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PAPER

Organocatalytic asymmetric syntheses of inthomycins A, B and C†

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The total syntheses of (+)-inthomycin A, (+)-inthomycin B and (−)-inthomycin C, the oxazole-triene antibiotics isolated from *Streptomyces* sp., have been accomplished *via* the highly enantio- and stereoselective construction of the C1–C7 (iododienyl)aldol units by taking advantage of a *Cinchona* alkaloid-catalyzed asymmetric β-lactone synthesis and their isomerisation-free Stille coupling with (*E*)-5-(3-(tributylstannyl)allyl)oxazole.

Introduction

Since Uemura and co-workers first reported the isolation of oxazolomycin A and neooxazolomycin in 1985,[1] many congeners containing a methylene-interrupted oxazolyl-triene motif and a spiro fused β-lactone/γ-lactam core have been isolated from strains of *Streptomyces* sp. (Fig. 1).[2] These antibiotics exhibit wide ranging and potent antibacterial and antiviral activities as well as *in vivo* antitumor activity.[2] Due to such intriguing biological properties and characteristic structures, a number of efforts have been dedicated towards the synthesis of the oxazolomycin family of antibiotics.[2,3] However, Kende's total synthesis[4] of neooxazolomycin had long been the only achievement until we recently reported the syntheses of neooxazolomycin[5] and oxazolomycin A.[6] In order to synthesize other members of this family, we need to develop an efficient methodology which allows us to secure the left hand segments having 4′*Z*,6′*Z*,8′*E*-, 4′*E*,6′*E*,8′*E*- and 4′*Z*,6′*E*,8′*E*-triene systems stereoselectively. Under this situation, we became interested in the synthesis of inthomycins A, B and C which have the structures corresponding to the left hand segments of the oxazolomycins.

In 1990, Ōmura *et al.* isolated phthoxazolin A from the strain of *Streptomyces* sp. OM-5714.[7] Then, the following year, Henkel and Zeek[8] discovered inthomycin A together with the geometrical isomers inthomycins B and C from the strain of *Streptomyces* sp. Gö 2, and proved inthomycin A to be identical with phthoxazolin A. These inthomycins are found to be highly specific inhibitors of cellulose biosynthesis, displaying significant antimicrobial[9] and herbicidal activities.[10] In addition, inthomycin A was also shown to strongly inhibit the growth of prostate cancer cells.[11] Although the syntheses of (±)-inthomycin A,[12] (+)-inthomycin B[12e,13] and (−)-inthomycin C[14] have

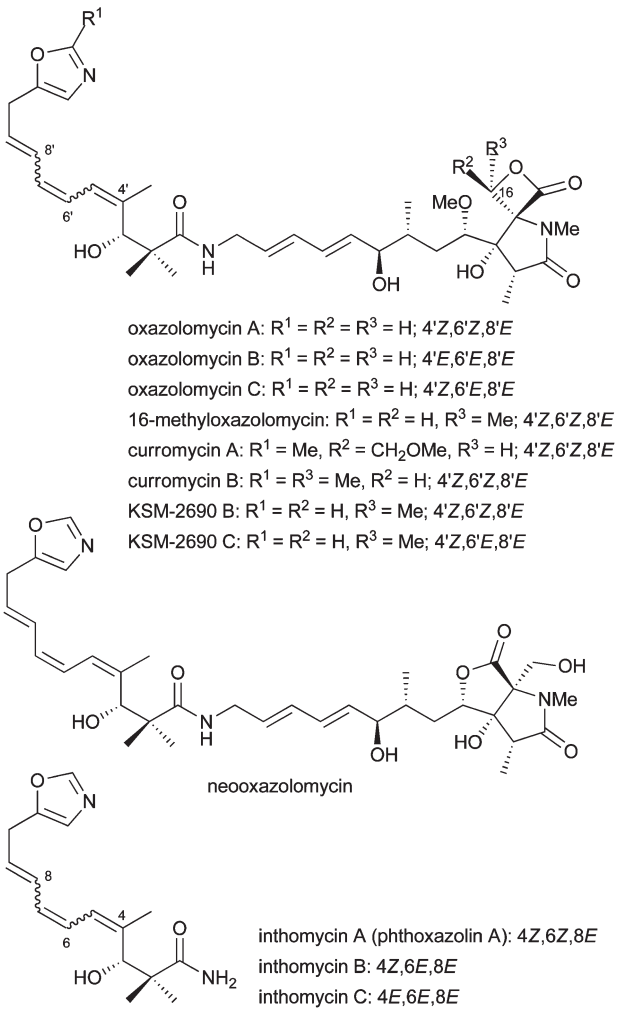

Fig. 1 The oxazolomycins and the inthomycins.

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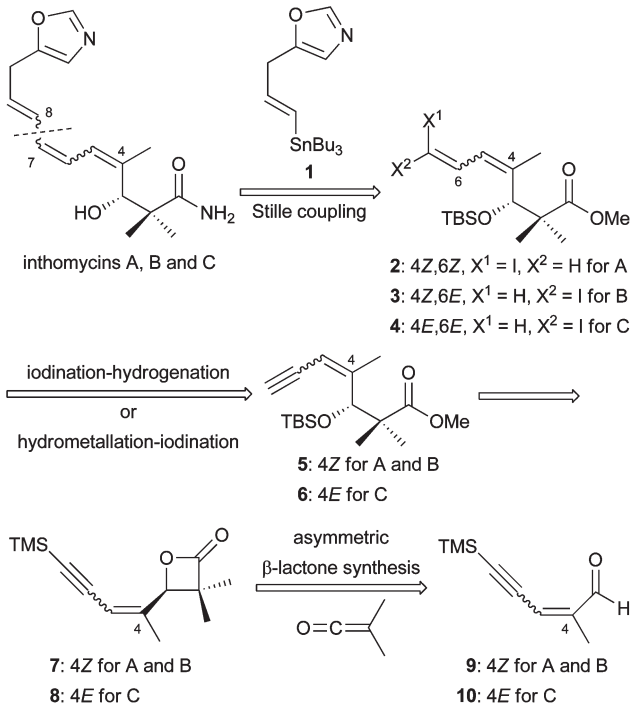
†Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra for all isolated intermediates and inthomycins A, B and C. See DOI: 10.1039/c2ob26084k



Scheme 1 Retrosynthetic analysis.

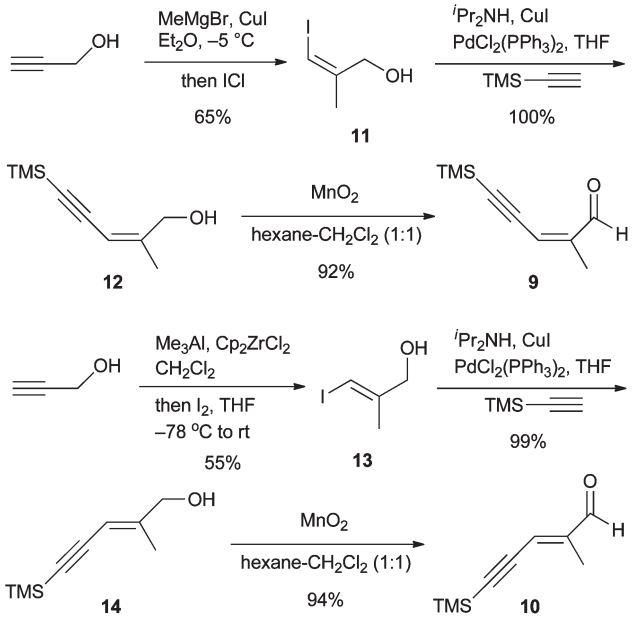
already been accomplished, there is no report of the asymmetric synthesis of all of these three compounds based on an unified methodology which enables us to secure the left-hand segments of most members of the oxazolomycin family. Herein, we report the highly enantio- and stereocontrolled total syntheses of (+)-inthomycin A, (+)-inthomycin B and (−)-inthomycin C starting with an organocatalytic asymmetric [2+2] cycloaddition reaction of an aldehyde and a ketene.[15]

Results and discussion

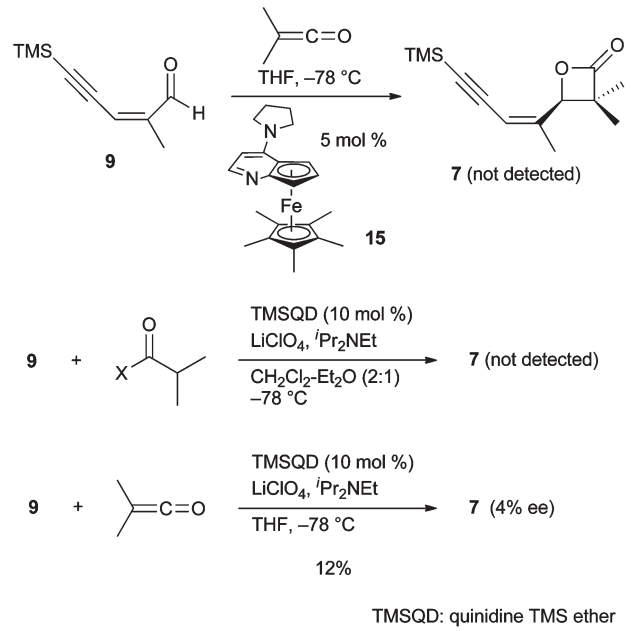
Scheme 1 illustrates our retrosynthetic analysis of inthomycins A, B and C. The disconnection of the C7–C8 bond by a Stille coupling gives us (*E*)-5-(3-(tributylstannyl)allyl)oxazole (**1**)[12c] and three iododienes *Z*,*Z*-**2**, *Z*,*E*-**3** and *E*,*E*-**4**. We assumed that each of these iododienes could be prepared regio- and stereoselectively *via* either iodination-semihydrogenation or hydrometallation-iodination from alkyne **5** or alkyne **6**. To expeditiously access **5** and **6** we envisioned organocatalytic asymmetric synthesis of β-lactones **7** and **8** from aldehydes **9** and **10** as a starting point. Although such a chiral amine-catalyzed [2+2] cycloaddition reaction involving an aldol-lactonization process has been well established by Romo *et al.*,[16] Fu *et al.*,[17] and Nelson *et al.*,[18] the reaction of a conjugated aldehyde such as **9** has rarely been examined to-date.‡ This strategy is therefore challenging, and an enantioselectivity issue of the key β-lactone formations is of great interest.

