and Ac_2O (14.4 mL, 153 mmol) and the mixture was stirred at room temperature for 20 h. The reaction was quenched with water (200 mL) at 0 °C, the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexane:AcOEt = 20:1) to give the corresponding acetate (10.2 g). The acetate (10.2 g) was dissolved in *t*-BuOH (240 mL) and K_2CO_3 (3.6 g, 25.7 mmol) was added at room temperature. After heating at 60 °C for 22 h, the reaction was quenched

with water (200 mL) at 0 °C. The mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2 100 g, hexane:Et_3N = 100:1) to give a 2:1 mixture of *E*-isomer **1** and *Z*-isomer **15** (6.96 g, 66%). Pure *E* and *Z*-isomers were partially separated during this chromatography.

Tributyl((1*E*,3*E*)-3-methyl-4-nitropenta-1,3-dienyl)stannane (1), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 19.2 Hz, $^2J_{Sn\text{-}H}$ = 61.6 Hz, 1H), 6.74 (d, *J* = 19.2 Hz, $^3J_{Sn\text{-}H}$ = 60.8 Hz, 1H), 2.30 (s, 3H), 1.98 (s, 3H), 1.60-1.45 (m, 6H), 1.36-1.25 (m, 6H), 0.91-0.85 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 141.6, 141.1, 133.1, 29.0 ($^2J_{Sn\text{-}C}$ = 20.6 Hz), 27.2 ($^3J_{Sn\text{-}C}$ = 54.4 Hz), 15.5, 14.8, 13.6, 9.7 ($^1J_{Sn\text{-}C}$ = 336 Hz); FTIR (neat) 2956, 2926, 1520, 1463, 1377, 1341, 1194 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{35}NO_2Sn$ (M^+) 417.1690, found 417.1704.

Tributyl((1*E*,3*Z*)-3-methyl-4-nitropenta-1,3-dienyl)stannane (15), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 19.2 Hz, $^2J_{Sn\text{-}H}$ = 55.6 Hz, 1H), 6.68 (d, *J* = 19.2 Hz, $^3J_{Sn\text{-}H}$ = 55.6 Hz, 1H), 2.27 (s, 3H), 1.93 (s, 3H), 1.60-1.40 (m, 6H), 1.36-1.25 (m, 6H), 0.98-0.82 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 140.7, 138.2, 132.5, 29.0 ($^2J_{Sn\text{-}C}$ = 20.6 Hz), 27.2 ($^3J_{Sn\text{-}C}$ = 54.4 Hz), 16.8, 14.5, 13.7, 9.6 ($^1J_{Sn\text{-}C}$ = 338 Hz); FTIR (neat) 2956, 2926, 1520, 1463, 1343 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{35}NO_2Sn$ (M^+) 417.1690, found 417.1703.

Ethyl 2-Hydroxy-2-methyl-3-nitrobutanoate (16). To a stirred suspension of $MgSO_4$ (53.5 g, 440 mmol) in nitroethane (200 mL) at room temperature was added ethyl pyruvate (22.5 mL, 200 mmol) and ^{i}Pr-PAP (5.03 g, 14.7 mmol). After being stirred at room temperature for 15 h, the mixture was filtered and concentrated. The residue was purified by column chromatography (SiO_2 10 g, hexane:AcOEt = 5:1) to give **16** (35.14 g, 91%, 2:1 diastereoisomeric mixture) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (q, *J* = 7.1, 0.66 x 2H), 4.81 (d, *J* = 7.1 Hz, 0.34 x 2H), 4.40-4.25 (m, 2H), 3.67 (s, 0.34 x 1H), 3.55 (0.66 x 1H), 1.66 (d, *J* = 6.8 Hz, 0.66 x 3H), 1.63 (d, *J* = 7.1 Hz, 0.34 x 3H), 1.50 (s, 0.34 x 3H), 1.42 (s, 0.66 x 3H), 1.35 (q, J = 7.1 Hz, 0.34 x 3H), 1.31 (q, J = 7.1 Hz, 0.66 x 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.1 (minor), 88.7 (minor), 86.6, 74.8 (minor), 74.7, 63.1 (minor), 62.8, 23.33, 23.30 (minor), 14.8 (minor), 14.0 (minor), 13.9, 12.6; FTIR (neat) 3495, 2988, 1738, 1556, 1450, 1390, 1260, 1183, 1015 cm^{-1}; HRMS (FAB) calcd for $C_7H_{14}NO_5$ [(M+H)]$^+$ 192.0872, found 192.0865.

