JOC The Journal of Organic Chemistry

Article

Asymmetric Total Synthesis of Inthomycins A, B and C

Jae Hyun Kim, Yeonghun Song, Min Jung Kim, and Sanghee Kim

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00017 • Publication Date (Web): 12 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

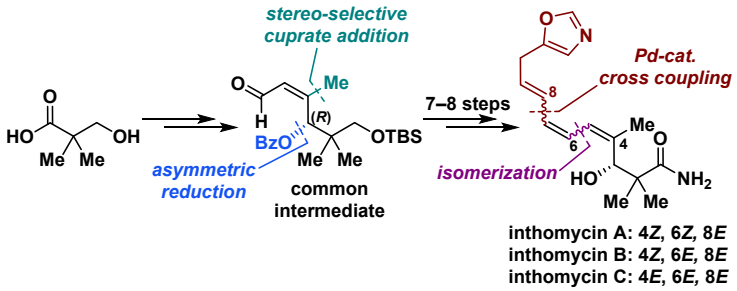
Asymmetric Total Synthesis of Inthomycins A, B and C

Jae Hyun Kim,† Yeonghun Song,† Min Jung Kim and Sanghee Kim*

College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea

pennkim@snu.ac.kr

Table of Contents



Abstract

Herein, we report the asymmetric total syntheses of inthomycin antibiotics containing a methylene-interrupted oxazolyl-triene motif. Utilizing the α,β-unsaturated aldehyde as a common intermediate, all three inthomycins A–C were divergently synthesized. The asymmetric ynone reduction provided an *R*-configured secondary alcohol as in the natural products with high enantioselectivity. The geometrically different triene units for each inthomycin were stereoselectively established via methyl cuprate conjugate addition, isomerization of the α,β-unsaturated aldehyde intermediate, and stereocontrolled cross-coupling reactions.

Introduction

Inthomycin A (**1**) and its geometrical isomers B (**2**) and C (**3**) are polyene natural products containing an oxazole ring (Figure 1). These compounds display a wide range of interesting biological activities including the specific inhibition of cellulose biosynthesis[1] as well as antifungal,[2] herbicidal[2,3] and anticancer activities.[4] This small family of natural products was isolated from *Streptomyces* sp. in the early 1990s.[1,5] However, prior to this isolation, the entire structure of **1** was found within other natural products, such as neooxazolomycin (**4**)[6] and oxazolomycin A (**5**).[7] Later, the structures of **2** and **3** were also found to be embedded in several natural products in the oxazolomycin family including oxazolomycins B (**6**) and C (**7**),[8] 16-methyloxazolomycin,[9] curro mycins[10] and KSM 2690.[11]

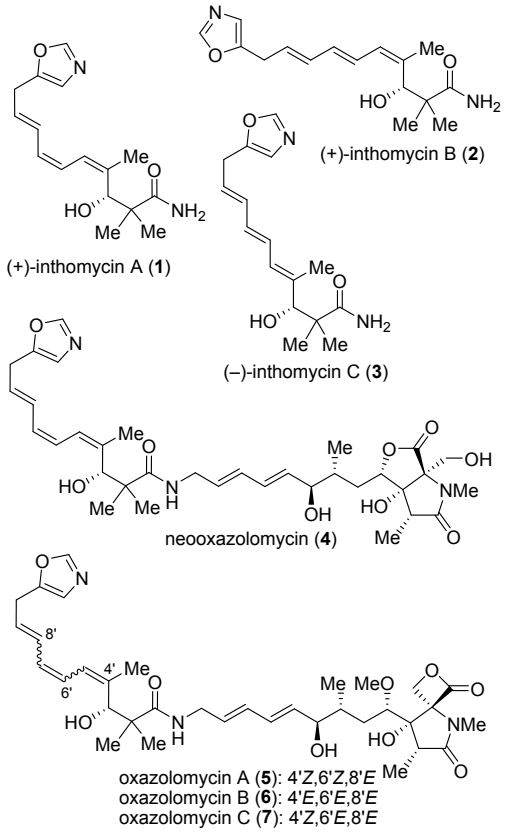
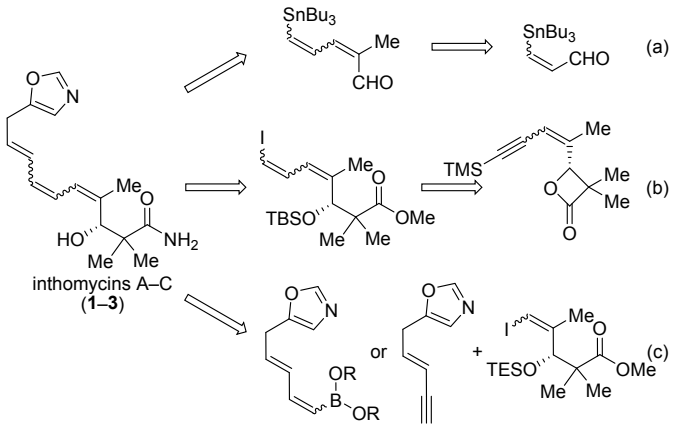


Figure 1. Inthomycins A–C (**1**–**3**) and related natural products **4**–**7**.

The synthesis of inthomycins has attracted much attention due to their interesting biological activities as well as the total synthesis of oxazolomycin family members.[12–15] Although inthomycins may appear to be simple synthetic targets, the synthesis is challenging due to the unusually interposed functional groups, such as the allylic alcohol with a α-quaternary carbon center and the methylene-interrupted oxazoyl-triene motif. An additional synthetic challenge involves controlling the configuration of the double bonds in the conjugated triene system, which is susceptible to *cis-trans* isomerization. Most synthetic efforts focused on this family of natural products have been directed toward the thermodynamically more favored inthomycin C, which has a 4*E*,6*E*,8*E*-triene system.[12] Less attention has been directed at the synthesis of other members.[13] Only three synthetic strategies that lead to the total synthesis of all three members are available (Scheme 1).[14] To construct the conjugated triene system, Taylor et al. utilized Stille coupling of an oxazole vinyl iodide unit with a stannyl diene that was derived from stannyl acrylaldehyde (Scheme 1a).[14a] Hatakeyama et al. also utilized Stille coupling to introduce the vinyl oxazole moiety to iododienes which was synthesized from *β*-lactone compounds (Scheme 1b).[14b] In Burton's synthesis, Suzuki or Sonogashira cross-couplings were employed to connect vinyl iodides with oxazole-containing dienyl boronic acid or enyne (Scheme 1c).[14c] These three

syntheses utilized stereoretentive cross-coupling reactions of (*E*)- or (*Z*)-vinyl coupling partners to install the configuration of the double bonds in the triene system.

Scheme 1. Previous Synthesis of Inthomycins A (1), B (2) and C (3)



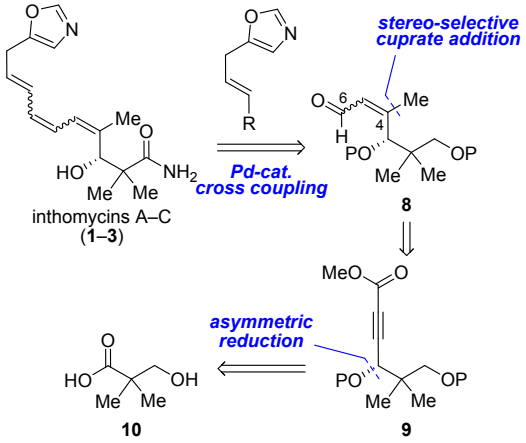
As part of our ongoing research program that is focused on the total synthesis of the oxazolomycin family of natural products,[15d] we have investigated the efficient synthesis of all three inthomycins. Herein, we report results from our synthetic studies of these polyene natural products. Our synthesis features the highly stereocontrolled installation of triene unit with alternating *E*/*Z* geometry from a common intermediate.

Results and Discussion

While seeking a unified strategy to access all inthomycins A–C, we envisioned that alkynoic ester **9** could serve as a common intermediate from which both 4*E*- and 4*Z*-configurations of α,β-unsaturated carbonyl compound **8** could be established by a stereoselective methyl cuprate

conjugate addition (Scheme 2). The C-6 carbonyl group could be a functional handle for the installation of the triene unit. Alkynoic ester **9** was envisioned from 3-hydroxy pivalic acid (**10**) through alkynylation with propiolate and asymmetric reduction.

Scheme 2. Retrosynthesis of Inthomycins A (1), B (2) and C (3)

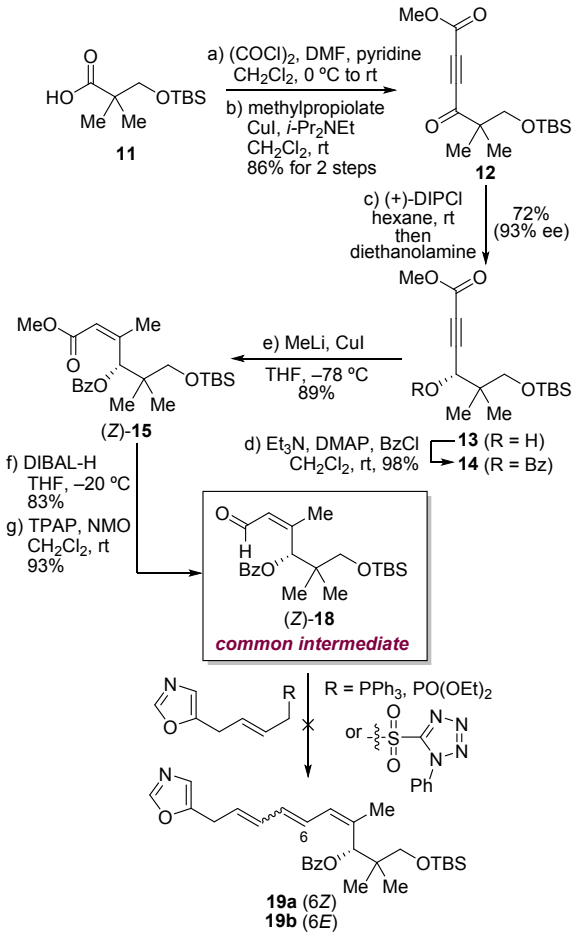


Our total synthesis began with the known TBS-protected hydroxy pivalic acid **11**[16] (Scheme 3), which was synthesized in one step from the commercially available 3-hydroxy pivalic acid (**10**). Activation of acid **11** to its acid chloride followed by CuI-catalyzed nucleophilic addition of methyl propiolate afforded ynone **12**.[15d,17]

Several asymmetric ynone reduction protocols, such as Noyori[18] and Corey–Bakshi–Shibata[19] (CBS) reductions, were examined for the installation of the stereocenter at the sterically hindered neopentyl position. The best enantioselectivity was obtained using DIPCl.[20] The treatment of **12** with (+)-DIPCl at room temperature, followed by the usual diethanolamine

workup afforded product **13** in 93% ee and 72% yield. The absolute configuration was assigned as *R* based on the well-established stereochemistry of DIP-chloride reduction and confirmed by NMR studies and X-ray crystallographic analysis of Mosher's esters of **13** (see the Supporting Information for details).[21] The CBS reduction of **12** with (*S*)-CBS catalyst at –30 °C afforded **13** with a slightly lower enantioselectivity (90% ee) but a higher yield (82%).