The required *Z*-aldehyde **9** and *E*-aldehyde **10** were prepared from propargyl alcohol in geometrically pure forms (Scheme 2). Thus, according to the procedure we previously established,[5a]

‡ Several successful reactions using simple ynals have been reported.[18a,b]



Scheme 2 Preparation of **9** and **10**.

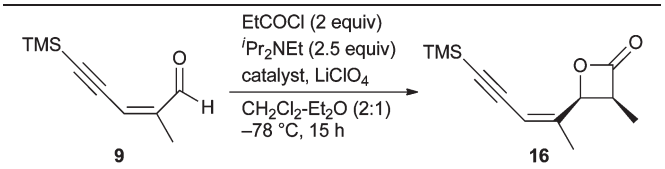


Scheme 3 Unsuccessful asymmetric [2+2] cycloadditions.

Z-aldehyde **9** was synthesized by a three-step sequence involving copper-catalyzed addition of methylmagnesium bromide followed by iodination,[12a] Sonogashira coupling of **11** with ethynyltrimethylsilane, and MnO_2 oxidation of **12**. Similarly, *E*-aldehyde **10** was obtained *via* Negishi methylation-iodination,[19] Sonogashira coupling of **13** with ethynyltrimethylsilane, and MnO_2 oxidation of **14**.

We first examined the reaction of **9** and dimethylketene, generated by Zn-mediated reduction of 2-bromo-2-methylpropanoyl bromide, using **15** as a catalyst under Fu's conditions;[17] however, the desired β-lactone **7** was not produced at all (Scheme 3).

Table 1 Asymmetric [2+2] cycloadditions

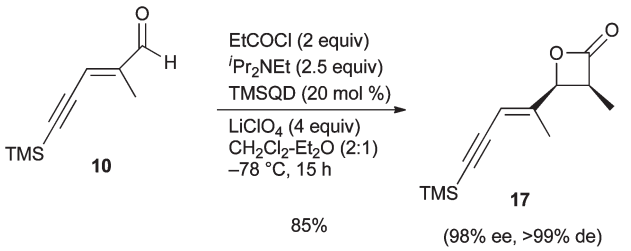


Entry	$LiClO_4$ (eq)	Catalyst (mol%)	Yield[a] (%)	ee[b] (%)	de[b] (%)
1	2	TMSQD (10)	14	98	>99
2	4	TMSQD (10)	87	97	>99
3	4	TMSQD (20)	92	98	>99
4	4	TMSQN (20)	84	−97[c]	>99

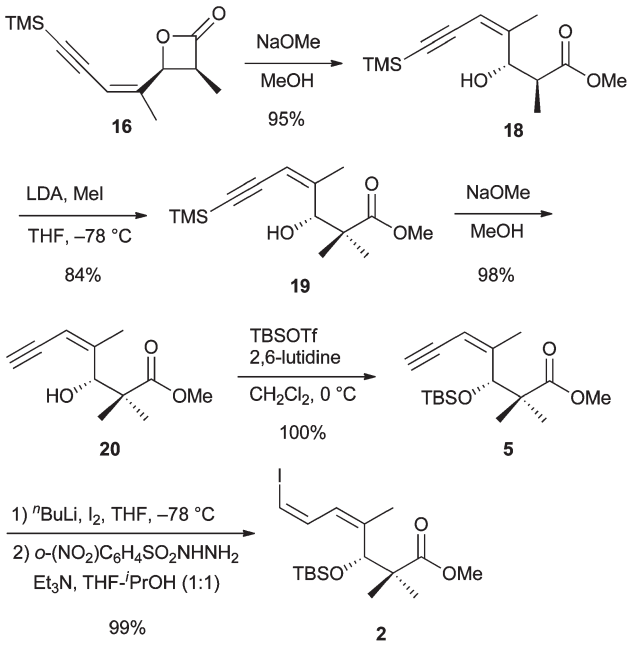
[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] The enantiomer of **16** was obtained.

We then investigated the *Cinchona* alkaloid-catalyzed reaction of **9** with isobutyryl chloride according to Nelson's procedure[18] using quinidine TMS ether (TMSQD), $LiClO_4$ and Hünig's base. This method again did not give us any encouraging results. Alternatively, we also explored the reaction of **9** with dimethylketene under the TMSQD/$LiClO_4$-catalyzed conditions. In this case, the desired β-lactone **7** was obtained but the yield and the enantioselectivity were disappointingly low. These results suggested that the gem-dimethyl groups of the ketene hampered this reaction, possibly because of steric hindrance. Therefore, we alternatively planned to introduce one methyl group after an asymmetric cycloaddition reaction using propionyl chloride instead of isobutyryl chloride.

Table 1 illustrates the results obtained from the chiral amine-catalyzed reaction of *Z*-aldehyde **9** and propionyl chloride. When **9** was reacted with 2 equiv of propionyl chloride using 2 equiv of $LiClO_4$ and 10 mol% of TMSQD in CH_2Cl_2–Et_2O (2 : 1) at −78 °C, asymmetric cycloaddition proceeded with high enantio- and diastereoselectivity to give β-lactone **16** although the yield was very low (entry 1). We then gratifyingly found that when the amount of $LiClO_4$ was increased from 2 equiv to 4 equiv, the yield was dramatically improved and both ee and de values were again very high (entry 2). When 4 equiv of $LiClO_4$ and 20 mol% of TMSQD were used, the best result was obtained and β-lactone **16** was produced in 92% yield, 98% ee and 99% de (entry 3). Similarly, when quinine TMS ether (TMSQN) was employed as a catalyst, the corresponding enantiomer of **16** was obtained in high yield and excellent enantio- and diastereoselectivities. In addition, this method can be also applied to *E*-aldehyde **10**, and β-lactone **17** was produced again in high yield and excellent enantio- and diastereoselectivities (Scheme 4). The stereostructure of **16** was confirmed by its NOESY spectrum and the absolute configuration was determined by its conversion to the known ester **5**.[5a]



Scheme 4 TMSQD-catalyzed reaction of **10** with propionyl chloride.



Scheme 5 Preparation of *Z*,*Z*-iododiene **2**.

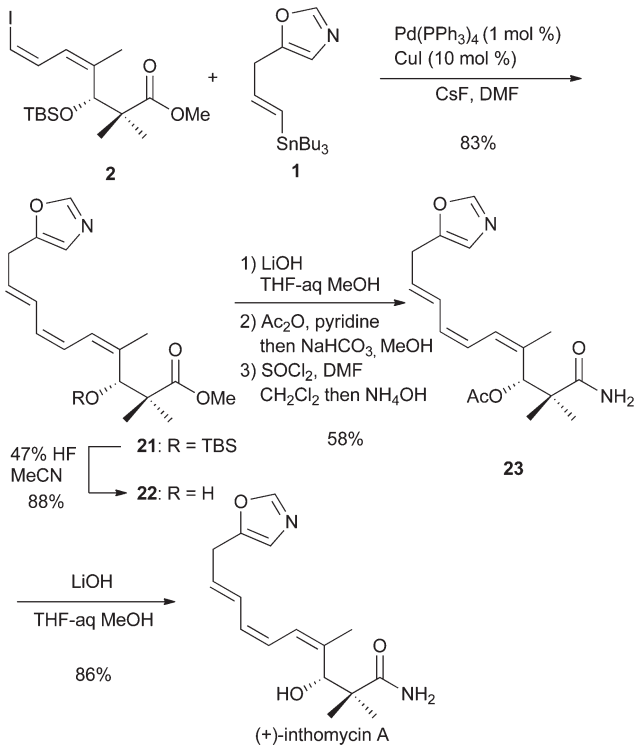
Synthesis of (+)-inthomycin A

The synthesis of (+)-inthomycin A began with the preparation of *Z*,*Z*-iododiene **2** from β-lactone **16** (Scheme 5). Thus, methanolysis of **16** gave methyl ester **18** which was methylated according to Seebach's protocol[20] to afford hydroxy ester **19** in good yield. Desilylation of **19** followed by TBS protection of **20** gave the known ester **5** which was stereoselectively converted to *Z*,*Z*-iododiene **2** following the previously established procedure[5a] involving an iodination and a diimide reduction.