Ethyl 2-Acetoxy-2-methyl-3-nitrobutanoate (17). To a stirred solution of **16** (10.0 g, 52,3 mmol) in Et_2O (250 mL) at –15 °C were added 4-dimethylaminopyridine (12.8 g, 104.7 mmol) and acetic anhydride (7.42 mL, 78.5 mmol). After stirring at –15 °C for 17 h, the reaction was quenched by the addition of H_2O (100 mL). The mixture was extracted with Et_2O, washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 10 g, hexane:AcOEt = 4:1) to give **17** (11.1 g, 91%, 2:1 diastereoisomeric mixture) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (q, *J* = 7.0 Hz, 0.66 x 1H), 4.93 (q, *J* = 7.0 Hz, 0.34 x 1H), 4.27-4.21 (m, 2H), 2.10 (s, 0.34 x 3H), 2.07 (s, 0.66 x 3H), 1.72 (s, 0.34 x 3H), 1.69 (s, 0.66 x 3H), 1.64 (d, *J* = 7.0 Hz, s, 0.66 x 3H), 1.63 (d, *J* = 7.0 Hz, 0.34 x 3H), 1.31-1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.1 (minor), 168.8, 168.4 (minor), 86.7 (minor), 85.2, 80.1 (minor), 79.8, 62.5 (minor), 62.4, 21.1 (minor), 20.8, 18.1 (minor), 17.3, 14.6, 13.92, 13.86 (minor), 13.85 (minor); IR (neat) 2991, 1753, 1559, 1451, 1375, 1268, 1136, 1020 cm^{-1}; HRMS (FAB) calcd for $C_9H_{16}NO_6$ [(M+H)$^+$] 234.0978, found: 234.0978.

(*E*)-Ethyl 2-Methyl-3-nitrobut-2-enoate (18) and (*Z*)-ethyl 2-methyl-3-nitrobut-2-enoate (19). To a solution of **17** (3.31 g, 14.2 mmol) in *t*-BuOH (142 mL) was added K_2CO_3 (2.36 g, 17.1 mmol) at room temperature. After heating at 50 °C for 2 h, the reaction was quenched with H_2O at 0 °C. The mixture was extracted with Et_2O, washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 150 g, hexane:AcOEt = 10:1) to give *E*-isomer **18** (2.11 g, 86%) and less polar *Z*-isomer **19** (220 mg, 9%).

***E*-isomer 18**, a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.2 Hz, 2H), 2.23 (q, *J* = 1.2 Hz, 3H), 2.06 (q, *J* = 1.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 167.1, 146.3, 132.0, 61.9, 16.7, 14.5, 13.6; IR (neat) 2983, 2928, 1728, 1529, 1277, 1187, 1100 cm^{-1}; HRMS (FAB) calcd for $C_7H_{12}NO_4$ [(M+H)$^+$] 174.0757, found: 174.0756.

***Z*-isomer 19**, a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (q, *J* = 7.0 Hz, 2H), 2.41 (q, *J* = 1.5 Hz, 3H), 1.98 (q, *J* = 1.5 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 153.9, 125.8, 62.0, 17.6, 15.8, 14.2; IR (neat) 2982, 2934, 1728, 1536, 1448, 1372, 1290, 1186, 1091, 1022, 861, 772 cm^{-1}; HRMS (EI) calcd for $C_7H_{11}NO_4$ (M)$^+$ 173.0688, found: 173.0688.