Scheme 3. Synthesis of Common Intermediate (*Z*)-18[a]



[a]Reagents and conditions: (a) $(COCl)_2$ (1.5 equiv), pyridine (4 equiv), DMF (3 mol%), CH_2Cl_2, 0 ºC to rt, 2h; (b) methylpropiolate (1 equiv), CuI (10 mol%), *i*-Pr_2NEt (1 equiv), CH_2Cl_2, rt, 16 h, 86% for 2 steps; (c) (+)-DIPCl (1.5

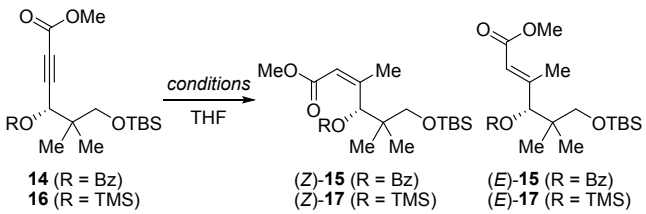
equiv), hexane, rt, 16 h; then diethanolamine (4 equiv), 0 ºC to rt, 2 h, 72%, 93% ee; (d) Et_3N (3 equiv), DMAP (3 mol%), BzCl (2 equiv), CH_2Cl_2, 0 ºC to rt, 30 min, 98%; (e) MeLi (6 equiv), CuI (3 equiv), THF, –78 ºC, 30 min, 89%; (f) DIBAL-H (2.5 equiv), THF, –78 ºC to –20 ºC, 2 h, 83%; (g) TPAP (10 mol%), NMO (1.5 equiv), CH_2Cl_2, rt, 30 min, 93%. DIPCl = *B*-chlorodiisopinocampheylborane, BzCl = benzoyl chloride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

With ynoate **13** in hand, the addition of methyl copper reagents was investigated to selectively form the trisubstituted olefin moiety in inthomycins. These type of reactions tend to proceed *cis*-selectively via *syn* addition at low temperatures.[22] However, stereoselectivity is sensitive to numerous factors, such as temperature, solvent, additives, coordinating groups, lithium salts and the nature of substituents.[23] For example, at a higher temperature, *cis*/*trans* mixtures are obtained. In some cases, *trans* products were observed with good to excellent stereoselectivities.[24] The loss of *cis* stereoselectivity was attributed to isomerization of the initial *cis*-organocopper intermediate to a *trans*-isomer through the corresponding allenolate.[25]

Prior to the conjugate addition of the methyl group, the hydroxyl group of ynoate substrate **13** was protected as a benzoate. Treatment of benzoate-protected ynoate **14** with MeLi in the presence of CuI at –78 °C led to the exclusive formation of the 4*Z*-configured α,β-unsaturated ester (*Z*)-**15** (Table 1, entry 1), which has suitable olefin geometry for inthomycins A and B. To

achieve the 4*E*-geometry of inthomycin C, we varied several factors in the reactions including temperature, additive, copper salt, and methyl anion source. Most trials yielded complex mixtures of unidentified products and produced **15** in poor yield (see, for example, entries 2–3). The highest *E* selectivity and modest yield were obtained when MeMgBr and CuBr·DMS were employed at room temperature (entry 4). These conditions afforded the product in 61% yield with a 1:3 ratio in favor of the *E*-isomer. However, substrate **16** with a TMS-protecting group exclusively afforded (*E*)-**17** in the reaction with MeMgBr in the presence of CuI (entry 5).[26] It is important to note that the reaction of **16** with MeLi instead of MeMgBr provided only (*Z*)-**17** at low temperature in good yield (entry 6). These results are consistent with previous studies in that the subtle changes in properties of nearby protecting groups, alkyl anion sources and reaction temperatures substantially affected the stereochemical outcome of the cuprate addition reaction to ynoates.[23–26]

Table 1. Stereo-selective Cuprate Addition to Ynones[a]



entry	starting material	reagents (equiv.)	temp	time	yield[b]	*Z*:*E*
1	**14**	MeLi (6), CuI (3)	–78 ºC	30 min	89	1:0

2	**14**	MeLi (10), CuI (5), TMSCl (5)	–78 ºC to 0 ºC	12 h	29	3:1
3	**14**	MeMgBr (2.6), CuI (2)	–78 ºC to rt	1.5 h	29	1:3
4	**14**	MeMgBr (7.5), CuBr·DMS (7.5)	0 ºC to rt	1.5 h	61	1:3
5	**16**	MeMgBr (6), CuI (3)	–78 ºC to rt	4 h	61	0:1
6	**16**	MeLi (6), CuI (3)	–78 ºC	3 h	81	1:0

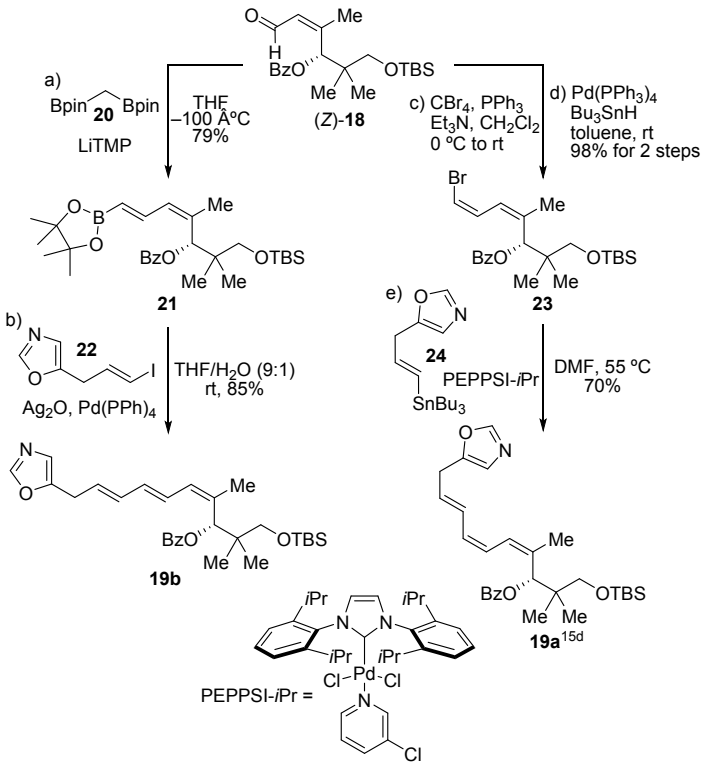
[a]Reactions were run with 0.2 mmol of **14** or **16**. [b]Combined yield of *Z*/*E* isomers.

Having established selective access to the *Z*- and *E*-isomers of **15** and **17**, we explored the incorporation of a triene unit. To synthesize inthomycins A and B, which possess a 4*Z*-trisubstituted olefin, the *Z*-configured α,β-unsaturated ester (*Z*)-**15** was first converted to aldehyde (*Z*)-**18** by employing a reduction-oxidation sequence using DIBAL-H followed by TPAP oxidation (Scheme 3). For the rapid assembly of a triene system in inthomycins A (**1**) or B (**2**) from (*Z*)-**18**, several olefination methods, such as Wittig reaction, Horner–Wadsworth–Emmons reaction and Julia–Kocienski olefination, were attempted under various conditions. However, these trials met with failure. Most reactions afforded **19** in very poor yields and stereoselectivities. Therefore, we resorted to the stepwise installation of the triene system.

Vinyl boronates or vinyl halides, which are synthetically useful in metal-catalyzed coupling reactions, are typically derived from alkyne or alkene intermediates. However, to reduce the number of steps in our synthesis, the direct conversion of aldehyde (*Z*)-**18** into vinyl boronates or vinyl halides was studied (Scheme 4). Applying the recently developed boron-Wittig reaction

with bis[(pinacolato)boryl]methane (**20**) by Morken,[27] *E*-vinyl boronate **21** was obtained in perfect stereoselectivity.[28] Vinyl boronate **21** was coupled with the known *E*-vinyl iodide **22**[13c] under Suzuki–Miyaura reaction conditions successfully to afford geometrically pure 4*Z*,6*E*,8*E*-triene **19b**. To synthesize inthomycin A (**1**) in a unified manner with inthomycin B (**2**), we sought to stereoselectively install a *Z*-vinyl boronate functional group from aldehyde (*Z*)-**18**. Due to the lack of appropriate reaction protocols that allow for this transformation in one or two steps, we decided to install *Z*-vinyl bromide (Scheme 4). The *Z*,*Z*-1-bromodiene **23** was obtained as a single isomer using Uenishi's two-step protocol,[29] consisting of Corey–Fuchs dibromoolefination and Pd-catalyzed hydrogenolysis. The vinyl bromide **23** was coupled with the known *E*-vinyl stannane **24**[13c] under PEPPSI-*i*Pr-catalyzed Stille coupling conditions[12b] to afford 4*Z*,6*Z*,8*E*-triene **19a** without significant isomerization.