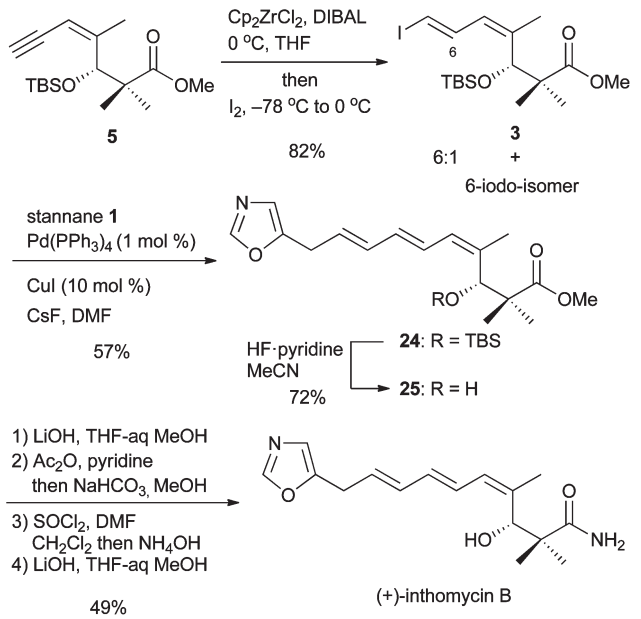
According to Baldwin's method,[12c,21] compound **2** was then subjected to Stille coupling with stannane **1** using $Pd(PPh_3)_4$, CuI and CsF in DMF at room temperature to give *Z*,*Z*,*E*-triene **21** in geometrically pure form (Scheme 6). When this coupling was carried out using Pd(0) catalyst alone, some extent of isomerization of the triene system was always observed.[21] After desilylation of **21**, compound **22** was successively subjected to saponification, acetylation, and amidation to give acetate **23**. Finally, removal of the acetyl group of **23** completed the first total synthesis of (+)-inthomycin A. The spectroscopic data and specific rotation were identical with those reported[7a,12c] for natural inthomycin A.

Synthesis of (+)-inthomycin B

For the synthesis of inthomycin B, *Z*,*E*-iododiene **3** was first synthesized from **5** by hydrozirconation[22] followed by iodination (Scheme 7). Thus, alkyne **5** was treated with *in situ* prepared

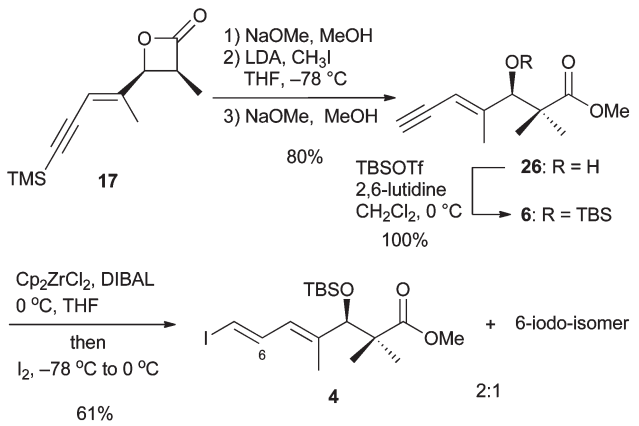


Scheme 6 Synthesis of (+)-inthomycin A.



Scheme 7 Synthesis of (+)-inthomycin B.

Schwartz's reagent from zirconocene dichloride and DIBAL followed by iodine to produce an inseparable 6 : 1 mixture of *Z*,*E*-iododiene **3** and its 6-iodo-isomer in 82% yield. The mixture was then subjected to Stille coupling with **1** under the same conditions mentioned for the coupling of **2** and **1** to give *Z*,*E*,*E*-triene **24** stereoselectively in moderate yield. From coupling product **24**, (+)-inthomycin B was successfully synthesized *via* a



Scheme 8 Preparation of *E*,*E*-iododiene **4**.

five step-sequence involving desilylation, hydrolysis, acetylation, amidation and removal of the acetyl group. The spectroscopic data were in accord with those reported[12c] for natural inthomycin B.

Synthesis of (−)-inthomycin C

E-Alkyne **6** was prepared from β-lactone **17** in 80% overall yield in the same manner as described for the synthesis of **5** from **16** (Scheme 8). *E*-Alkyne **6** was then subjected to hydrozirconation followed by iodination but the transformation proceeded with poor regioselectivity to afford a 2 : 1 mixture of **4** and its 6-iodo-isomer in 61% yield. We then examined the hydrostannylation[23] and hydrosilylation[24] of **6** under various conditions. However, as seen in Table 2, these methods did not exhibit high regioselectivity although the yields were satisfying in all cases.

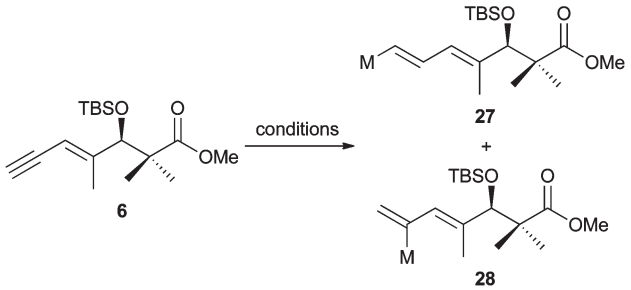
After considerable experimentation, we eventually found that a stannylcupration-iodination[23a] converted **26** to *E*,*E*-iododiene **29** with high regioselectivity (Scheme 9). Thus, when **26** was treated with $Bu_3Sn(Bu)CuCNLi_2$ in THF at −78 °C followed by iodine, a 7 : 1 mixture of **29** and its 6-iodo-isomer was obtained in 60% yield. Stille coupling of **29** with **1** using $Pd(PPh_3)_4$, CuI, and CsF in DMF proceeded at room temperature without isomerisation and geometrically pure *E*,*E*,*E*-triene **30** was produced in 83% yield. From coupling product **30**, the total synthesis of (−)-inthomycin C was accomplished *via* a four-step sequence involving hydrolysis, acetylation, amidation and removal of the acetyl group. The spectroscopic data§ and specific rotation were identical with those reported[12c,14] for natural inthomycin C.

Conclusions

We have achieved highly enantio- and stereoselective syntheses of inthomycins A, B and C in naturally occurring forms starting with a *Cinchona* alkaloid-catalyzed asymmetric [2+2] cycloaddition of an aldehyde and a ketene. The present methodology

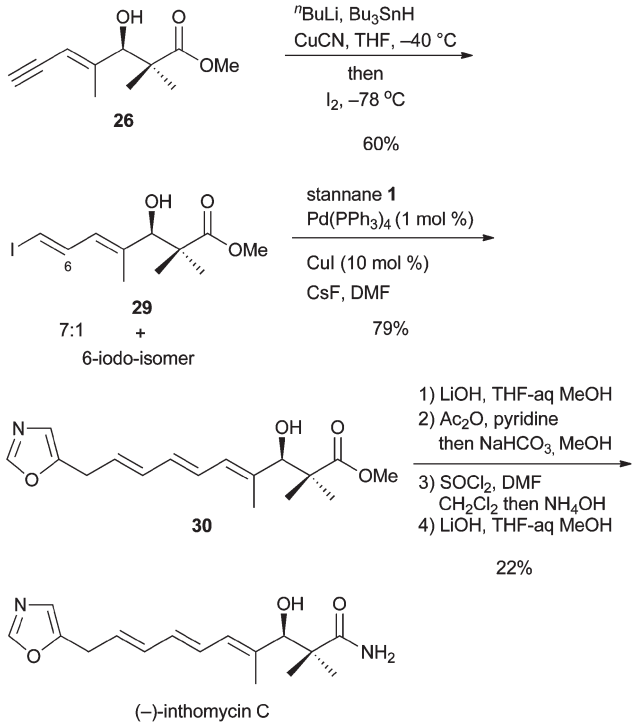
§ Taylor *et al.* reported[12c] that inthomycin C showed $[\alpha]_D^{21}$ +25.9 (*c* 0.27, $CHCl_3$). Recently, Ryu *et al.* reported[14] it to be $[\alpha]_D^{20}$ −34.3 (*c* 0.10, $CHCl_3$) which is close to our observation ($[\alpha]_D^{23}$ −41.5 (*c* 0.10, $CHCl_3$)).

Table 2 Hydrometallations of alkyne **6**



Entry	M	Conditions	Yield[a] (%)	**27** : **28**[b]
1	Bu_3Sn	Bu_3SnH (1.5 eq), AIBN (5 mol%), benzene (0.1 M), reflux, 2.5 h	91	1 : 1
2	Bu_3Sn	$PdCl_2(PPh_3)_2$ (20 mol%), Bu_3SnH (1.5 eq), THF (0.1 M), rt	80	2 : 5
3	Bu_3Sn	$Pd_2(dba)_3$ (0.5 mol%), Bu_3SnH (1.2 eq), Cy_3PHBF_4 (2 mol%), $^iPr_2NEt$, toluene (0.04 M), rt, 30 min	67	1.1 : 1
4	Bu_3Sn	$Pd_2(dba)_3$ (0.5 mol%), Bu_3SnH (1.2 eq), Cy_3PHBF_4 (2 mol%), $^iPr_2NEt$, toluene (0.04 M), 0 °C, 30 min	73	4 : 1
5[c]	$(EtO)_3Si$	$(EtO)_3SiH$ (3 eq), Pt(dvds) (3 mol%), CH_2Cl_2 (0.05 M), 0 °C to rt	82	1.3 : 1
6[c]	$(EtO)_3Si$	$(EtO)_3SiH$ (3 eq), Pt(dvds) (3 mol%), CH_2Cl_2 (0.05 M), −78 to −40 °C	80	1.1 : 1

[a] Isolated yield. [b] Determined by ^1H NMR analysis. [c] Pt(dvds) = platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex



Scheme 9 Synthesis of (−)-inthomycin C.

is of general value in approaches to the related oxazolomycins, the syntheses of which are currently under investigation.