Coupling reaction listed in entry 2 in Table 1. To a solution of **1** (304 mg, 730 μmol) and **3** (215 mg, 664 μmol) in degassed DMF (6.6 mL) were added CuI (12.6 mg, 66.4 μmol), CsF (20.2 mg, 133 μmol), and $Pd(PPh_3)_4$ (15.3 mg, 13.3 μmol) at room temperature. After the mixture was stirred at room temperature for 26 h in the dark, the reaction was quenched by the addition of H_2O, and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by column chromatography (SiO_2 15 g, hexane: AcOEt = 5:1 to give a 2:1 mixture of **22** and **23** (157 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 15.0 Hz, 0.34 x 1H), 6.73 (dd, *J* = 11.5, 15.0 Hz, 0.66 x 1H), 6.64 (dd, *J* = 11.5, 15.0 Hz, 0.66 x 1H), 6.61 (dd, *J* = 11.5, 15.0 Hz, 0.34 x 1H), 6.60 (dd, *J* = 11.5, 15.0 Hz, 0.34 x 1H), 6.42 (d, *J* = 15.0 Hz, 0.66 x 1H), 6.36 (dd, *J* = 11.5, 15.0 Hz, 0.66 x 1H), 6.31 (dd, *J* = 11.5, 15.0 Hz, 0.34 x 1H), 6.11 (d, *J* = 11.5 Hz, , 0.66 x 1H), 6.08 (d, *J* = 11.5 Hz, , 0.34 x 1H), 4.21 (d, J = 5.5 Hz, 0.66 x 1H), 4.19 (d, J = 5.5 Hz, 0.34 x 1H), 3.71 (s, 0.66 x 3H), 3.71 (s, 0.34 x 3H), 3.09 (d, *J* = 5.5 Hz, 0.66 x 1H), 3.07 (d, *J* = 5.5 Hz, 0.34 x 1H), 2.31 (s, 0.66 x 3H), 2.29 (s, 0.34 x 3H), 2.05 (s, 0.66 x 3H), 1.99 (s, 0.34 x 3H), 1.79 (s, 0.66 x 3H), 1.78 (s, 0.34 x 3H), 1.22 (s, 0.66 x 3H), 1.21 (s, 0.34 x 3H), 1.17 (s, 0.66 x 3H), 1.16 (s, 0.34 x 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 145.7, 144.6, 140.3, 139.6, 137.1, 135.6, 133.9, 133.0, 133.0, 132.8, 132.3, 132.0, 128.7, 128.5, 128.5, 127.8, 82.3, 82.2, 52.3, 52.3, 47.2, 23.8, 21.0, 20.9, 17.1, 16.0, 15.3, 15.2, 14.4, 14.3; IR (neat) 3505, 2982, 1726, 1589, 1510, 1327, 1136, 1047 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{25}NO_5$ (M)$^+$ 323.1733, found: 323.1732.

Coupling reaction listed in entry 3 in Table 1. The reaction was conducted using **15** (142 mg, 339 μmol) and **3** (100 mg, 309 μmol) in degassed DMF (6.6 mL) were added CuI (5.8 mg, 30.9 μmol), CsF (9.4 mg, 61.7 μmol), and $Pd(PPh_3)_4$ (3.6 mg, 3.09 μmol) at room temperature for 5 h in the dark in the same manner as described for the reaction of **3** and **1**. Purification by column chromatography gave a 2.5:1 mixture of **22** and **23** (71 mg, 71%) as a yellow oil.