Scheme 4. Synthesis of Inthomycins B and A Precursors[a]

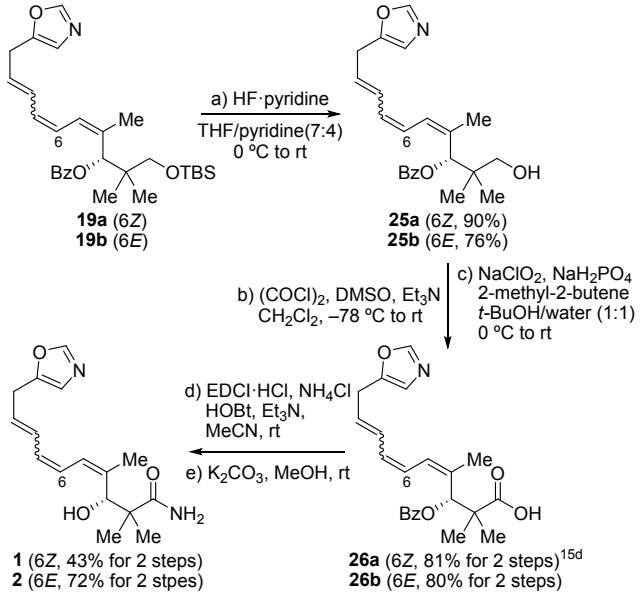


[a]Reagents and conditions: (a) **20** (3 equiv), LiTMP (3 equiv), THF, –100 ºC, 1 h, 79%; (b) **22** (2 equiv), Ag_2O (3.7 equiv), $Pd(PPh)_4$ (13 mol%), THF/H_2O (9:1), rt, 5 min, 85%; (c) CBr_4 (3 equiv), PPh_3 (6 equiv), Et_3N (10 equiv), CH_2Cl_2, 0 ºC to rt, 16 h; (d) $Pd(PPh_3)_4$ (10 mol%), Bu_3SnH (1.05 equiv), toluene, rt, 16 h, 98% for 2 steps; (e) **24** (2 equiv), PEPPSI-*i*Pr (6 mol%), DMF, 55 ºC, 36 h, 70%. LiTMP = lithium tetramethylpiperidide, PEPPSI-*i*Pr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.

To complete the total synthesis of inthomycin A (**1**) and B (**2**), the final task involves the conversion of the protected primary alcohol to a primary amide (Scheme 5). First, cleavage of the silyl ether of **19** with HF•pyridine in a THF/pyridine co-solvent system delivered alcohol **25** without noticeable isomerization of the triene system. Other desilylating reagents, such as TBAF, TBAF-AcOH and TAS-F, caused olefin isomerization to some degree. Then the resulting alcohol

25 was oxidized to the acid **26** via Swern oxidation and the following Pinnick oxidation. Acid **26** was unstable and prone to decomposition, especially under acidic conditions and light exposure. Finally, EDCI-mediated amidation followed by treatment with K_2CO_3 in methanol for debenzoylation afforded (+)-inthomycin A (**1**) and (+)-inthomcyin B (**2**), which were purified by preparative TLC.

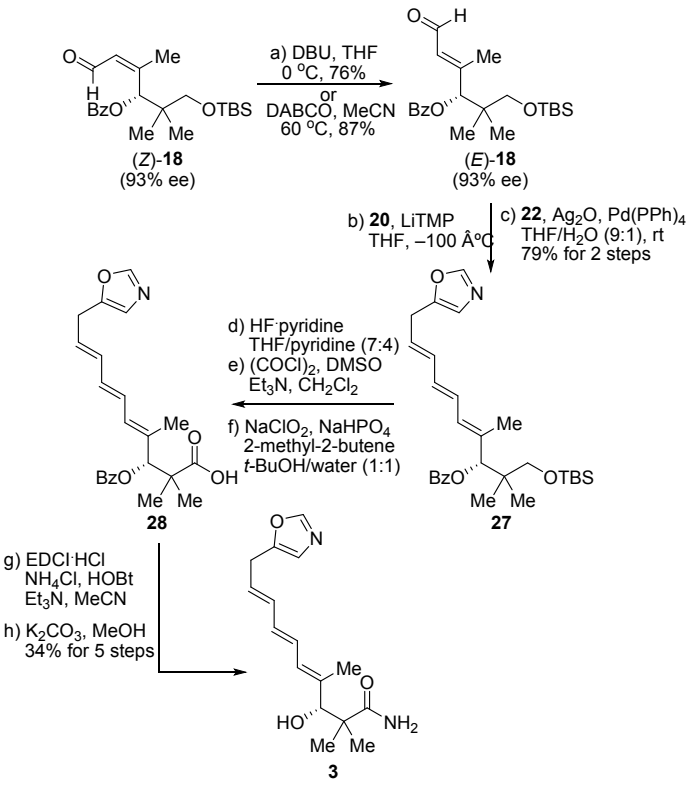
Scheme 5. Completion of Total Synthesis of Inthomycins A (1) and B (2)[a]



[a]Reagents and conditions: (a) HF·pyridine (excess), THF/pyridine (7:4), 0 ºC to rt, 20 h, 90% for **25a**, 76% for **25b**; (b) $(COCl)_2$ (3 equiv), DMSO (6 equiv), Et_3N (13 equiv), CH_2Cl_2, –78 ºC to rt, 40 min; (c) $NaClO_2$ (3 equiv), NaH_2PO_4 (3 equiv), 2-methyl-2-butene (37 equiv), *t*-BuOH/water (1:1), 0 ºC, 30 min, 81% for **26a** for 2 steps, 80% for **26b** for 2 steps; (d) EDCI·HCl (1.2 equiv), NH_4Cl (4 equiv), HOBt (1.2 equiv), Et_3N (3 equiv), MeCN, rt, 3 h; (e) K_2CO_3 (5 equiv), MeOH, rt, 15 h, 43% for **1** for 2 steps, 72% for **2** for 2 steps. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = hydroxybenzotriazole.

Having succeeded with the synthesis of **1** and **2**, we explored the synthesis of inthomycin C (**3**), which contains a 4*E*,6*E*,8*E*-triene system. Unfortunately, the selective removal of one silyl protecting group proved to be a major obstacle when the *E*-configured ester (*E*)-**17** was employed as the substrate. To avoid laborious protecting group manipulations, we decided to use the *Z*-configured unsaturated aldehyde (*Z*)-**18**, which was the common intermediate for **1** and **2**. *Z*-configured unsaturated aldehydes have been isomerized to the more thermodynamically stable *E*-isomer.[30] With this in mind, a wide range of conditions were investigated for isomerization. Among the tested conditions, successful isomerization was delivered with tertiary amine bases. Treatment of (*Z*)-**18** with sterically hindered DBU in THF at 0 °C led to complete isomerization to the *E*-isomer (Scheme 6). When (*Z*)-**18** was treated with less basic DABCO in MeCN at 60 °C, isomerization was also achieved. The enantiomeric purity of the obtained (*E*)-**18** remained unchanged in both cases (93% ee). The isomerization might be promoted by enolization by abstraction of the γ-methyl proton rather than the sterically hindered γ-methine proton. Alternatively, a nucleophilic 1,4-addition–elimination of the tertiary amine might be involved in this isomerization reaction.

Scheme 6. Isomerization of (*Z*)-18 to (*E*)-18 and Total Synthesis of Inthomycin C (3)[a]



[a]Reagents and conditions: (a) DBU (1.5 equiv), THF, 0 ºC, 18 h, 76%, or DABCO (5 equiv), MeCN, 60 ºC, 20 h, 87%; (b) **20** (3 equiv), LiTMP (3 equiv), THF, –100 ºC, 1 h; (c) **22** (2 equiv), Ag_2O (3.7 equiv), $Pd(PPh)_4$ (13 mol%), THF/H_2O (9:1), rt, 5 min, 79% for 2 steps; (d) HF·pyridine (excess), THF/pyridine (7:4), 0 ºC to rt, 20 h; (e) $(COCl)_2$ (3 equiv), DMSO (6 equiv), Et_3N (13 equiv), CH_2Cl_2, –78 ºC to rt, 40 min; (f) $NaClO_2$ (3 equiv), NaH_2PO_4 (3 equiv), 2-methyl-2-butene (37 equiv), *t*-BuOH/water (1:1), 0 ºC, 30 min; (g) EDCI·HCl (1.2 equiv), NH_4Cl (4 equiv), HOBt (1.2 equiv), Et_3N (3 equiv), MeCN, rt, 3 h; (h) K_2CO_3 (5 equiv), MeOH, rt, 15 h, 34% (8:1 mixture) for 5 steps. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

The total synthesis of inthomycin C (**3**) was achieved in good overall yield from (*E*)-**18** utilizing the same sequence of reactions as applied to the synthesis of inthomycin B (**2**) from (*Z*)-**18** (Scheme 6). Although **3** has all *trans*-configured double bonds and is expected to be

thermodynamically more favored than **1** and **2**,[31] some triene intermediates for **3** were prone to isomerization more readily than the corresponding triene intermediates for **1** and **2**. For example, partial isomerization was encountered in Swern and Pinnick oxidation steps. Therefore, an 8:1 mixture of the isomer of (–)-inthomycin C (**3**) was obtained after the final step. The minor isomer was neither **1** nor **2**. Pure **3** was obtained by careful flash column chromatography with some degree of material sacrifice. The spectroscopic data and specific rotation of the three inthomycins (**1**–**3**) were consistent with those reported for inthomycins A–C.[12d,e,14c] The absolute configuration of inthomycin C remained unclear until Hale and Hatakeyama established the absolute configuration to be *R*.[12d] In this study, we reconfirmed the absolute configurations of inthomycins A–C by the unambiguous assignment of common intermediate **13** as *R*, which supports Hale and Hatakeyama's work.[12d]

Conclusion

In conclusion, we have developed efficient asymmetric total syntheses of all three inthomycins in 15–16 steps from a commercially available material in 8–12% overall yields. In this report, we introduced the *R*-configured secondary hydroxy group in the inthomycins by the asymmetric reduction of ynone **12**. The methyl cuprate conjugate addition to alkynoic ester can be achieved

either with *E* or *Z* selectivity based on the use of different protecting groups and reaction conditions. The C-6 carbonyl group was converted to (*E*)-vinyl boronate or (*Z*)-vinyl bromide to further establish the methylene-interrupted oxazolyl-triene motif using stereoretentive palladium-catalyzed cross-coupling reactions. This synthesis also features the use of an isomerizable common intermediate (*Z*)-**18** to access all three inthomycins. In particular, this report provides a synthetic approach involving stereocontrolled construction of geometrically distinctive polyene systems. This synthetic study will be further utilized in the total synthesis of inthomycin-embedded natural products which is currently underway.