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 the following exceptions. *N*,*N*-Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), benzene and toluene were distilled from CaH_2. Methanol (MeOH) was distilled from sodium. 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 were measured on a Fourier transform infrared spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured using $CDCl_3$ as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, ^1H; 77.0 ppm, ^{13}C). Mass spectra (MS and HRMS) were taken in EI mode.

(*Z*)-3-Iodo-2-methylprop-2-en-1-ol (11). To a suspension of propargyl alcohol (2.0 g, 35.6 mmol) and CuI (6.78 g, 35.6 mmol) in Et_2O (100 mL) was added MeMgBr (1.65 M in Et_2O, 45 mL, 74.8 mmol) at −5 °C. The mixture was gradually allowed to warm to room temperature and stirred for additional 2 h. ICl (5.78 g, 35.6 mmol) was then added at −5 °C, and the mixture was allowed to warm to room temperature and stirring was continued for 16 h. The mixture was diluted with saturated NH_4Cl (50 mL) at 0 °C and filtered through Celite®. The filtrate was extracted with Et_2O, washed with brine, dried and concentrated. Purification of the residue by column chromatography (SiO_2 150 g, hexane–AcOEt = 5 : 1) gave **11**[12b] (4.60 g, 65%) as a pale yellow oil. ^1H NMR δ 5.99 (s, 1H), 4.25 (s, 2H), 1.98 (s, 3H); ^{13}C NMR δ 146.1, 74.9, 68.1, 21.6; FTIR (neat) 3419, 2911, 2187, 2012, 1618, 1283, 1137, 1046 cm^{-1}; HRMS calcd for C_4H_7OI (M^+) 197.9541; found 197.9515.

(*Z*)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (12). To a solution of **11** (4.0 g, 20.2 mmol) in degassed THF (102 mL)

were added ethynyltrimethylsilane (5.6 mL, 40.8 mmol), diisopropylamine (24 mL, 153.7 mmol), $PdCl_2(PPh_3)_2$ (288.2 mg, 0.4 mmol) and CuI (272 mg, 1.6 mmol) at room temperature. After being stirred at room temperature for 1 h under sonication, the mixture was diluted with saturated $NaHCO_3$ (200 mL), extracted with Et_2O, washed with brine, dried and concentrated. Purification of the residue by column chromatography (SiO_2 180 g, hexane–AcOEt = 10 : 1 to 5 : 1) gave **12** (3.46 g, 100%) as a reddish brown oil. ^{1}H NMR δ 5.41 (s, 1H), 4.36 (d, J = 6.4 Hz, 2H), 1.88 (s, 3H), 0.19 (s, 9H); ^{13}C NMR δ 151.9, 106.7, 101.6, 64.1, 20.3; FTIR (neat) 3393, 2143, 1629, 1448, 1254, 1100 cm^{-1}; HRMS calcd for $C_9H_{16}OSi$ (M^+) 168.0970, found 168.0964.

(*Z*)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-ynal (9). To a suspension of activated MnO_2 (14.4 g, 177 mmol) in hexane–CH_2Cl_2 (3 : 2) (50 mL) was added a solution of **12** (2.0 g, 11.8 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred at room temperature for 24 h and filtered through Celite® which was washed with Et_2O. The combined filtrate and washings were concentrated and the residue was purified by column chromatography (SiO_2 100 g, hexane–AcOEt = 100 : 1) to give **9** (1.80 g, 92%) as a brown oil. ^{1}H NMR δ 10.25 (s, 1H), 6.53 (s, 1H), 1.86 (s, 3H), 0.22 (s, 9H); ^{13}C NMR δ 192.5, 147.4, 125.8, 106.5, 92.3, 15.5, 0.3; FTIR (neat) 3557, 3357, 2138, 1697, 1257, 1100 cm^{-1}; MS m/z 57, 131, 151 (100), 166 (M^+); HRMS calcd for $C_9H_{14}OSi$ (M^+) 166.0814, found 166.0800.

(*E*)-3-Iodo-2-methylprop-2-en-1-ol (13). To a solution of Me_3Al (2.0 M in hexane, 78 mL, 156 mmol) and Cp_2ZrCl_2 (18.2 g, 62.4 mmol) in CH_2Cl_2 (80 mL) was added propargyl alcohol (3.5 g, 62.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 h. A solution of I_2 (2.08 g, 8.21 mmol) in THF (5.0 mL) was added at −78 °C, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 1 h, the mixture was acidified with 3 M HCl at 0 °C, extracted with AcOEt, washed with saturated $NaHCO_3$, saturated $Na_2S_2O_3$ and brine, dried and concentrated. Purification of the residue by column chromatography (SiO_2 250 g, hexane–AcOEt = 3 : 1) gave **13** (6.82 g, 55%) as a yellow oil. ^{1}H NMR δ 6.29 (s, 1H), 4.13 (d, J = 5.9 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR δ 147.1, 77.3, 66.7, 21.3; FTIR (neat) 3316, 2914, 1624, 1274, 1012 cm^{-1}; MS m/z 71, 198 (100, M^+); HRMS calcd for C_4H_7OI (M^+) 197.9542, found 197.9536.

(*E*)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (14). Iodide **13** (1.82 g, 9.19 mmol) was subjected to Sonogashira coupling using ethynyltrimethylsilane (2.6 mL, 18.4 mmol), diisopropylamine (9.4 mL, 68.9 mmol), $PdCl_2(PPh_3)_2$ (110 mg, 0.18 mmol), and CuI (110 mg, 0.64 mmol) in the same manner as described for the preparation of **12** from **11**. Purification by column chromatography (SiO_2 80 g, hexane–AcOEt = 7 : 1 to 5 : 1) afforded **14** (1.53 g, 99%) as a reddish brown oil. ^{1}H NMR δ 5.61 (s, 1H), 4.12 (d, J = 6.3 Hz, 2H), 1.91 (s, 3H), 0.20 (s, 9H); ^{13}C NMR δ 151.6, 104.6, 102.4, 98.4, 66.7, 16.5, 0.0; FTIR (neat) 3329, 2138, 1252, 1098 cm^{-1}; MS m/z 153 (100) 168 (M^+); HRMS calcd for $C_9H_{16}OSi$ (M^+) 168.0970, found 168.0961.

(*E*)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-ynal (10). Alcohol **14** (2.5 g, 14.9 mmol) was oxidized using activated MnO_2 (12.9 g, 149 mmol) in the same manner as described for the preparation of **9** from **12**. Purification by column chromatography (SiO_2 120 g, hexane–AcOEt = 80 : 1) gave **10** (2.32 g, 94%) as a brown oil. ^{1}H NMR δ 9.46 (s, 1H), 6.33 (s, 1H), 1.94 (s, 3H), 0.24 (s, 9H); ^{13}C NMR δ 194.1, 149.0, 128.6, 113.8, 100.1, 11.8, −0.4; FTIR (neat) 2961, 2821, 2713, 2137, 1689, 1604, 1092 cm^{-1}; MS m/z 43, 151, 166 (100, M^+); HRMS calcd for $C_9H_{14}OSi$ (M^+) 166.0814, found 166.0784.

(3*S*,4*S*)-3-Methyl-4-((*Z*)-5-(trimethylsilyl)pent-2-en-4-yn-2-yl)-oxetan-2-one (16). To a solution of $LiClO_4$ (1.28 g, 12.0 mmol) and TMSQD[18] (240 mg, 0.60 mmol) in CH_2Cl_2–hexane (1 : 1) (10 mL) were added a solution of **9** (500 mg, 3.0 mmol) in CH_2Cl_2 (2.5 mL) and diisopropylethylamine (1.32 mL, 7.50 mmol) at −78 °C. A solution of propionyl chloride (0.50 mL, 6.0 mmol) in CH_2Cl_2 (2.0 mL) was then added slowly over 2 h. After being stirred at −78 °C for 20 h, the mixture was diluted with Et_2O (50 mL) and filtered through a short silica gel column. The filtrate was concentrated and chromatographed (SiO_2 50 g, hexane–AcOEt = 80 : 1 to 20 : 1) to give **16** (0.61 g, 92%) as a yellow oil. $[\alpha]_D^{20}$ −267.3 (c 0.92, $CHCl_3$); ^{1}H NMR δ 5.57 (s, 1H), 5.52 (d, J = 6.8 Hz, 1H), 3.94 (qd, J = 7.8, 6.8 Hz, 1H), 1.87 (s, 3H), 1.18 (d, J = 7.8 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR δ 171.8, 147.0, 108.6, 101.3, 100.3, 74.9, 50.0, 19.5, 8.8, −0.3; FTIR (neat) 2138, 1836, 1763, 1446, 1253, 1102 cm^{-1}; MS m/z 57 (100), 151, 222 (M^+); HRMS calcd for $C_{12}H_{18}O_2Si$ (M^+) 222.1076, found 222.1096. The enantiomeric excess and diastereomeric excess were determined to be 98% ee and >99% de by chiral HPLC analysis: Daicel Chiralcel AS, 2-propanol–hexane = 1 : 800 (0.5 mL min^{-1}), t_R = 20.2 min (*S*,*S*) and 25.2 min (*R*,*R*).