Coupling reaction listed in entry 4 in Table 1. The reaction was conducted using *E*,*Z*-mixture of stannane (30.4 mg, 73 μmol) and **3** (21.5 mg, 66.4 μmol) in degassed DMF (6.6 mL) were added CuI (1.3 mg, 6.64 μmol), CsF (2.0 mg, 13.3 μmol), and $Pd(PPh_3)_4$ (1.5 mg, 1.32 μmol) at room temperature for 71 h in the dark in the same manner as described for the reaction of **3** and **1**. Purification by column chromatography gave a 2:1 mixture of **22** and **23** (16.3 mg, 76%) as a yellow oil.

(*R*,4*E*,6*E*)-3-Acetoxy-7-iodo-2,2,4-trimethylhepta-4,6-dienoic Acid (24). To an ice-cooled solution of hydroxy ester **3** (800 mg, 2.47 mmol) in THF-MeOH-H_2O (3:1:1, 25 mL) was added LiOH·H_2O (259 mg, 6.17 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was acidified with 0.5 M HCl (10 mL) at 0 °C and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to give the corresponding carboxylic acid (784 mg) as a pale yellow oil. The crude carboxylic acid (784 mg) was dissolved in pyridine (2.0 mL) and Ac_2O (2.0 mL, 21.1 mmol) was added at 0 °C. The mixture was stirred at room temperature for 20 h. A solution of $NaHCO_3$ (600 mg, 7.14 mmol) in MeOH (10 mL) was added to the mixture and stirring was continued at room temperature for 1 h. The mixture was extracted with AcOEt, washed with brine, dried, and concentrated to give **24** (870 mg, 100%) as a yellow oil: $[\alpha]_D^{22}$ +5.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 11.2, 14.0 Hz, 1H), 6.35 (d, *J* = 14.0 Hz, 1H), 5.95 (d, *J* = 11.2 Hz, 1H), 5.33 (s, 1H), 2.04 (s, 3H), 1.73 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 169.6, 140.7, 134.0, 129.1, 81.0, 80.8, 46.7, 22.2, 20.8, 20.5, 15.4; FTIR (neat) 3152, 2985, 1742, 1705, 1370, 1232, 1031 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{17}O_4I$ (M^+) 352.0171, found 352.0168.

(4a*S*,7*R*,7a*R*)-((Triisopropylsilyl)oxy)methyl 7a-((1*S*,3*R*,4*R*,5*E*,7*E*)-4-Acetoxy-9-((*R*,4*E*,6*E*)-3-acetoxy-7-iodo-2,2,4-trimethylhepta-4,6-dienamido)-1-methoxy-3-methylnona-5,7-dien-1-yl)-2,2-diisopropyl-5,7-dimethyl-6-oxohexahydro-[1,3,2]dioxasilino[5,4-*b*]pyrrole-4a-carboxylate (25). A solution of **4** (48.0 mg, 49.9 mmol) and DBU (11.0 μL, 72.7 mmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min to afford the corresponding free amine. To a solution of **24** (36.5 mg, 99.6 mmol) in CH_2Cl_2 (1 mL) were added BOPCl (31.7 mg, 125 μmol) and triethylamine (35 μL, 249 mmol). The mixture was stirred at room temperature for 2.5 h. To this solution was added the above mixture prepared from **4**, and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was extracted with AcOEt, washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by preparative TLC (AcOEt:hexane = 1:1) to give **25** (33.0 mg, 62%) as a colorless oil: $[\alpha]_D^{24}$ +18.9 (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 11.2, 14.0 Hz, 1H), 6.33 (d, *J* = 14.0 Hz, 1H), 6.20 (dd, *J* = 11.2, 14.4 Hz, 1H), 6.12 (t, *J* = 14.4 Hz, 1H), 5.92 (d, *J* = 11.6 Hz, 1H), 5.85 (brt, *J* = 6.8 Hz, 1H), 5.65 (dt, *J* = 7.6, 14.4 Hz, 1H), 5.55 (dd, *J* = 7.8, 15.0 Hz, 1H), 5.50 (d, *J* = 4.0 Hz, 1H), 5.41 (d, *J* = 4.0 Hz, 1H), 5.25 (s, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.71 (d, *J* = 13.2 Hz, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 3.89 (m, 2H), 3.60 (m, 1H), 3.36 (m, 1H), 3.29 (s, 3H), 2.77 (s, 3H), 2.70 (q, *J* = 7.2 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.87 (m, 1H), 1.71 (s, 3H), 1.55-1.45 (m, 2H), 1.25-0.78 (m, 47H); ^{13}C NMR (100 MHz $CDCl_3$) δ 176.5, 174.6, 170.0, 169.3, 169.0, 140.8, 134.5, 133.2, 131.3, 130.5, 129.2, 128.9, 85.5, 84.9, 83.0, 81.9, 80.8, 77.8, 77.3, 72.1, 61.0, 58.7, 46.2, 44.3, 43.2, 41.4, 34.6, 32.9, 27.2, 25.8, 22.7, 21.7, 22.2, 21.0, 17.7, 17.0, 17.0, 16.8, 16.7, 16.4, 15.3, 13.8, 13.3, 11.8, 8.1; FTIR ($CDCl_3$) 3372, 2945, 2868, 1738, 1701, 1658, 1525, 1464, 1372, 1237, 1174, 1129 cm^{-1}; HRMS (FAB) calcd for $C_{49}H_{84}N_2O_{12}Si_2I$ [$(M+H)^+$] 1075.4607, found 1075.4597.