Experimental Section

General Information. All chemicals were reagent grade and used as received. All reactions were performed under an inert atmosphere that consisted of dry nitrogen using distilled dry solvents. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel 60 F-254 TLC plates. The compound spots were visualized using UV light (254 nm) and staining with either potassium permanganate or anisaldehyde solutions. Flash column chromatography was performed on silica gel (230-400 mesh). The melting points were measured using a Buchi B-540 melting point apparatus without correction. The optical rotations were measured using sodium light (D line 589.3 nm), and the values are reported as the specific optical rotation with exact temperature, concentration (c/(10 mg/mL)) and solvent. ^{1}H NMR (400, 600 or 800 MHz) and ^{13}C NMR (100, 150, 175 or 200 MHz) spectra were recorded in δ units relative to the non-deuterated solvent as the internal reference. The IR spectra were recorded on a Fourier transform infrared spectrometer. High-resolution mass spectra (HRMS) were obtained using a

magnetic sector type mass spectrometer (JEOL JMS-700) and recorded using fast atom bombardment (FAB). HPLC was performed on an Agilent 1200 series instrument with a diode array detector (DAD) and CHIRALCEL OD-H column (0.46 × 25 cm, 5 μm).

Methyl 6-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-4-oxohex-2-ynoate (12). To an ice-cold solution of acid **11** (9.30 g, 40.0 mmol) in CH_2Cl_2 (200 mL) was added DMF (0.1 mL), pyridine (12.4 mL, 160 mmol) and oxalyl chloride (5.2 mL, 60.0 mmol) under dry N_2 atmosphere. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. The resulting mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was concentrated *in vacuo* to yield crude mixture of acyl chloride of **11** as a dark red oil, which was used in the next step without further purification. To a suspension of CuI (762 mg, 4.0 mmol) in CH_2Cl_2 (100 mL) was added DIPEA (7.0 mL, 40.0 mmol) and methyl propiolate (3.56 mL, 40.0 mmol) at room temperature under a N_2 atmosphere. The solution of the acyl chloride of **11** in CH_2Cl_2 (30 mL) was slowly added into the above solution at room temperature and stirred for 16 h at the same temperature. The reaction mixture was diluted with hexane, filtered through a pad of silica gel and rinsed with hexane/EtOAc (4:1, *v*/*v*). The combined organic layer was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1, *v*/*v*) to yield **12** (10.3 g, 86% for 2 steps) as a light yellow oil. R_f = 0.45 (hexane/EtOAc, 10:1); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 3.66 (s, 2H), 1.15 (s, 6H), 0.84 (s, 9H), 0.02 (s, 6H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 190.9, 152.7, 80.0, 78.9, 69.2, 53.2, 50.8, 25.7 (3C), 20.3 (2C), 18.1, –5.7 (2C); IR (neat, cm^{-1}) υ_{max} 2955, 2930, 2857, 1724, 1687, 1435, 1241, 970, 834, 775; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{15}H_{27}O_4Si$ 299.1679; Found 299.1691.

Methyl (*R*)-6-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5,5-dimethylhex-2-ynoate (13). To **12** (6.72 g, 22.5 mmol) was added (+)-DIPCl (1.6 M in hexane; 21.1 mL, 33.8 mmol) at room temperature under dry N_2 atmosphere and stirred for 16 h at the same temperature. The reaction mixture was cooled to 0 ºC and diethanolamine (8.7 mL, 90.1 mmol) was added. The mixture was diluted with Et_2O and warmed to room temperature. After 2 h stirring, the mixture was filtered through a pad of silica gel and rinsed with

hexane/EtOAc (4:1, *v*/*v*). The combined organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (hexane/EtOAc, 10:1, *v*/*v*) to yield **13** (4.87 g, 72%, 93% ee) as a light yellow oil. R_f = 0.18 (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ –5.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 4.30 (d, *J* = 6.9 Hz, 1H), 3.89 (d, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 9.8 Hz, 1H), 3.75 (s, 3H), 3.39 (d, *J* = 9.8 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ = 153.8, 87.2, 71.1, 70.6, 52.6, 39.3, 25.7 (3C), 21.7 (2C), 20.5, 18.1, –5.8 (2C); IR (neat, cm^{-1}) υ_{max} 3439, 2930, 2857, 1717, 1470, 1246, 1077, 834, 775; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{15}H_{29}O_4Si$ 301.1835; Found 301.1841.

(*R*)-MTPA ester of 13. To a solution of **13** (15 mg, 0.05 mmol) in CH_2Cl_2 (0.3 mL), DMAP (6.1 mg, 0.05 mmol), Et_3N (14 μL, 0.10 mmol) and (+)-(*S*)-MTPA-Cl (11 μL, 0.06 mmol) were added successively at room temperature. After 20 min at the same temperature, the reaction was quenched with a saturated aqueous NH_4Cl solution, poured into water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 20:1) to yield the (*R*)-MTPA ester of **13** (17.5 mg, 68%) as a white crystalline solid. R_f = 0.47 (hexane/EtOAc, 10:1); mp 49–52 °C; $[\alpha]^{25}_D$ +8.5 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.50 (m, 2H), 7.44–7.38 (m, 3H), 5.62 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 3.39 (dd, *J* = 26.1, 9.6 Hz, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 165.5, 153.2, 131.7, 129.7, 128.4 (2C), 127.6 (2C), 123.1 (q, *J* = 286.4 Hz), 84.9 (q, *J* = 27.9 Hz), 82.1, 78.4, 69.5, 67.9, 55.4, 52.8, 40.1, 25.7 (3C), 21.0, 19.6, 18.1, –5.6, –5.7; IR (neat, cm^{-1}) υ_{max} 2955, 2935, 2987, 2239, 1756, 1723, 1470, 1436, 1257, 1172, 1102, 1004, 838; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{36}F_3O_6Si$ 517.2233; Found 517.2246.

(*S*)-MTPA ester of 13. Following the same experimental procedure as described for the preparation of the (*R*)-MTPA ester of **13**, compound **13** (15 mg, 0.05 mmol) was treated with (–)-(*R*)-MTPA-Cl (11 μL, 0.06 mmol) to afford the (*S*)-MTPA ester of **13** (18.5 mg, 72%) as a white crystalline solid. R_f = 0.44 (hexane/EtOAc, 10:1); mp 71–73 °C; $[\alpha]^{25}_D$ –11.5 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.63–

7.50 (m, 2H), 7.43–7.39 (m, 3H), 5.69 (s, 1H), 3.80 (s, 3H), 3.57 (s, 3H), 3.31 (s, 2H), 1.01 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); $^{13}C\{^{1}H\}$ NMR (200 MHz, $CDCl_3$) δ 165.4, 153.2, 132.2, 129.7, 128.5 (2C), 127.4 (2C), 123.3 (q, J = 286.4 Hz), 84.4 (q, J = 28.0 Hz), 82.3, 78.7, 69.2, 67.7, 55.4, 52.8 40.4, 25.7 (3C), 20.9, 19.4, 18.1, –5.6, –5.8; IR (neat, cm^{-1}) υ_{max} 2958, 2932, 2859, 2242, 1759, 1722, 1470, 1433, 1260, 1229, 1173, 1105, 1018, 839; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{25}H_{36}F_3O_6Si$ 517.2233; Found 517.2236.

(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-2,2-dimethyl-6-oxohex-4-yn-3-yl benzoate (14). To an ice-cold solution of **13** (4.87 g, 16.2 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (6.8 mL, 48.6 mmol), DMAP (59.4 mg, 0.49 mmol) and BzCl (3.7 mL, 32.4 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution at 0 ºC, and the mixture was extracted with EtOAc three times. The combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1, *v*/*v*) to yield **14** (6.43 g, 98%) as a colorless oil. R_f = 0.35 (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ –10.9 (*c* 0.56, $CHCl_3$); ^1H NMR (800 MHz, $CDCl_3$) δ = 8.02–8.01, (m, 2H), 7.57–7.55 (m, 1H), 7.44–7.24 (m, 2H), 5.69 (s, 1H), 3.73 (s, 3H), 3.47 (d, J = 9.7 Hz, 1H), 3.43 (d, J = 9.8 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 0.84 (s, 9H), –0.01 (s, 3H), –0.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (200 MHz, $CDCl_3$) δ = 164.9, 153.4, 133.3, 129.7 (2C), 129.6, 128.4 (2C), 83.8, 77.5, 68.2, 67.7, 52.7, 40.6, 25.7 (3C), 21.0, 20.0, 18.1, –5.75, –5.76; IR (neat, cm^{-1}) υ_{max} 2955, 2932, 1734, 1720, 1774, 1674, 1248, 1524, 837, 711; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{33}O_5Si$ 405.2097; Found 405.2088.