(3*R*,4*R*)-3-Methyl-4-((*Z*)-5-(trimethylsilyl)pent-2-en-4-yn-2-yl)-oxetan-2-one. The reaction of **9** (50 mg, 0.30 mmol) and propionyl chloride (50 μL, 0.60 mmol) was carried out using $LiClO_4$ (1.28 g, 12.0 mmol), TMSQN[18] (0.24 mg, 0.60 mmol) and diisopropylethylamine (0.13 ml, 0.75 mmol) at −78 °C for 20 h in the same manner as described for the preparation of **16** from **9**. Purification by column chromatography (SiO_2 6.0 g, hexane–AcOEt = 80 : 1 to 10 : 1) to give the title compound (56 mg, 84%), an enantiomer of **16**, as a yellow oil. $[\alpha]_D^{20}$ +262.9 (c 0.88, $CHCl_3$). The enantiomeric excess and diastereomeric excess were determined to be 97% ee and >99% de by chiral HPLC analysis: Daicel Chiralcel AD, 2-propanol–hexane = 1 : 800 (0.7 mL min^{-1}), t_R = 21.5 min (*R*,*R*) and 32.9 min (*S*,*S*).

(3*S*,4*S*)-3-Methyl-4-((*E*)-5-(trimethylsilyl)-pent-2-en-4-yn-2-yl)-oxetan-2-one (17). The reaction of **10** (2.12 g, 12.7 mmol) with propionyl chloride (2.22 mL, 25.4 mmol) was carried out using $LiClO_4$ (5.40 g, 50.8 mmol), TMSQD (1.0 g, 2.54 mmol) and diisopropylethylamine (5.54 mL, 50.8 mmol) in the same manner as described for the preparation of **16** from **9**. Purification by column chromatography (SiO_2 120 g, hexane–AcOEt = 80 : 1 to 20 : 1) gave **17** (2.39 g, 85%) as a yellow oil. $[\alpha]_D^{22}$ −123.9 (c 1.02, $CHCl_3$); ^{1}H NMR δ 5.73 (s, 1H), 4.98 (d, J = 6.4 Hz, 1H), 3.91 (qd, J = 7.5, 6.4 Hz, 1H), 1.89 (s, 3H), 1.21 (d, J = 7.5 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR δ 171.1, 144.3, 107.9, 100.9, 100.7, 75.7, 49.7, 16.4, 8.7, −0.1; FTIR (neat)

2961, 2137, 1839, 1254, 1104 cm^{-1}; MS *m/z* 43 (100), 163, 222 (M^+); HRMS calcd for $C_{12}H_{18}O_2Si$ (M^+) 222.1076, found 222.1091.

(2*S*,3*S*,*Z*)-Methyl 3-hydroxy-2,4-dimethyl-7-(trimethylsilyl)-hept-4-en-6-ynoate (18). To a solution of **16** (2.49 g, 11.2 mmol) in MeOH (110 mL) was added NaOMe (6.0 mg, 0.112 mmol) at 0 °C. After being stirred at room temperature for 30 min, the mixture was diluted with saturated NH_4Cl (50 mL), concentrated, and extracted with AcOEt. The extract was washed with brine concentrated and chromatographed (SiO_2 80 g, hexane–AcOEt = 8 : 1) to give **18** (2.71 g, 95%) as a yellow oil. $[\alpha]_D^{24}$ −58.2 (*c* 1.02, $CHCl_3$); ^1H NMR δ 5.41 (s, 1H), 5.02 (d, *J* = 4.6 Hz, 1H), 3.70 (s, 3H), 2.95 (dq, *J* = 4.6, 7.1 Hz,, 1H), 2.80 (brs, 1H), 1.84 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR δ 175.5, 153.5, 106.5, 101.4, 100.1, 72.8, 51.8, 43.9, 19.1, 11.4, −0.2; FTIR (neat) 3495, 2136, 1730, 1445, 1254, 1201, 1093, 1032 cm^{-1}; MS *m/z* 73, 167 (100), 254 (M^+); HRMS calcd for $C_{13}H_{22}O_3Si$ (M^+) 254.1338, found 254.1329.

(*R*,*Z*)-Methyl 3-hydroxy-2,2,4-trimethyl-7-(trimethylsilyl)hept-4-en-6-ynoate (19). To a solution of diisopropylamine (3.9 mL, 27.7 mmol) in THF (40 mL) was added dropwise *n*-BuLi (2.67 M in hexane, 8.8 mL, 24.4 mmol) at −78 °C. After stirring at −78 °C for 45 min, a solution of **18** (1.68 g, 6.60 mmol) in THF (10 mL) was added, and the mixture was allowed to warm to −20 °C and stirring was continued for 20 min. Iodomethane (4.1 mL, 66.0 mmol) was then added at −78 °C, and the mixture was allowed to warm to −20 °C. After stirring at −20 °C for 4 h, the reaction was quenched with saturated NH_4Cl (50 mL), and the mixture was extracted with AcOEt. The extract was washed with brine, concentrated and purified by flash column chromatography (SiO_2 60 g, $CHCl_3$–hexane = 4 : 1) to give **19** (1.48 g, 84%) as a yellow oil. $[\alpha]_D^{24}$ −32.7 (*c* 1.24, $CHCl_3$); ^1H NMR δ 5.48 (s, 1H), 4.90 (d, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 3.49 (d, *J* = 7.3 Hz, 1H), 1.73 (s, 3H), 1.34 (s, 3H), 1.20 (s, 3H), 0.18 (s, 9H); ^{13}C NMR δ 178.2, 151.0, 110.0, 102.3, 99.3, 77.2, 52.1, 46.9, 24.5, 20.5, 18.3, −0.2; FTIR (neat) 3506, 2132, 1727, 1464, 1260, 1137, 1045 cm^{-1}; MS *m/z* 139, 151 (100), 168, 181, 195, 268 (M^+); HRMS calcd for $C_{14}H_{24}O_3Si$ (M^+) 268.1495, found 268.1500.

(*R*,*Z*)-Methyl 3-hydroxy-2,2,4-trimethylhept-4-en-6-ynoate (20). To a solution of **19** (129 mg, 0.48 mmol) in MeOH (5.0 mL) was added NaOMe (13 mg, 0.24 mmol) at 0 °C. After being stirred at room temperature for 4 h, the mixture was diluted with saturated NH_4Cl (10 mL), extracted with AcOEt, washed with brine and concentrated. Purification of the residue by column chromatography (SiO_2 5.0 g, hexane–AcOEt = 6 : 1) gave **20** (92 mg, 98%) as a yellow oil. $[\alpha]_D^{24}$ −18.0 (*c* 1.20, $CHCl_3$); ^1H NMR δ 5.47 (s, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 3.73 (s, 3H), 3.58 (d, *J* = 7.5 Hz, 1H), 3.08 (s, 1H), 1.75 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 178.1, 151.2, 108.5, 81.7, 80.3, 58.2, 52.0, 46.3, 24.3, 20.4, 18.0; FTIR (neat) 3474, 3290, 2371, 2096, 1719, 1441, 1263, 1049 cm^{-1}; HRMS calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1092.

(*R*,*Z*)-Methyl 3-(*tert*-buthyldimethylsilyloxy)-2,2,4-trimethyl-hept-4-en-6-ynoate (5). To a solution of **20** (600 mg, 3.1 mmol) in CH_2Cl_2 (13 mL) were added 2,6-lutidine (1.4 mL, 12.4 mmol) and TBSOTf (2.7 mL, 7.9 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirring was continued for 0.5 h. The mixture was diluted with saturated NH_4Cl (10 mL) at 0 °C and extracted with AcOEt. The extract was washed with brine, dried, concentrated and chromatographed (SiO_2 30 g, hexane–AcOEt = 100 : 1) to give **5**[4] (900 mg, 100%) as a colorless oil. $[\alpha]_D^{22}$ +115.3 (*c* 1.1, CH_2Cl_2); ^1H NMR δ 5.44 (s, 1H), 5.15 (s, 1H), 3.66 (s, 3H), 3.13 (d, *J* = 1.5 Hz, 1H), 1.80 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), −0.02 (s, 3H); ^{13}C NMR δ 177.2, 153.1, 108.8, 82.2, 80.9, 52.0, 49.4, 25.9, 22.9, 21.0, 18.9, 18.3, −4.6, −5.3; FTIR (neat) 3311, 1735, 1468, 1256, 1136, 1083 cm^{-1}; HRMS calcd for $C_{17}H_{30}O_3Si$ (M^+) 310.1965, found 310.1938.

(*R*,*Z*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-7-iodo-2,2,4-trimethylhept-4-en-6-ynoate. To a solution of **5** (600 mg, 1.94 mmol) in THF (10 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 1.34 mL, 2.14 mmol) at −78 °C. After stirring at −78 °C for 1 h, a solution of I_2 (984 mg, 3.88 mmol) in THF (2.0 mL) was added and stirring was continued at −78 °C for 1 h. The mixture was allowed to warm to 0 °C and saturated $Na_2S_2O_3$ (10 mL) was added. The mixture was extracted with AcOEt, washed with brine, dried, concentrated and chromatographed (SiO_2 50 g, hexane–AcOEt = 7 : 1) to give the corresponding iodide[4] (841 mg, 99%) as a pale yellow oil. $[\alpha]_D^{23}$ +93.4 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 5.55 (s, 1H), 5.10 (s, 1H), 3.67 (s, 3H), 1.80 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), −0.03 (s, 3H); ^{13}C NMR δ 176.7, 154.0, 109.6, 91.4, 76.5, 51.8, 49.0, 25.7, 22.4, 20.9, 18.4, 18.0, −4.9, −5.6; FTIR (neat) 1736, 1468, 1388, 1255, 1137, 1079, 1000 cm^{-1}; HRMS calcd for $C_{17}H_{29}O_3SiI$ (M^+) 436.0931, found 436.0922.