(*R*,4*E*,6*E*)-3-Hydroxy-*N*-((2*E*,4*E*,6*R*,7*R*,9*S*)-6-hydroxy-9-((4*S*,7*R*,8*S*)-8-hydroxy-5,7-dimethyl-1,6-dioxo-2-oxa-5-azaspiro[3.4]octan-8-yl)-9-methoxy-7-methylnona-2,4-dien-1-yl)-7-iodo-2,2,4-trimethylhepta-4,6-dienamide (2). To a solution of **25** (149 mg, 139 μmol) in THF (10 mL) was added HF·pyridine (1 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h in the dark. The mixture was diluted with AcOEt, washed with saturated $NaHCO_3$, dried, and concentrated. The resulting carboxylic acid (140 mg) was dissolved in THF-H_2O (4:1, 5.0 mL) and LiOH·H_2O (63.4 mg, 1.51 mmol) was added at 0 °C. After being stirred at room temperature for 6 h in the dark, the mixture was acidified to pH 4-5 by the addition of Amberlite IRC-76 at room temperature and filtered, and the resin was washed with THF. The filtrate and washings were concentrated to give the corresponding tetrahydroxy acid **26** (128 mg). The crude tetrahydroxy acid **26** (128 mg) was dissolved in THF (4.5 mL) and HATU (115 mg, 302 μmol) and diisopropylethylamine (74 μL, 603 mmol) were added at 0 °C. After being stirred at room temperature for 10 h in the dark, the mixture was diluted with brine and extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by preparative TLC (AcOEt:MeOH = 20:1) to give **2** (27 mg) and the activated intermediate (28 mg). The activated intermediate (28 mg) was dissolved in THF (2.0 mL) and diisopropylethylamine (74 μL, 603 mmol) was added at 0 °C. The mixture was stirred at room temperature for 10 h in the dark and concentrated. The residue was purified by preparative TLC (AcOEt:MeOH = 20:1) to give **2** (14.3 mg). After all, compound **2** (41.3 mg, 44%) was obtained in total: $[\alpha]_D^{22}$ –3.7 (*c* 0.20, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 14.2, 11.2 Hz, 1H), 6.31 (d, *J* = 14.4 Hz, 1H), 6.27 (dd, *J* = 2.8, 10.2 Hz, 1H), 6.20 (t, *J* = 13.6 Hz, 1H), 6.17-6.13 (m, 1H), 5.92 (d, *J* = 11.6 Hz, 1H), 5.71-5.63 (m, 2H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.39 (d, *J* = 6.6 Hz, 1H), 3.97-3.88 (m, 4H), 3.61-3.57 (m, 2H), 3.42 (s, 3H), 2.92 (s, 3H), 2.46 (q, *J* = 6.8 Hz, 1H), 2.08-2.02 (m, 1H), 1.89-1.81 (m, 1H), 1.70 (s, 3H), 1.45-1.37 (m, 1H), 1.30 (s, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.06 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 174.8, 170.2, 141.1, 138.5, 134.1, 131.5, 131.1, 129.7, 129.8, 128.4, 86.0, 83.5, 82.4, 79.9, 79.6, 65.6, 57.1, 44.8, 42.2, 41.1, 38.6, 37.1, 32.8, 26.2, 25.5, 21.6, 17.5, 13.7; FTIR ($CDCl_3$) 3371, 2936, 1823, 1688, 1631, 1528, 1389 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{43}IN_2O_8$ (M^+) 674.2177, found 674.2187.