(*R*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-2,2,4-trimethyl-6-oxohex-4-en-3-yl benzoate ((*Z*)-15). To a solution of CuI (9.08 g, 47.7 mmol) in dry THF (130 mL) was slowly MeLi (1.6 M in Et_2O; 59.6 mL, 95.4 mmol) at –78 ºC under dry N_2 atmosphere and stirred for 1 h. **14** (6.43 g, 15.9 mmol) in THF (15 mL) was added slowly to the above mixture at –78 ºC and stirred for 30 min at the same temperature. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution and cooling bath was removed. After vigorous stirring for 2 h at room temperature, the mixture was diluted

with water and EtOAc and extracted with EtOAc twice. The combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1, *v*/*v*) to yield (*Z*)-**15** (5.95 g, 89%) as a light yellow oil. R_f = 0.62 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ +71.5 (*c* 3.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.05–8.03 (m, 2H), 7.55–7.53 (m, 1H), 7.44–7.41 (m, 2H), 6.80 (s, 1H), 5.86 (s, 1H), 3.70 (s, 3H), 3.56 (d, *J* = 9.6 Hz, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.85 (s, 9H), –0.02 (s, 3H), –0.05 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ = 165.8, 165.2, 153.8, 132.9, 130.4, 129.5 (2C), 128.4 (2C), 120.4, 75.5, 69.2, 51.1, 41.0, 25.8 (3C), 21.3, 21.2, 21.1, 18.2, –5.7 (2C); IR (neat, cm^{-1}) υ_{max} 2952, 2856, 1720, 1643, 1267, 1082, 834, 773, 709; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{37}O_5Si$ 421.2410; Found 421.2417. The configuration was determined by NOESY experiments (see the Supporting Inforamtion for details).

(*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-2,2,4-trimethyl-6-oxohex-4-en-3-yl benzoate ((*E*)-15). To a solution of CuBr·DMS (308 mg, 1.5 mmol) in distilled THF (2.0 mL), MeMgBr (3.0 M in diethyl ether, 0.5 mL, 1.5 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After 1 h, **14** (81 mg, 0.20 mmol) in THF (0.5 mL) was added at 0 °C. Then, the mixture was warmed to room temperature and stirred for 90 min. After 90 min, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. Then, the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1) to yield (*Z*)-**15** (13.0 mg, 15%) and (*E*)-**15** (39.0 mg, 46%). (*E*)-**15**: light yellow oil. R_f = 0.43 (hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ +65.0 (*c* 1.04, $CHCl_3$); ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.57–7.55 (m, 1H), 7.45–7.43 (m, 2H), 5.89 (s, 1H), 5.32 (s, 1H), 3.65 (s, 3H), 3.44 (d, *J* = 9.7 Hz, 1H), 3.30 (d, *J* = 9.7 Hz, 1H), 2.24 (d, *J* = 1.2 Hz, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.86 (s, 9H), –0.02 (s, 3H), –0.06 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 166.6, 165.3, 156.2, 133.1, 130.2, 129.5 (2C), 128.5 (2C), 117.8, 80.8, 69.2, 50.9, 40.3, 25.8 (3C), 21.1, 20.9, 18.20, 18.17, –5.6, –5.7; IR (neat, cm^{-1}) υ_{max} 2953, 2931, 2858, 1722, 1651, 1268, 1216, 1153, 1097, 838, 776,

712; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{37}O_5Si$ 421.2410; Found 421.2412. The configuration was determined by NOESY experiments (see the Supporting Inforamtion for details).

Methyl (*R*)-6-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-4-((trimethylsilyl)oxy)hex-2-ynoate (16). To a solution of **13** (350 mg, 1.5 mmol) in CH_2Cl_2 (15 mL), Et_3N (418 μL, 3.0 mmol), DMAP (183 mg, 1.5 mmol) and TMSCl (381 μL, 3.0 mmol) were added at 0 °C. The reaction mixture was warmed to room temperature. After 1 h, a saturated aqueous NH_4Cl solution was added to the mixture and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 20:1) to yield **16** (475 mg, 85%) as a colorless oil. R_f = 0.41 (hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ –20.7 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.45 (s, 1H), 3.77 (s, 3H), 3.46 (d, *J* = 9.6 Hz, 1H), 3.26 (d, *J* = 9.6 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.16 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 154.2, 88.7, 77.2, 68.1, 66.6, 52.8, 41.4, 26.1 (3C), 20.9, 19.4, 18.5, 0.2 (3C), –5.3, –5.4; IR (neat, cm^{-1}) υ_{max} 2956, 2931, 2858, 2234, 1720, 1249, 1091, 1063, 871, 838, 775, 750; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{18}H_{37}O_4Si_2$ 373.2230; Found 373.2226.

Methyl (*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5,5-trimethyl-4-((trimethylsilyl)oxy)hex-2-enoate ((*Z*)-17). To a solution of CuI (114 mg, 0.60 mmol) in distilled THF (2.0 mL), MeLi (1.6 M in diethyl ether, 0.75 mL, 1.2 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. Then, **16** (65 mg, 0.20 mmol) in THF (0.5 mL) was added to the reaction mixture at –78 °C. After 3 h of stirring at –78 °C, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. The mixture was warmed to 0 °C and stirred for an additional 1 h. The mixture was extracted twice with ethyl acetate, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1) to yield (*Z*)-**17** (64 mg, 81%) as a yellow oil. R_f = 0.59 (hexane/EtOAc, 10:1); $[\alpha]^{25}_D$ +29.3 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.69 (s, 1H), 5.53 (s, 1H), 3.64 (s, 3H), 3.39 (d, *J* = 9.6 Hz, 1H), 3.25 (d, *J* = 9.2 Hz, 1H), 1.87 (s, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.80 (s, 3H), 0.05 (s, 9H), –0.00 (s, 3H), –0.01 (s, 3H); ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$) δ = 166.6, 160.6, 118.1, 72.3, 69.3, 51.1, 41.5, 26.2 (3C), 21.3, 21.1, 20.5, 18.6, 0.1 (3C), –5.2, –5.3; IR (neat, cm^{-1}) υ_{max} 2955, 2931, 2858, 1722, 1252, 1148, 1093, 1073, 1051, 891, 839, 774; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{41}O_4Si_2$ 389.2543; Found 389.2540. The configuration was determined by NOESY experiments (see the Supporting Inforamtion for details).

Methyl (*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5,5-trimethyl-4-((trimethylsilyl)oxy)hex-2-enoate ((*E*)-17). To a solution of CuI (114 mg, 0.60 mmol) in distilled THF (2.0 mL), MeMgBr (3.0 M in diethyl ether, 0.40 mL, 1.2 mmol) was added at –40 °C. The reaction mixture was stirred at the same temperature for 30 min. Then, **16** (65 mg, 0.20 mmol) in THF (0.5 mL) was added to the reaction mixture at –78 °C. After 2 h of stirring at –78 °C, the reaction mixture was warmed to room temperature and stirred for 2 h. Then, the reaction was quenched by addition of acetic acid at 0 °C. After 20 min, the mixture was warmed to room temperature and stirred for 20 min. Then, the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/Et_2O, 40:1) to yield (*E*)-**17** (48 mg, 61%) as a colorless oil. R_f = 0.41 (hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ +13.1 (*c* 1.11, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 5.80 (s, 1H), 4.10 (s, 1H), 3.68 (s, 3H), 3.36 (d, *J* = 9.2 Hz, 1H), 3.13 (d, *J* = 9.6 Hz, 1H), 2.10 (s, 3H), 0.88 (s, 9H), 0.81 (s, 3H), 0.73 (s, 3H), 0.03 (s, 9H), 0.01 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.3, 161.2, 117.3, 79.7, 69.4, 51.1, 41.2, 26.2 (3C), 21.2, 20.6, 18.5, 17.4, 0.1 (3C), –5.2, –5.4; IR (neat, cm^{-1}) υ_{max} 2954, 2931, 2858, 1722, 1251, 1212, 1152, 1086, 880, 838, 775; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{19}H_{41}O_4Si_2$ 389.2543; Found 389.2540. The configuration was determined by NOESY experiments (see the Supporting Inforamtion for details).

(*R*,*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-6-oxohex-4-en-3-yl benzoate ((*Z*)-18). To a solution of (*Z*)-**15** (5.94 g, 14.1 mmol) in dry THF (30 mL) was added a solution of DIBAL–H (1.0 M in THF; 35.3 mL, 35.3 mmol) at –78 ºC under a N_2 atmosphere. The resulting mixture was allowed to warm to –20 ºC and was stirred for 2 h. The reaction was quenched by the addition of aqueous Rochelle salt at –20 ºC and the mixture was allowed to stir for an additional 2 h at room temperature. The mixture was

diluted with water and EtOAc and extracted with EtOAc three times. The combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 15:1, *v*/*v*) to yield the corresponding alcohol (4.60 g, 83%) as a colorless oil. R_f = 0.37 (hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ +31.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.02–8.01 (m, 2H), 7.55–7.53 (m, 1H), 7.43–7.41 (m, 2H), 5.89 (s, 1H), 5.78–5.75 (m, 1H), 4.56 (dd, *J* = 12.8, 9.2 Hz, 1H), 3.92–3.91 (m, 1H), 3.46 (d, *J* = 9.2, 1H), 3.22 (d, *J* = 9.6 Hz, 1H), 2.82–2.81 (m, 1H), 1.76 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H), 0.86 (s, 9H), –0.03 (s, 3H), –0.07 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ = 165.9, 134.4, 133.0, 131.0, 130.4, 129.4 (2C), 128.4 (2C), 74.9, 69.2, 58.1, 39.9, 25.8 (3C), 21.6, 21.2, 20.2, 18.1, –5.7 (2C); IR (neat, cm^{-1}) υ_{max} 3502, 2954, 2930, 2857, 1720, 1706, 1471, 1270, 1093, 834, 709; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{37}O_4Si$ 393.2461; Found 393.2446.