(*R*,4*Z*,6*Z*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-7-iodo-2,2,4-trimethylhepta-4,6-dienoate (2). To a solution of the iodide (50 mg, 0.11 mmol) in THF–i-PrOH (1 : 1) (1.4 mL) were added triethylamine (0.024 mL, 0.17 mmol) and *o*-nitrobenzenesulfonyl hydrazide (40 mg, 0.18 mmol), and the mixture was stirred at room temperature. Triethylamine (0.012 mL, 0.085 mmol) and *o*-nitrobenzenesulfonyl hydrazide (20 mg, 0.090 mmol) were further added each 14 h later and 20 h later. After being stirred at room temperature for additional 6 h, the mixture was diluted with AcOEt, washed with H_2O and brine, dried and concentrated. Purification of the residue by flash column chromatography (SiO_2 4.0 g, hexane–AcOEt = 10 : 1) gave **2**[4] (48 mg, 100%) as a pale yellow oil. $[\alpha]_D^{23}$ +77.5 (*c* 1.35, CH_2Cl_2); ^1H NMR δ 7.00 (br, 1H), 6.25 (d, *J* = 6.3 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 4.91 (brs, 1H), 3.63 (s, 3H), 1.84 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 0.88 (s, 9H), 0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR δ 176.8, 143.1, 133.2, 129.3, 83.0, 75.2, 51.8, 49.4, 25.6, 21.1, 18.0, −4.8, −5.6; FTIR (neat) 1741, 1469, 1386, 1260, 1091, 1012 cm^{-1}; HRMS calcd for $C_{17}H_{31}O_3SiI$ (M^+) 438.1087, found 438.1072.

(*R*,4*Z*,6*Z*,8*E*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (21). To a solution **2** (50 mg, 0.11 mmol) and stannane **1**[12c] (50 mg, 0.13 mmol) in degassed DMF (4.0 mL) were added CuI (2 mg, 0.011 mmol), CsF (35 mg, 0.23 mmol), and $Pd(PPh_3)_4$ (1 mg, 1.1 μmol) at room temperature. The mixture was stirred at room temperature for 5 h and concentrated. Purification of the residue by flash

column chromatography (SiO_2 8.0 g, hexane–AcOEt = 1 : 1 to 5 : 1) gave **21** (40 mg, 83%) as a pale yellow oil. $[\alpha]_D^{23}$ +123.1 (*c* 1.25, CH_2Cl_2); ^{1}H NMR δ 7.79 (s, 1H), 6.81 (s, 1H), 6.68 (dd, *J* = 11.2, 14.2 Hz, 1H), 6.41 (d, *J* = 12.0 Hz, 1H), 6.25 (dd, *J* = 11.0, 12.0 Hz, 1H), 5.95 (dd, *J* = 11.2, 11.0 Hz, 1H), 5.77 (td, *J* = 7.0, 14.2 Hz, 1H), 4.99 (brs, 1H), 3.62 (s, 3H), 3.52 (d, *J* = 7.0 Hz, 2H), 1.83 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.87 (s, 9H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 177.0, 150.7, 150.4, 139.0, 128.3, 127.5, 124.3, 124.1, 122.5, 73.7, 51.7, 49.4, 29.0, 25.6, 22.3, 21.2, 20.1, 18.0, −4.9, −5.6; FTIR (neat) 2950, 1732, 1508, 1465, 1255, 1078 cm^{-1}; MS *m*/*z* 173, 236, 318 (100), 362, 419 (M^+); HRMS calcd for $C_{23}H_{37}NO_4Si$ (M^+) 419.2492, found 419.2493.

(*R*,4*Z*,6*Z*,8*E*)-Methyl 3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (22). To a solution of **21** (210 mg, 0.51 mmol) in MeCN (10 mL) was added 47% HF (1.0 mL) at 0 °C, and the mixture was stirred at room temperature for 6 h. The mixture was basified with saturated $NaHCO_3$ (20 mL) at 0 °C and extracted with AcOEt. The extract was washed with brine, dried, concentrated and chromatographed (SiO_2 10 g, hexane–AcOEt = 2 : 1) to give **22**[4] (137 mg, 88%) as colorless needles; $[\alpha]_D^{21}$ +100.6 (*c* 0.7, CH_2Cl_2); ^{1}H NMR δ 7.80 (s, 1H), 6.81 (s, 1H), 6.67 (dd, *J* = 11.7, 14.8 Hz, 1H), 6.44 (d, *J* = 11.7 Hz, 1H), 6.21 (dd, *J* = 11.1, 11.7 Hz, 1H), 5.96 (dd, *J* = 11.1, 11.7 Hz, 1H), 5.77 (td, *J* = 6.8, 14.8 Hz, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 3.52 (d, *J* = 6.8 Hz, 2H), 3.33 (d, *J* = 6.8 Hz, 1H), 1.80 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H); ^{13}C NMR δ 178.3, 150.7, 150.4, 137.7, 128.5, 128.2, 127.9, 124.9, 124.8, 122.5, 74.6, 52.2, 46.9, 29.0, 24.31, 21.0, 19.7; FTIR (neat) 3474, 2951, 2246, 1736, 1512, 1469, 1142 cm^{-1}; HRMS calcd for $C_{17}H_{23}NO_4$ (M^+) 305.1627, found 305.1621.

(*R*,4*Z*,6*Z*,8*E*)-3-Acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoic acid. To a solution of **22** (60 mg, 0.196 mmol) in THF–MeOH–H_2O (3 : 1 : 1) (4.8 mL) was added LiOH (28 mg, 0.57 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The mixture was acidified with 1 M HCl at 0 °C and extracted with AcOEt. The extract was washed with brine, dried and concentrated to give the corresponding carboxylic acid (50 mg) as a yellow oil. The crude carboxylic acid (50 mg) was dissolved in pyridine (162 μL) and Ac_2O (162 μL, 1.70 mmol) was added at 0 °C. After stirring at room temperature for 20 h, a solution of $NaHCO_3$ (142 mg) in MeOH (1.0 mL) was added and stirring was continued for 1 h. The mixture was extracted with AcOEt, washed with brine, dried and concentrated. Purification of the residue by column chromatography (SiO_2 2 g, $CHCl_3$–MeOH = 1 : 19) gave the acetoxy acid[4] (65 mg, 100%) as a yellow oil. ^{1}H NMR δ 7.80 (s, 1H), 6.82 (s, 1H), 6.63 (dd, *J* = 11.5, 14.4 Hz, 1H), 6.52 (d, *J* = 12.2 Hz, 1H), 6.36 (dd, *J* = 11.0, 12.2 Hz, 1H), 6.01 (s, 1H), 5.98 (dd, *J* = 11.0, 11.5 Hz, 1H), 5.77 (td, *J* = 6.8, 14.4 Hz, 1H), 3.51 (d, *J* = 6.8 Hz, 2H), 2.05 (s, 3H), 1.82 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR δ 180.4, 170, 150.8, 150.6, 133.2, 128.7, 128.6, 126.4, 124.3, 122.3, 75.8, 47.3, 29.0, 23.1, 21.0, 20.8, 20.7; FTIR (neat) 3528, 2923, 2532, 1749, 1512, 1471, 1370, 1271 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1603, found 333.1573.

(*R*,4*Z*,6*Z*,8*E*)-2-Carbamoyl-2,4-dimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl acetate (23). To a solution of the acetoxy acid (21 mg, 0.062 mmol) in CH_2Cl_2 (1.0 mL) were added $SOCl_2$ (7.0 μL, 0.10 mmol) and one drop of DMF at 0 °C. After stirring at room temperature for 2 h, 25% NH_4OH (2 mL) was added at 0 °C and the mixture was stirred at room temperature for 1 h. The mixture was diluted with H_2O (2.0 mL) and extracted with AcOEt. The extract was washed with brine, dried, concentrated and purified by flash column chromatography (SiO_2 3.0 g, hexane–AcOEt = 9 : 1) to give **23** (12 mg, 58%) as a yellow oil. $[\alpha]_D^{24}$ +134.2 (*c* 0.84, $CHCl_3$); ^{1}H NMR δ 7.79 (s, 1H), 6.80 (s, 1H), 6.62 (dd, *J* = 11.7, 14.4 Hz, 1H), 6.49 (d, *J* = 11.7 Hz, 1H), 6.36 (dd, *J* = 11.0, 11.7 Hz, 1H), 6.04–5.98 (m, 2H), 5.86 (s, 1H), 5.79 (td, *J* = 6.8, 14.4 Hz, 1H), 5.86 (brs, 1H), 3.51 (d, *J* = 6.8 Hz, 2H), 2.10 (s, 3H), 1.82 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 178.2, 169.6, 151.0, 150.7, 133.4, 129.3, 128.5, 127.1, 124.2, 122.9, 46.5, 29.3, 25.1, 21.9, 21.2, 20.7; FTIR (neat) 3357, 3208, 2976, 2928, 1739, 1676, 1371, 1241, 1102, 1029 cm^{-1}; MS *m*/*z* 43, 204 (100), 332 (M^+); HRMS calcd for $C_{18}H_{24}N_2O_4$ (M^+) 332.1736, found 332.1732.