Lajollamycin B (27). To a solution of **1** (43.4 mg, 104 μmol) and **2** (35 mg, 51.9 μmol) in degassed DMF (1.0 mL) were added CuI (1.0 mg, 5.19 μmol), CsF (1.58 mg, 10.4 μmol), and $Pd(PPh_3)_4$ (3.0 mg, 2.60 μmol) at room temperature. After the mixture was stirred at room temperature for 30 min in the dark, the reaction was quenched with water (5 mL), and the mixture was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by reverse phase column chromatography (ODS 4 g, MeOH:H_2O = 2:1), preparative TLC (AcOEt), and HPLC (ODS, 45% aq MeCN) to give lajollamycin B (**27**) (7.8 mg, 22 %) and the isomer **28** (8.4 mg, 24%).

Lajollamycin B (**27**), a yellow powder: $[\alpha]_D^{24}$ –14.4 (*c* 0.10, MeOH) {lit.[3] $[\alpha]_D^{25}$ +70 (*c* 0.1, MeOH)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 15.4 Hz, 1H), 6.62 (dd, *J* = 11.0, 15.4, 1H), 6.59 (dd, *J* = 11.0, 15.0, 1H), 6.36 (t, *J*= 5.5 Hz, 1H), 6.30 (dd, *J* = 11.0, 15.0 Hz, 1H), 6.22 (dd, *J* = 10.5, 14.0 Hz, 1H), 6.18 (dd, *J* = 10.5, 14.0 Hz, 1H), 6.06 (d, *J* = 11.0 Hz, 1H), 5.69 (m, 2H), 4.71 (d, *J* = 6.5 Hz, 1H), 4.39 (d, *J* = 6.5 Hz, 1H), 4.25 (brs, 1H), 4.01 (s, 1H), 3.95 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.92 (m, 2H), 3.60 (t, *J* = 4.6 Hz, 1H), 3.59 (s, 1H), 3.39 (s, 3H), 2.92 (s, 3H), 2.46 (q, *J* = 7.5 Hz, 1H), 2.30 (s, 3H), 2.05 (m, 1H), 1.99 (s, 3H), 1.85 (m, 1H), 1.78 (s, 3H), 1.40 (m, 1H), 1.31 (s, 3H), 1.22 (d, *J*= 7.5 Hz, 3H), 1.11 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 177.6, 174.8, 170.2, 144.5, 140.4, 135.4, 134.0, 132.9, 132.8, 132.0, 131.5, 131.1, 129.8, 128.6, 127.6, 86.0, 83.8, 82.4, 79.6, 76.7, 65.6, 57.1, 45.0, 42.2, 41.2, 37.1, 32.8, 26.2, 25.7, 21.6, 17.5, 17.0, 15.2, 13.7, 10.1; FTIR (neat) 3352, 2928, 1825, 1691, 1512, 988, 892, 752 cm^{-1}; CD (1.4 *μ*M, MeOH) (Δε) 209 (5.12) nm [lit.[3] CD (1.4 *μ*M, MeOH) (Δε) 216 (1.26) nm]; HRMS (FAB) calcd for $C_{35}H_{52}N_3O_{10}$, [$(M+H)^+$] 674.3653, found 674.3649.