To a solution of the previously obtained alcohol (4.60 g, 11.7 mmol) in CH_2Cl_2 (115 mL) was added TPAP (412 mg, 1.17 mmol) and NMO (2.06 g, 17.6 mmol) at room temperature. The reaction mixture was stirred for 30 min and filtered through a pad of silica gel and rinsed with hexane/EtOAc (4:1, *v*/*v*). The residue was concentrated *in vacuo* to yield (*Z*)-**18** (4.26 g, 93%) as a colorless oil. R_f = 0.48 (hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ +85.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.18 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.33 (br, 1H), 6.01 (d, *J* = 7.3 Hz, 1H), 3.52 (d, *J* = 10.1 Hz, 1H), 3.30 (d, *J* = 9.7 Hz, 1H), 1.99 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.84 (s, 9H), –0.03 (s, 3H), –0.08 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ = 190.5, 165.3, 156.6, 133.2, 131.8, 129.8, 129.4 (2C), 128.5 (2C), 74.9, 68.9, 40.3, 25.8 (3C), 21.9, 21.3 (2C), 18.1, –5.73, –5.77; IR (neat, cm^{-1}) υ_{max} 2956, 2931, 2858, 1723, 1678, 1267, 1093, 837, 777, 712; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{35}O_4Si$ 391.2305; Found 391.2304.

(*R*,4*Z*,6*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-4,6-dien-3-yl benzoate (21). To a solution of 2,2,6,6-tetramethylpiperidine (510 μL, 3.0 mmol) in distilled THF (10 mL), *n*-BuLi (1.6 M in hexane, 1.9 mL, 3.0 mmol) was slowly

added at 0 °C. After 30 min, **20** (804 mg, 3.0 mmol) in THF (2 mL) was slowly added to the mixture at 0 °C. After stirring at the same temperature for 5 min, the reaction mixture was cooled to –100 °C. Then, a solution of (*Z*)-**18** (390 mg, 1.0 mmol) in THF (2 mL) was added to the reaction mixture. The reaction mixture was stirred at the same temperature for 1 h. Then, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution and warmed to room temperature. The mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 20:1) to yield **21** (406 mg, 79%) as a colorless oil. R_f = 0.59 (hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ +159.4 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.56–7.52 (m, 1H), 7.46–7.41 (m, 3H), 6.13 (d, *J* = 11.6 Hz, 1H), 6.01 (brs, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 3.52 (d, *J* = 9.6 Hz, 1H), 3.25 (d, *J* = 9.6 Hz, 1H), 1.83 (s, 3H), 1.20–1.24 (m, 12H), 1.04 (s, 3H), 0.97 (s, 3H), 0.88 (s, 9H), –0.01 (s, 3H), –0.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4, 145.2, 137.9, 133.3, 133.0, 130.8, 129.74 (2C), 129.70, 128.6 (2C), 83.2 (2C), 77.4, 69.4, 41.2, 26.2 (3C), 26.1, 25.04 (2C), 25.02 (2C), 22.3, 21.4, 18.5, –5.38, –5.42; IR (neat, cm^{-1}) υ_{max} 2972, 2932, 2854, 1723, 1591, 1332, 1464, 1265, 1091; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{29}H_{48}BO_5Si$ 515.3364; Found 515.3370.

(*R*,4*Z*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl benzoate (19b). The reaction flask was wrapped with aluminum foil to perform the reaction in the dark. To a solution of **21** (240 mg, 0.47 mmol) in THF/H_2O (9:1, 8.0 mL), Ag_2O (400 mg, 1.73 mmol) and $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) were added at 0 °C. After 5 min, **22** (226 mg, 0.96 mmol) in THF/H_2O (9:1, 2.0 mL) was added to the mixture. The reaction mixture was warmed to room temperature. After 5 min, the reaction mixture was quenched by addition of a saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to yield **19b** (198 mg, 85%) as a yellow oil. R_f = 0.31 (hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ +148.2 (c 2.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.77 (s, 1H), 7.56–7.52 (m,

1H), 7.44–7.41 (m, 2H), 6.78 (s, 1H), 6.66 (dd, J = 14.0, 11.7 Hz, 1H), 6.23–6.00 (m, 4H), 5.73–5.66 (m, 1H), 3.48–3.45 (m, 3H), 3.23 (d, J = 9.6 Hz, 1H), 1.82 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.88 (s, 9H), –0.03 (s, 3H), –0.06 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 165.3, 150.9, 150.4, 134.3 133.7, 132.8, 131.7, 130.9, 130.6, 129.5 (2C), 128.5, 128.4 (2C), 126.8, 122.5, 75.3, 69.2, 40.8, 29.7, 25.9 (3C), 22.0 (2C), 21.2, 18.2, –5.6 (2C); IR (neat, cm^{-1}) υ_{max} 2955, 2921, 2854, 1720, 1509, 1453, 1270, 1088; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{29}H_{42}NO_4Si$ 496.2883; Found 496.2894.

(*R*,*4Z*,6*Z*)-7-Bromo-1-((*tert*-butyldimethylsilyl)oxy)-2,2,4-trimethylhepta-4,6-dien-3-yl benzoate (23). To an ice-cooled mixture solution of CBr_4 (10.8 g, 32.7 mmol) in CH_2Cl_2 (70 mL) was added PPh_3 (17.2 g, 65.4 mmol) and stirred for 10 min. To the mixture was added Et_3N (15.2 mL, 109 mmol) and (*Z*)-**18** (4.26 g, 10.9 mmol) in CH_2Cl_2 (15 mL) at 0 ºC. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The solution was diluted with hexane and filtered through a pad of silica gel and rinsed with hexane/EtOAc (4:1, *v*/*v*). The combined organic solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (hexane/EtOAc, 40:1, *v*/*v*) to yield 1,1-dibromoolefin compound (5.90 g, 99%) as a colorless oil. R_f = 0.26 (hexane/EtOAc, 40:1); $[\alpha]^{25}_D$ +175 (*c* 0.33, $CHCl_3$); ^1H NMR (800 MHz, $CDCl_3$) δ = 8.05–8.04 (m, 2H), 7.57–7.55 (m, 1H), 7.47–7.43 (m, *3*H), 6.09 (d, J = 10.8 Hz, 1H), 5.85 (br, 1H), 3.48 (d, J = 9.6 Hz, 1H), 3.24 (d, J = 9.6 Hz, 1H), 1.84 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.90 (s, 9H), 0.01 (s, 3H), –0.04 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 165.2, 138.7, 132.9, 132.8, 130.2, 129.4 (2C), 128.4 (2C), 127.0, 91.7, 75.8, 69.0, 40.5, 25.9 (3C), 21.9, 21.1 (2C), 18.2, –5.62, –5.65; IR (neat, cm^{-1}) υ_{max} 2954, 2928, 2856, 1722, 1268, 1096, 838, 776, 710; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{35}Br_2O_3Si$ 545.0722; Found 545.0715.

To a solution of previously obtained 1,1-dibromoolefin compound (5.72 g, 10.5 mmol) and $Pd(PPh_3)_4$ (1.21 g, 1.05 mmol) in toluene (100 mL), Bu_3SnH (2.95 mL, 11.0 mmol) was added slowly over 2 h at room temperature under a N_2 atmosphere. The resulting suspension was stirred for 16 h and then diluted with hexane. The mixture was filtered through a pad of silica gel/Celite and rinsed with hexane/EtOAc (4:1, *v*/*v*). The residue was concentrated *in vacuo* and purified by flash chromatography on silica gel

(hexane/EtOAc, 10:1, *v*/*v*) to yield **23** (4.85 g, 99%) as a colorless oil. R_f = 0.26 (hexane/EtOAc, 40:1); $[\alpha]^{25}_D$ +131 (*c* 0.9, $CHCl_3$); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 8.03–8.02 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.13 (dd, *J* = 10.7, 7.2 Hz, 1H), 6.38 (d, *J* = 10.8 Hz, 1H), 6.15 (d, *J* = 7.1 Hz, 1H), 5.91 (br, 1H), 3.43 (d, *J* = 9.6 Hz, 1H), 3.25 (d, *J* = 9.7 Hz, 1H), 1.86 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H), 0.86 (s, 9H), –0.03 (s, 3H), –0.06 (s, 3H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ = 165.5, 138.7, 133.1, 130.5, 129.6 (2C), 128.6 (2C), 128.4, 126.3, 108.8, 75.5, 69.2, 40.9, 26.0 (3C), 21.9, 21.6 (2C), 18.4, –5.45, –5.50; IR (neat, cm^{-1}) υ_{max} 2954, 2930, 2856, 1721, 1269, 1097, 838, 776, 710; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{36}BrO_3Si$ 467.1617; Found 467.1632.