(+)-Inthomycin A. To a solution of **23** (8.3 mg, 0.025 mmol) in THF–MeOH–H_2O (3 : 1 : 1) (1.5 mL) was added LiOH (2.0 mg, 0.05 mmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was acidified with 1 M HCl at 0 °C and extracted with AcOEt. The extract was washed with brine, dried, concentrated and purified by preparative TLC ($CHCl_3$–MeOH = 9 : 1) to give (+)-inthomycin A (6.2 mg, 86%) as a yellow oil. $[\alpha]_D^{21}$ +37.3 (*c* 0.62, $CHCl_3$) (lit.[7a] $[\alpha]_D^{21}$ +37.4 (*c* 1.0, $CHCl_3$)); ^{1}H NMR δ 7.80 (s, 1H), 6.81 (s, 1H), 6.68 (dd, *J* = 11.5, 14.0 Hz, 1H), 6.42 (d, *J* = 11.7 Hz, 1H), 6.23–6.17 (m, 2H), 5.95 (dd, *J* = 11.0, 11.5 Hz, 1H), 5.78 (td, *J* = 6.4, 14.0 Hz, 1H), 5.54 (brs, 1H), 4.65 (s, 1H), 4.05 (s, 1H), 3.52 (d, *J* = 6.4 Hz, 2H), 1.85 (s, 3H), 1.36 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 181.0, 150.7, 150.4, 138.3, 128.7, 128.2, 124.9, 123.7, 122.5, 75.4, 44.6, 29.0, 26.1, 21.7, 19.4; FTIR (neat) 3341, 2926, 1658, 1510, 1468, 1263, 1109, 1039 cm^{-1}; MS *m*/*z* 87 (100), 290 (M^+); HRMS calcd for $C_{16}H_{22}N_2O_3$ (M^+) 290.1630, found 290.1629.

(*R*,4*Z*,6*E*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-7-iodo-2,2,4-trimethylhepta-4,6-dienoate (3). DIBAL (1.04 M in hexane; 7.7 mL, 8.05 mmol) was placed into a 100 mL flask and most of the hexane was evaporated. The residual DIBAL was dissolved in THF (5.0 mL) and added dropwise to a solution of Cp_2ZrCl_2 (2.35 g, 8.05 mmol) in THF (5.0 mL) at 0 °C. After stirring at 0 °C for 1 h, a solution of **5** (500 mg, 1.61 mmol) in THF (5.0 mL) was added, and the mixture was stirred at 0 °C for 1 h. The mixture was cooled to −78 °C and a solution of I_2 (2.08 g, 8.21 mmol) in THF (5.0 mL) was added. The mixture was allowed to warm to 0 °C and stirring was continued for 2 h. The reaction was quenched with saturated $Na_2S_2O_3$ (30 mL) at 0 °C, and the mixture was extracted with AcOEt. The extract was washed with brine, dried, concentrated and chromatographed (SiO_2 40 g, hexane–AcOEt = 100 : 1) to give **3** (580 mg, 82%), a yellow oil, as a 6 : 1 inseparable mixture with its 6-iodo-isomer. ^{1}H NMR δ 7.33–7.21 (m, 1H), 6.22 (br d, *J* = 13.7 Hz, 1H), 5.89 (d, *J* = 11.5 Hz, 1H), 4.84 (brs, 1H), 3.66 (s, 3H), 1.80 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 176.6, 140.6, 133.1, 128.4, 79.0,

74.1, 51.8, 49.3, 25.7, 23.5, 21.8, 18.0, −4.8, −5.4; FTIR (neat) 2952, 1736, 1467, 1256, 1080 cm^{-1}; MS *m/z* 337, 381 (100), 438 (M^+); HRMS calcd for $C_{17}H_{31}O_3SiI$ (M^+) 438.1087, found 438.1103.

(*R*,4*Z*,6*E*,8*E*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (24). Compound **3** containing its 6-iodo-isomer (260 mg, 0.59 mmol) was dissolved in degassed DMF (5.0 mL) and stannane **1**[12c] (260 mg, 0.65 mmol), CuI (11 mg, 0.059 mmol), CsF (180 mg, 1.18 mmol) and $Pd(PPh_3)_4$ (7 mg, 5.90 μmol) were added at room temperature in the dark. After stirring at room temperature for 3 h, the reaction was quenched with saturated NH_4Cl (10 mL). The mixture was extracted with AcOEt, washed with brine, dried and concentrated. Purification of the residue by flash column chromatography (SiO_2 20 g, hexane–AcOEt = 15 : 1 to 7 : 1) gave **24** (142 mg, 57%) as a yellow oil. $[\alpha]_D^{27}$ +117.1 (*c* 1.41, $CHCl_3$); ^1H NMR δ 7.79 (s, 1H), 6.80 (s, 1H), 6.44–6.08 (m, 3H), 5.97 (d, *J* = 11.5 Hz, 1H), 5.73 (td, *J* = 6.8, 14.9 Hz, 1H), 4.94 (brs, 1H), 3.62 (s, 3H), 3.48 (d, *J* = 6.8 Hz, 2H), 1.78 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), −0.07 (s, 3H); ^{13}C NMR δ 177.4, 151.2, 150.7, 138.6, 133.8, 131.8, 129.8, 128.2, 127.3, 122.8, 74.5, 52.0, 50.0, 29.2, 26.0, 22.6, 21.5, 20.1, 18.3, −4.6, −5.3; FTIR (neat) 2952, 2858, 1733, 1467, 1256, 1077 cm^{-1}; MS *m/z* 318 (100), 419 (M^+); HRMS calcd for $C_{23}H_{37}NO_4Si$ (M^+) 419.2492, found 419.2487.

(*R*,4*Z*,6*E*,8*E*)-Methyl 3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (25). To a solution of **24** (90 mg, 0.21 mmol) in MeCN (4.0 mL) was added HF-pyridine (0.2 mL) at 0 °C. After being stirred at room temperature for 4 h, the mixture was basified with saturated $NaHCO_3$ (30 mL) at 0 °C and extracted with AcOEt. The extract was washed with brine, dried, concentrated and purified by flash column chromatography (SiO_2 6.0 g, hexane–AcOEt = 3 : 1 to 2 : 1) to give **25** (47.2 mg, 72%) as a yellow oil. $[\alpha]_D^{27}$ +81.9 (*c* 0.99, $CHCl_3$); ^1H NMR δ 7.78 (s, 1H), 6.79 (s, 1H), 6.43 (dd, *J* = 11.5, 14.0 Hz, 1H), 6.22–6.08 (m, 2H), 6.02 (d, *J* = 11.5 Hz, 1H), 5.75 (td, *J* = 6.8, 14.0 Hz, 1H), 4.76 (d, *J* = 4.9 Hz, 1H), 3.71 (s, 3H), 3.47 (d, *J* = 6.8 Hz, 2H), 3.29 (d, *J* = 6.0 Hz, 1H), 1.75 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H); ^{13}C NMR δ 178.7, 151.1, 150.7, 132.1, 128.8, 128.4, 127.6, 125.3, 124.4, 122.8, 74.9, 52.5, 47.1, 29.3, 24.7, 21.3, 20.0; FTIR (neat) 3430, 3122, 2949, 1726, 1260, 1136 cm^{-1}; MS *m/z* 102, 204 (100), 305 (M^+); HRMS calcd for $C_{17}H_{23}NO_4$ (M^+) 305.1627, found 305.1624.

(+)-Inthomycin B. In the same manner as described for the synthesis of (+)-inthomycin A from **22**, (+)-inthomycin B (35 mg) was obtained as a yellow oil from **25** (77 mg, 0.25 mmol) in 49% yield (4 steps) after purification by preparative TLC ($CHCl_3$–MeOH = 9 : 1). $[\alpha]_D^{26}$ +46.8 (*c* 1.25, $CHCl_3$) (lit.[12c] $[\alpha]_D^{22}$ +19.3 (*c* 1.0, $CHCl_3$)); ^1H NMR δ 7.79 (s, 1H), 6.80 (s, 1H), 6.46 (dd, *J* = 11.5, 14.0 Hz, 1H), 6.28 (brs, 1H), 6.23–6.11 (m, 2H), 6.01 (d, *J* = 11.5 Hz, 1H), 5.74 (td, *J* = 6.8, 14.0 Hz, 1H), 5.55 (brs, 1H), 4.61 (d, *J* = 4.4 Hz, 1H), 3.98 (brs, 1H), 3.48 (d, *J* = 6.8 Hz, 2H), 1.81 (s, 3H), 1.36 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 181.0, 150.8, 150.4, 137.6, 133.3, 131.9, 130.1, 127.5, 127.4, 122.5, 75.8, 44.7, 28.8, 26.1, 21.7, 19.2; FTIR (neat) 3343, 2933, 1658, 1602, 1511, 1468, 1376, 1110, 1047 cm^{-1}; MS *m/z* 69 (100), 204, 290 (M^+); HRMS calcd for $C_{16}H_{22}N_2O_3$ (M^+) 290.1630, found 290.1620.