Isomer **28**, a yellow powder: $[\alpha]_D^{23}$ –11.7 (*c* 0.20, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 11.0, 15.1 Hz, 1H), 6.64 (dd, *J* = 11.0, 14.8 Hz, 1H), 6.42 (d, *J* = 15.1 Hz, 1H), 6.36 (dd, *J* = 11.0, 14.8 Hz, 1H), 6.32 (t, *J* = 5.6 Hz, 1H), 6.22 (dd, *J* = 10.5, 14.0 Hz, 1H), 6.17 (dd, *J* = 10.5, 14.0 Hz, 1H), 6.08 (d, *J* = 11.0 Hz, 1H), 5.68 (m, 2H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.39 (d, *J* = 6.6 Hz, 1H), 4.33 (d, *J* = 4.5 Hz, 1H), 4.03 (d, *J* = 4.5 Hz, 1H), 3.93 (m, 3H), 3.60 (t, *J* = 4.5 Hz, 1H), 3.57 (s, 1H), 3.40 (s, 3H), 2.92 (s, 3H), 2.46 (q, *J*= 7.3 Hz, 1H), 2.41 (brs, 1H), 2.31 (q, *J* = 1.2 Hz, 3H), 2.05 (q, *J* = 1.2 Hz, 3H), 2.04 (m, 1H), 1.83 (m, 1H), 1.79 (s, 3H), 1.41 (m,

1H), 1.31 (s, 3H), 1.22 (d, *J* = 7.3 Hz, 3H), 1.12 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ 177.7, 174.8, 170.1, 145.6, 140.9, 136.9, 134.1, 133.7, 132.6, 132.1, 131.5, 131.1, 129.7, 128.5, 128.4, 86.0, 83.8, 82.4, 79.6, 76.9, 65.6, 57.1, 45.0, 42.2, 41.2, 37.1, 32.8, 26.2, 25.6, 21.5, 17.5, 15.8, 15.1, 13.7, 10.1; FTIR (neat) 3362, 2969, 2935, 1827, 1693, 1638, 1519, 1331, 990, 905, 733 cm^{-1}; HRMS (FAB) calcd for $C_{35}H_{51}N_3O_{10}Na$, [$(M+Na)^+$] 696.3472, found 696.3471.

Acknowledgements

We thank Prof. Dong-Chan Oh (Seoul National University) for providing us with the copy of CD spectrum of lajollamycin B and the valuable information. This work was supported by JSPS KAKENHI Grant Numbers JP25253002 and JP16H05074.

Keywords: lajollamycin • antibiotic • natural product synthesis

[1] a) W. Fenical, P. R. Jensen, *Nat. Chem. Biol.* **2006**, *2*, 666–673; b) Z.-Q. Xiong, J.-F. Wang, Y.-Y. Hao, Y. Wang, *Mar. Drugs* **2013**, *11*, 700-717; c) I. Bhatnager, S.-K. Kim. *Environ. Toxicol. Phatmacol.* **2012**, *34*, 631-643.

[2] R. R. Manam, S. Teisan, D. J. White, B. Nicholson, J. Grodberg, S. T. C. Neuteboom, K. S. Lam, D. A. Mosca, G. K. Lloyd, B. C. M. Potts, *J. Nat. Prod*. **2005**, *68*, 240-243.

[3] K. Ko, S.-H. Lee, S.-J. Kim, E.-H. Kim, K.-B. Oh, J. Shin, D.-C. Oh, *J. Nat. Prod.* **2014**, *77*, 2099-2104.