(*R*,4*Z*,6*Z*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl benzoate (19a). To a stirred solution of **23** (480 mg, 1.03 mmol) in degassed DMF was added **24** (818 mg, 2.05 mmol) and PEPPSI-*i*Pr (41.9 mg, 0.06 mmol) at room temperature under protection from light. The resulting suspension was allowed to warm to 55 ºC and stirred for 36 h under a N_2 atmosphere. After the completion of the reaction, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite and washed with EtOAc. The combined organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 20:1 to 3:1, *v*/*v*) to yield **19a** (356 mg, 70%) as a light yellow oil. The *Z*/*E* selectivity of **19a** was determined by ^{1}H NMR in >30:1 ratio. R_f = 0.42 (hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ +162 (*c* 0.73, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 8.04–8.02 (m, 2H), 7.76 (s, 1H), 7.54–7.52 (m, 1H), 7.43–7.41 (m, 2H), 6.78 (s, 1H), 6.64 (dd, *J* = 14.4, 11.7 Hz, 1H), 6.49–6.44 (m, *2*H), 6.00 (br, 1H), 5.96 (t, *J* = 10.6 Hz, 1H), 5.74 (dt, *J* = 14.6, 7.2 Hz, 1H), 3.49 (d, *J* = 7.0 Hz, 2H), 3.45 (d, *J* = 9.6 Hz, 1H), 3.25 (d, *J* = 9.5 Hz, 1H), 1.86 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H), 0.86 (s, 9H), –0.03 (s, 3H), –0.06 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ = 165.3, 150.8, 150.4, 135.1, 132.8, 130.6, 129.5 (2C), 128.44, 128.36 (2C), 128.0, 127.9, 125.6, 124.8, 122.5, 75.1, 69.2, 40.9, 29.0, 25.8 (3C), 21.9 (2C), 21.4, 18.2, –5.6, –5.7; IR (neat, cm^{-1}) υ_{max} 2954, 2929, 2856, 1720, 1270, 1097, 954, 837, 776, 712; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{29}H_{42}NO_4Si$ 496.2883; Found 496.2877.

(*R*,4*Z*,6*Z*,8*E*)-1-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl benzoate (25a). The reaction flask was wrapped with aluminum foil to perform the reaction in the dark. To a solution of **19a** (219 mg, 0.44 mmol) in THF (2.8 mL) and pyridine (1.6 mL) was added HF·pyridine 70 wt% solution (1.4 mL) at 0 ºC. The resulting mixture was stirred for 15 h at the same temperature and then warmed to room temperature. The mixture was stirred for an additional 5 h, and re-cooled to 0 ºC. To the reaction mixture was added a saturated $NaHCO_3$ aqueous solution and extracted with EtOAc twice. The combined organic fraction was washed with brine and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1, *v*/*v*) to yield **25a** (152 mg, 90%) as a light yellow oil. R_f = 0.24 (hexane/EtOAc, 1:1) $[\alpha]^{25}_D$ +192 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 8.04–8.03 (m, 2H), 7.77 (s, 1H), 7.57–7.55 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.78(s, 1H), 6.64–6.61 (m, 1H), 6.50 (d, *J* = 12.3 Hz, 1H), 6.40 (t, *J* = 11.5 Hz, 1H), 6.10 (s, 1H), 6.00 (t, *J* = 11.1 Hz, 1H), 5.77 (dt, *J* = 14.6, 7.2 Hz, 1H), 3.49 (d, *J* = 7.0 Hz, 2H), 3.46 (d, *J* = 11.7 Hz, 1H), 3.25–3.23 (m, 1H), 2.35 (br, 1H), 1.95 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ = 166.2, 150.7, 150.4, 134.6, 133.2, 130.0, 129.8 (2C), 128.8, 128.6, 128.5 (2C), 128.2, 125.8, 124.1, 122.5, 75.1, 69.3, 41.1, 29.0, 21.8, 21.4, 21.1; IR (neat, cm^{-1}) υ_{max} 3302, 2963, 2922, 2873, 1713, 1509, 1268, 1107, 949, 824, 711; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{27}NO_4$ 381.1940; Found 381.1932.

(*R*,4*Z*,6*E*,8*E*)-1-Hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl benzoate (25b). Following the same experimental procedure as described for the preparation of **25a**, compound **19b** (150 mg, 0.30 mmol) was converted to **25b** (86.9 mg, 76%), which was obtained as a yellow oil. R_f = 0.30 (hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ +168.9 (c 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.04 (m, 2H), 7.78 (s, 1H), 7.58–7.55 (m, 1H), 7.45–7.43 (m, 2H), 6.78 (s, 1H), 6.61 (dd, *J* = 14.4, 11.7 Hz, 1H), 6.25 (dd, *J* = 15.0, 10.7 Hz, 1H), 6.15 (dd, *J* = 14.6, 10.7 Hz, 1H), 6.10–6.08 (m, 2H), 5.72 (td, *J* = 5.6, 10.9 Hz, 1H), 3.45–3.50 (m, 3H), 3.25–3.23 (m, 1H), 1.92 (s, 3H), 1.02 (s, 6H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 166.3, 150.8, 150.4, 133.8, 133.5, 133.2, 132.4, 131.1, 130.0, 129.7 (2C), 128.5 (2C), 127.8,

127.5, 122.5, 75.4, 69.3, 41.1, 28.9, 21.9, 21.2, 21.1; IR (neat, cm^{-1}) υ_{max} 3471, 2980, 2935, 2904, 1734, 1445, 1374, 1231; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{27}NO_4$ 381.1934; Found 381.1940.

(*R*,4*Z*,6*Z*,8*E*)-3-(Benzoyloxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoic acid (26a). The reaction flask was wrapped with aluminum foil to perform the reaction in the dark. To a solution of oxalyl chloride (2.0 M in CH_2Cl_2; 0.3 mL, 0.67 mmol) in CH_2Cl_2 (3.0 mL) was added DMSO (95 μL, 1.34 mmol) at –78 ºC. After the 30 min stirring, **25a** (85.0 mg, 0.22 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise to the above mixture at –78 ºC. The resulting mixture was stirred for an additional 30 min, and Et_3N (0.4 mL, 2.90 mmol) was added at the same temperatrue. After 10 min, the reaction was allowed to warm to room temperature and stirred for an additional 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2 three times. The combined organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 3:1, *v*/*v*) to yield the corresponding aldehyde (81.2 mg, 96%) as a light yellow oil. R_f = 0.62 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +249 (*c* 0.5, CH_2Cl_2); ^1H NMR (800 MHz, $CDCl_3$) δ = 9.78 (s, 1H), 8.00–7.99 (m, 2H), 7.77 (s, 1H), 7.57–7.55 (m, 1H), 7.44–7.42 (m, 2H), 6.79 (s, 1H), 6.62 (dd, *J* = 14.8, 11.5 Hz, 1H), 6.53 (d, *J* = 12.1 Hz, 1H), 6.38 (t, *J* = 11.5 Hz, 1H), 6.13 (s, 1H), 6.05 (t, *J* = 11.1 Hz, 1H), 5.80 (dt, *J* = 15.6, 7.2 Hz, 1H), 3.50 (d, *J* = 6.9 Hz, 2H), 1.82 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 203.7, 165.2, 150.6, 150.4, 133.3, 132.6, 129.6 (2C), 129.5, 129.3, 128.5 (2C), 128.5, 128.1, 126.7, 123.5, 122.6, 75.9, 50.5, 29.0, 20.7, 20.4, 18.3; IR (neat, cm^{-1}) υ_{max} 2972, 2924, 1720, 1509, 1268, 1103, 957, 713; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}NO_4$ 380.1862; Found 380.1855.

To an ice-cold solution of obtained aldehyde (57.4 mg, 0.15 mmol) in *t*-BuOH/water (3 mL, 1:1, *v*/*v*) was added $NaClO_2$ (80%, 50.8 mg, 0.45 mmol), $NaH_2PO_4 \cdot H_2O$ (62.0 mg, 0.45 mmol), and 2-methyl-2-butene (0.6 mL) under protection from light. The reaction mixture was stirred for 30 min and quenched by addition of a saturated $Na_2S_2O_3$ aqueous solution at 0 ºC. The mixture was extracted with EtOAc three times. The combined organic phase was dried over $MgSO_4$, concentrated under reduced pressure and

purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, *v*/*v*) to yield **26a** (50.3 mg, 84%) as a pale yellow oil. R_f = 0.37 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +206 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–8.00 (m, 2H), 7.79 (s, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 6.79 (s, 1H), 6.66–6.53 (m, 2H), 6.41 (t, *J* = 11.5 Hz, 1H), 6.18 (s, 1H), 6.00 (t, *J* = 11.2 Hz, 1H), 5.75 (dt, *J* = 14.6, 7.2 Hz, 1H), 3.50–3.45 (m, 2H), 1.82 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ = 180.0, 165.1, 150.8, 150.6, 133.1, 133.0, 129.9, 129.6 (2C), 128.9, 128.8, 128.4 (2C), 128.3, 126.7, 124.1, 122.4, 76.5, 29.67, 29.0, 23.2, 21.1, 20.8; IR (neat, cm^{-1}) υ_{max} 3249, 2984, 2924, 1719, 1638, 1471, 1270, 1107, 981, 712; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{25}NO_5$ 395.1733; Found 395.1729.

(*R*,4*Z*,6*E*,8*E*)-3-(Benzoyloxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoic acid (26b).

Following the same experimental procedure as described for the preparation of the corresponding aldehyde from **25a**, compound **25b** (44 mg, 0.11 mmol) was converted to the corresponding aldehyde (41 mg, 96%), which was obtained as a yellow oil. R_f = 0.51 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +205.3 (c 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.00–7.98 (m, 2H), 7.78 (s, 1H), 7.58–7.54 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 6.80 (s, 1H), 6.62–6.56 (m, 1H), 6.28–6.10 (m, 4H), 5.75 (td, *J* = 5.6, 10.5 Hz, 1H), 3.48 (d, *J* = 6.9 Hz, 2H), 1.78 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 203.8, 165.2, 150.7, 150.4, 133.32, 133.28, 133.27, 132.0, 131.7, 129.7, 129.6 (2C), 128.5 (2C), 128.2, 127.1, 122.6, 76.3, 50.5, 28.9, 20.51, 20.46, 18.4; IR (neat, cm^{-1}) υ_{max} 2972, 2921, 2851, 2722, 1776, 1723, 1599, 1442, 1259, 1105; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}NO_4$ 380.1862; Found 380.1858.