(*E*,2*S*,3*S*)-Methyl 3-hydroxy-2,4-dimethyl-7-(trimethylsilyl)-hept-4-en-6-ynoate. β-Lactone **17** (1.59 g, 0.72 mmol) was subjected to methanolysis using NaOMe (4 mg, 0.072 mmol) in MeOH (70 mL) in the same manner as described for the preparation of **18** from **16**. Purification by column chromatography (SiO_2 70 g, hexane–AcOEt = 8 : 1) gave the methyl ester (1.82 g, 100%) as a yellow oil. $[\alpha]_D^{24}$ −24.0 (*c* 1.03, $CHCl_3$); ^1H NMR δ 5.73 (s, 1H), 4.49 (brs, 1H), 3.72 (s, 3H), 2.70 (dq, *J* = 3.4, 7.1 Hz, 1H), 2.67 (d, *J* = 3.4 Hz, 1H), 1.86 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR δ 176.0, 150.4, 106.6, 102.4, 99.0, 74.5, 52.0, 42.1, 16.3, 10.0, 0.0; FTIR (neat) 3496, 2359, 2135, 1730, 1445, 1253 cm^{-1}; MS *m/z* 167 (100), 254 (M^+); HRMS calcd for $C_{13}H_{22}O_3Si$ (M^+) 254.1338, found 254.1349.

(*R*,*E*)-Methyl 3-hydroxy-2,2,4-trimethyl-7-(trimethylsilyl)hept-4-en-6-ynoate. The methyl ester (0.98 g, 3.85 mmol) was methylated in the same manner described for the preparation of **19** from **18**. Purification by flash column chromatography (SiO_2 60 g, $CHCl_3$–hexane = 4 : 1) gave the corresponding methylated ester (0.82 g, 80%) as a colorless oil. $[\alpha]_D^{24}$ +17.1 (*c* 1.05, $CHCl_3$); ^1H NMR δ 5.53 (s, 1H), 4.17 (d, *J* = 5.8 Hz, 1H), 3.71 (s, 3H), 3.04 (d, *J* = 5.8 Hz, 1H), 1.86 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 0.19 (s, 9H); ^{13}C NMR δ 177.9, 151.1, 109.2, 102.2, 99.7, 80.8, 60.4, 52.1, 46.6, 23.4, 20.6, 16.7, 14.1, 0.0; FTIR (neat) 3501, 2959, 2360, 2135, 1724, 1253 cm^{-1}; MS *m/z* 102, 167 (100), 268 (M^+); HRMS calcd for $C_{14}H_{24}O_3Si$ (M^+) 268.1494, found 268.1501.

(*R*,*E*)-Methyl 3-hydroxy-2,2,4-trimethylhept-4-en-6-ynoate (26). The methylated ester (0.57 g, 2.12 mmol) was desilylated under methanolytic conditions using NaOMe (57 mg, 1.06 mmol) in MeOH (20 mL) at 0 °C in the same manner as described for the preparation of **20** from **19**. Purification by column chromatography (SiO_2 20 g, hexane–AcOEt = 6 : 1) gave **26** (0.42 g, 100%) as a yellow oil. $[\alpha]_D^{24}$ −15.9 (*c* 1.04, $CHCl_3$); ^1H NMR δ 5.51 (s, 1H), 4.19 (d, *J* = 5.8 Hz, 1H), 3.72 (s, 3H), 3.16–3.14 (m, 1H), 1.88 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H); ^{13}C NMR δ 178.1, 152.0, 108.5, 82.6, 81.1, 80.9, 52.5, 46.9, 23.8, 21.0, 16.9; FTIR (neat) 3492, 3291, 2983, 1721, 1443, 1259, 1138, 1073 cm^{-1}; MS *m/z* 102 (100), 196 (M^+); HRMS calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1088.

(*R*,4*E*,6*E*)-Methyl 3-hydroxy-7-iodo-2,2,4-trimethylhepta-4,6-dienoate (29). To a solution of CuCN (62 mg, 0.69 mmol) in THF (1.5 mL) was added dropwise *n*-BuLi (2.66 M in hexane, 0.52 mL, 1.39 mmol) at −78 °C. After stirring at −40 °C for 10 min, *n*-Bu_3SnH (0.36 mL, 1.39 mmol) was added dropwise at −78 °C. After stirring at −40 °C for 10 min, a solution of **26** (30 mg, 0.15 mmol) in THF (1.5 mL) was added, and the mixture was allowed to warm to −30 °C. After stirring at −30 °C for 1 h, saturated NH_4Cl (2.5 mL) and NH_4OH (0.5 mL) were added, and the mixture was allowed to warm to −10 °C. After being stirred at −10 °C for 0.5 h, the mixture was extracted

with AcOEt, washed with brine, dried and concentrated to give the alkenylstannane (444 mg). The crude alkenylstannane (444 mg) was dissolved in THF (2.0 mL) and a solution of I_2 (240 mL, 0.94 mmol) in THF (1.0 mL) was added at −78 °C in the dark, and the mixture was stirred at room temperature for 20 h. The reaction was quenched with saturated $Na_2S_2O_3$ (10 mL), and the mixture was extracted with AcOEt. The extract was washed with brine, dried, concentrated and purified by flash column chromatography (SiO_2 6.0 g, hexane–AcOEt = 7 : 1) to give **29** (29 mg, 60%) as a yellow oil. $[\alpha]_D^{23}$ +8.6 (*c* 1.32, $CHCl_3$); ^{1}H NMR δ 7.26 (dd, *J* = 11.2, 14.3 Hz, 1H), 6.33 (d, *J* = 14.3 Hz, 1H), 5.94 (d, *J* = 11.2 Hz, 1H), 4.12 (d, *J* = 5.5 Hz, 1H), 3.71 (s, 3H), 3.09 (d, *J* = 5.5 Hz, 1H), 1.70 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR δ 178.1, 141.1, 137.6, 128.4, 81.7, 80.0, 52.2, 46.7, 23.6, 20.7, 14.2; FTIR (neat) 3491, 2979, 2945, 1726, 1462, 1258, 1138, 1047 cm^{-1}; MS *m*/*z* 102 (100), 324 (M^+); HRMS calcd for $C_{17}H_{17}O_3I$ (M^+) 324.0222, found 324.0222.

(*R*,4*E*,6*E*,8*E*)-Methyl 3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoate (30). To a solution **29** (24 mg, 74 μmol) and oxazole stannane **1**[12c] (32 mg, 81 μmol) in degassed DMF (1.0 mL) were added CuI (1.4 mg, 1.4 μmol), CsF (22 mg, 148 μmol), and $Pd(PPh_3)_4$ (1 mg, 0.74 μmol) at room temperature in the dark. The reaction mixture was stirred at room temperature for 3 h, quenched with saturated KF (1.0 mL), and extracted with AcOEt. The extract was washed with brine, dried and concentrated. Purification of the residue by flash column chromatography (SiO_2 6.0 g, hexane–AcOEt = 15 : 1 to 2 : 1) gave **30** (18 mg, 79%) as a yellow oil. $[\alpha]_D^{22}$ +0.78 (*c* 1.39, $CHCl_3$); ^{1}H NMR δ 7.79 (s, 1H), 6.80 (s, 1H), 6.43–6.37 (m, 1H), 6.27–6.18 (m, 2H), 6.02 (d, *J* = 11.0 Hz, 1H), 5.75 (td, *J* = 6.7, 13.8 Hz, 1H), 4.17 (d, *J* = 5.4 Hz, 1H), 3.71 (s, 3H), 3.49 (d, *J* = 6.7 Hz, 2H), 3.09 (d, *J* = 5.4 Hz, 1H), 1.74 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR δ 177.8, 150.5, 150.1, 137.0, 133.1, 131.8, 128.2, 127.8, 127.0, 122.2, 81.8, 51.8, 46.7, 28.5, 23.3, 20.4, 13.6; FTIR (neat) 3383, 3128, 2982, 2949, 1727, 1510, 1463, 1257, 1134 cm^{-1}; MS *m*/*z* 102, 204 (100), 305 (M^+); HRMS calcd for $C_{17}H_{23}NO_4$ (M^+) 305.1627, found 305.1624.

(−)-Inthomycin C. In the same manner as described for the synthesis of (+)-inthomycin A from **22**, (−)-inthomycin C (19 mg) was obtained as a yellow oil from **30** (117 mg, 0.38 mmol) in 22% yield (4 steps) after purification by preparative TLC ($CHCl_3$–MeOH = 9 : 1). $[\alpha]_D^{23}$ −41.5 (*c* 0.10, $CHCl_3$) (lit.[14] $[\alpha]_D^{20}$ −34.3 (*c* 0.10, $CHCl_3$)); ^{1}H NMR δ 7.79 (s, 1H), 6.79 (s, 1H), 6.39 (dd, *J* = 11.2, 14.2 Hz, 1H), 6.24–6.20 (m, 3H), 6.02 (d, *J* = 11.2 Hz, 1H), 5.75 (td, *J* = 6.8, 14.2 Hz, 1H), 5.40 (brs, 1H), 4.01 (d, *J* = 4.6 Hz, 1H), 3.72 (brs, 1H), 3.48 (d, *J* = 6.8 Hz, 2H), 1.79 (s, 3H), 1.30 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 180.6, 150.8, 150.4, 137.8, 133.4, 132.4, 128.8, 127.4, 122.5, 83.8, 45.0, 28.8, 25.7, 21.7, 13.3; FTIR (neat) 3341, 2925, 2849, 1739, 1658, 1510, 1469, 1372, 1103 cm^{-1}; MS *m*/*z* 87 (100), 204, 290 (M^+); HRMS calcd for $C_{16}H_{22}N_2O_3$ (M^+) 290.1630, found 290.1629.

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