[4] M. G. Moloney, P. C. Trippier, M. Yaqoob, Z. Wang, *Curr. Drug Discovery Technol.* **2004**, *1*, 181-199.

[5] a) E. O. Onyango, J. Tsurumoto, N. Imai, K. Takahashi, J. Ishihara, S. Hatakeyama, *Angew. Chem. Int. Ed*. **2007**, *46*, 6703-6405; b) K. Eto, M. Yoshino, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2011**, *13*, 5398-5401; c) J. Ishihara, S. Hatakeyama, *Chem. Rec.* **2014**, *14*, 663-677; d) K. Eto, J. Ishihara, S. Hatakeyama, *Tetrahedron* **2018**, *74*, 711-719.

[6] a) M. Yoshino, K. Eto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Biomol. Chem.* **2012**, *10*, 8164-8174; b) K. J. Hale, S. Hatakeyama, F. Urabe, J. Ishihara, S. Manaviazar, M. Grabski, M. Maczka, *Org. Lett*. **2014**, *16*, 3536-3539.

[7] T. D. Michels, J. U. Rhee, C. D. Vanderwal, *Org. Lett.* **2008**, *10*, 4787-4790.

[8] K. Yamada, S. Tanaka, S. Kohmoto, M. Yamamoto, *J. Chem. Soc., Chem. Commun.* **1989**, 110-111.

[9] a) H. Oda, T. Kobayashi, M. Kosugi, T. Migita, *Tetrahedron* **1995**, *51*, 695-702; b) K. C. Nicolaou, G. Bellavance, M. Buchman, K. K. Pulukuri, *J. Am. Chem. Soc.* **2017**,*139*, 15636-15639

[10] a) S. E. Denmark, L. Gometz, *Org. Lett.* **2001**, *3*, 2907-2910; b) S. E. Denmark, L. Gometz, *J. Org. Chem.* **2003**, *68*, 8015-8024.

[11] P. B. Kisanga, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 4298-4303.

[12] The *Z*-configuration was determined by the fact that the NOESY correlation between two methyls was observed.

[13] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.

[14] D. M. Hodgson, L. T. Boulton, G. N. Maw, *Tetrahedron* **1995**, *51*, 3713-3724.

[15] K. Takai, N. Shinomiya, H. Kaihara, N. Yoshida, T. Moriwake, K. Utimoto, *Synlett* **1995**, 963-964.

[16] a) S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132-1136; b) S. P. H. Mee, V. Lee, J. E. Baldwin, *Chem. Eur. J.* **2005**, *11*, 3294-3308.

[17] M. R. Webb, M. S. Addie, C. M. Crawforth, J. W. Dale, X. Franci, M. Pizzonero, C. Donald, R. J. K. Taylor, *Tetrahedron* **2008**, *64*, 4778-4791.

[18] L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397.

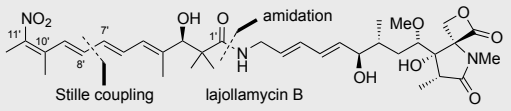
[19] Natural lajollamycin B contains some unignorable impurities which caused an incorrect assignment.

[20] This is further supported by the fact that both compound **27** and natural lajollamycin B showed the positive Cotton effect at around 209-216 nm in CD (see Supporting Information).

10.1002/chem.201901069

WILEY-VCH

FULL PAPER



Tatsuya Nishimaru, Kohei Eto, Keita Komine, Jun Ishihara, and Susumi Hatakeyama**

Page No. – Page No.

Total Synthesis of Lajollamycin B

Described is the first total synthesis of lajollamycin B in naturally occurring form, which involves Stille coupling of the C8'-C11' nitrodienylstannane with the segment prepared by amidation of the C1'-C7' ω-iodoheptadienoic acid and the right-hand heterocyclic fragment. The revision of the geometry of the terminal $\Delta^{10',11'}$-double bond from *E* to *Z* is also described.