Following the same experimental procedure as described for the preparation of **26a**, previously obtained aldehyde (35.0 mg, 0.092 mmol) was converted to the corresponding **26b** (30 mg, 83%), which was obtained as a white gum. R_f = 0.31 (hexane/EtOAc, 1:1); $[\alpha]^{20}_D$ +186.0 (c 0.94, $CHCl_3$); ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.02–8.00 (m, 2H), 7.80 (s, 1H), 7.54–7.52 (m, 1H), 7.42–7.39 (m, 2H), 6.78 (s, 1H), 6.62 (dd, *J* = 14.0, 11.6 Hz, 1H), 6.23 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.18–6.11 (m, 3H), 5.71 (td, *J* =10.8, 5.6 Hz, 1H), 3.46–3.45 (m, 2H), 1.79 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, CDCl3) δ

179.6, 165.1, 150.8, 150.6, 133.5, 133.1, 132.7, 132.2, 131.9, 129.9, 129.6 (2C), 128.5 (2C), 127.8, 127.6, 122.3, 76.7, 47.4, 28.8, 23.1, 21.2, 20.5; IR (neat, cm^{-1}) υ_{max} 3491, 3129, 2972, 2921, 2848, 1714, 1593, 1268, 1099; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}NO_5$ 396.1811; Found 396.1798.

(+)-Inthomycin A (1). The reaction flask was wrapped with aluminum foil to perform the reaction in the dark. To a solution of **26a** (16.7 mg, 0.042 mmol) in MeCN (1 mL), Et_3N (18 μL, 0.13 mmol), HOBt (6.8 mg, 0.051 mmol), EDCI·HCl (9.7 mg, 0.051 mmol) and NH_4Cl (9.0 mg, 0.17 mmol) were added at room temperature. After 3 h, a saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1) to yield *O*-benzoylated **1** (13 mg, 80%) as a light yellow oil. R_f = 0.37 (hexane/EtOAc, 1:3); $[\alpha]^{25}_D$ +250.8 (*c* 0.45, CH_2Cl_2); ^1H NMR (800 MHz, $CDCl_3$) δ = 8.01–7.99 (m, 2H), 7.76 (s, 1H), 7.57–7.55 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 6.61 (dd, *J* = 14.8, 12.4 Hz, 1H), 6.53 (d, *J* = 12.1 Hz, 1H), 6.43 (t, *J* = 11.5 Hz, 1H), 6.12 (s, 1H), 6.02 (t, *J* = 11.1 Hz, 1H), 5.98 (br, 1H), 5.77 (dt, *J* = 14.6, 7.2 Hz, 1H), 5.62 (br, 1H), 3.49 (d, *J* = 6.9 Hz, 2H), 1.87 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ = 177.8, 165.1, 150.6, 150.4, 133.3, 133.1, 129.9, 129.5 (2C), 129.1, 129.0, 128.6 (2C), 128.2, 126.8, 123.9, 122.5, 77.1, 46.6, 29.0, 24.5, 21.8, 20.5; IR (neat, cm^{-1}) υ_{max} 3349, 2924, 2853, 1719, 1672, 1271, 1109, 990, 713; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{26}N_2O_4$ 394.1893; Found 394.1891.

The reaction flask was wrapped with aluminum foil to perform the reaction in the dark. To a solution of the previously prepared *O*-benzoylated **1** (9 mg, 0.023 mmol) in MeOH (0.5 mL), K_2CO_3 (16 mg, 0.11 mmol) was adde at room temperature followed by stirring for 15 h at the same temperature. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution, and MeOH was removed using a rotary evaporator. The mixture was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC (hexane/EtOAc, 1:2) to yield (+)-inthomycin A (**1**, 3.6 mg, 54%) as a light yellow oil. R_f = 0.20

(hexane/EtOAc, 1:3); $[\alpha]^{21}_{D}$ +35.8 (*c* 0.24, $CHCl_3$) (lit.[14b] $[\alpha]^{21}_{D}$ +37.3 (c 0.62, $CHCl_3$), lit.[14c] $[\alpha]^{25}_{D}$ +32.3 (c 0.42, $CHCl_3$)); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 6.79 (s, 1H), 6.63 (dd, *J* = 15.0, 11.4 Hz, 1H), 6.41 (d, *J* = 12.1 Hz, 1H), 6.19 (t, *J* = 11.4 Hz, 2H), 5.94 (t, *J* = 11.1 Hz, 1H), 5.76 (dt, *J* = 14.7, 7.2 Hz, 1H), 5.34 (br, 1H), 4.64 (s, 1H), 3.50 (d, *J* = 6.9 Hz, 2H), 1.84 (s, 3H), 1.34 (s, 3H), 1.09 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ = 180.9, 150.7, 150.4, 138.2, 128.7, 128.18, 128.16, 124.9, 123.7, 122.5, 75.5, 44.6, 29.0, 26.1, 21.7, 19.4; IR (neat, cm^{-1}) υ_{max} 3340, 2923, 2853, 1658, 1599, 1510, 1378, 1111, 1047, 992, 825; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{23}N_2O_3$ 291.1709; Found 291.1703.

(+)-Inthomycin B (2). Following the same experimental procedure as described for the preparation of *O*-benzoylated **1**, compound **26b** (8.0 mg, 0.022 mmol) was converted to *O*-benzoylated **2** (6.4 mg, 73%), which was obtained as a yellow oil. R_f = 0.32 (hexane/EtOAc, 1:3); $[\alpha]^{20}_{D}$ +235.3 (c 0.65, $CHCl_3$); ^{1}H NMR (800 MHz, $CDCl_3$) δ = 8.01–8.00 (m, 2H), 7.78 (s, 1H), 7.57–7.55 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.78 (s, 1H), 6.64 (dd, *J* = 14.6, 11.5 Hz, 1H), 6.25 (dd, *J* = 15.1, 10.8 Hz, 1H), 6.17 (dd, *J* = 14.6, 10.8 Hz, 1H), 6.12 (d, *J* = 11.4 Hz, 1H), 6.10 (s, 1H), 5.96 (brs, 1H), 5.73 (dt, *J* = 14.6, 7.2 Hz, 1H), 5.46 (brs, 1H), 3.47 (d, *J* = 6.8 Hz, 2H), 1.84 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 177.7, 165.1, 150.7, 150.4, 133.4, 133.3, 133.0, 132.2 (2C), 129.9 (2C), 129.5 (2C), 128.6, 127.8, 127.6, 122.6, 77.4, 46.6, 28.9, 24.6, 21.9, 20.2; υ_{max} 3356, 3199, 2919, 2852, 1719, 1674, 1271, 1108, 991, 713; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{26}N_2O_4$ 394.1893; Found 394.1900.

Following the same experimental procedure as described for the preparation of **1**, *O*-benzoylated **2** (5 mg, 0.013 mmol) was converted to (+)-inthomycin B (**2**, 3.6 mg, 98%) as a yellow oil. R_f = 0.14 (hexane/EtOAc, 1:3); $[\alpha]^{20}_{D}$ +43.9 (c 0.28, $CHCl_3$) (lit.[14b] $[\alpha]^{26}_{D}$ +46.8 (c 1.25, $CHCl_3$), lit.[14c] $[\alpha]^{25}_{D}$ +40.9 (c 0.82, $CHCl_3$)); ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.79 (s, 1H), 6.41 (dd, *J* = 14.1, 11.5 Hz, 1H), 6.21–6.12 (m, 3H), 6.00 (d, *J* = 11.4 Hz, 1H), 5.73 (td, *J* = 14.4, 7.1 Hz, 1H), 5.35 (brs, 1H), 4.60 (s, 1H), 3.47 (d, *J* = 6.6 Hz, 2H), 1.80 (s, 3H), 1.35 (s, 3H), 1.09 (s, 3H); ^{13}C{^{1}H} NMR (200 MHz, $CDCl_3$) δ 180.8, 150.8, 150.4, 137.5, 133.3, 132.0, 130.2, 127.44, 127.42, 122.6, 75.9, 44.6, 28.8, 26.1, 21.7, 19.2;

IR (neat, cm^{-1}) υ_{max} 3342, 2921, 1706, 1658, 1599, 1512, 1464, 1363, 1265, 1097, 1046; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{16}H_{22}N_2O_3$ 290.1630; Found 290.1622.

(*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-6-oxohex-4-en-3-yl benzoate ((*E*)-18). To a solution of (*Z*)-**18** (21.6 mg, 0.055 mmol) in MeCN (1 mL), DABCO (31 mg, 0.28 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C for 20 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. Then, the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1) to yield (*E*)-**18** (18.8 mg, 87%, 93% ee) as a yellow oil.

Alternatively, the large-scale synthesis of (*E*)-**18** from (*Z*)-**18** was conducted with DBU instead of DABCO. To a solution of (*Z*)-**18** (1.0 g, 2.56 mmol) in THF (25 mL), DBU (573 μL, 3.84 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 18 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. Then, the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 40:1) to yield (*E*)-**18** (760 mg, 76%, 93% ee) as a yellow oil. R_f = 0.43 (hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ +55.4 (c 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.03 (d, *J* = 7.6 Hz, 1H), 8.02–8.00 (m, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.04 (d, *J* = 8.0 Hz, 1H), 5.30 (s, 1H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 2.30 (d, *J* = 0.8 Hz, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.86 (s, 9H), –0.01 (s, 3H), –0.05 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 190.8, 165.5, 159.8, 133.3, 129.9, 129.5 (2C), 128.5 (2C), 128.4, 80.2, 69.2, 40.5, 25.8 (3C), 21.1, 21.0, 18.2, 17.0, –5.6, –5.7; IR (neat, cm^{-1}) υ_{max} 2955, 2927, 2856, 1723, 1672, 1596, 1473, 1259, 1097; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{22}H_{35}O_4Si$ 391.2305; Found 391.2305.

(*R*,4*E*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trien-3-yl benzoate (27). Following the same experimental procedure as described for the preparation of **21** from (*Z*)-**18**, (*E*)-**18** (336 mg, 0.86 mmol) was converted to the corresponding vinyl boronate (424 mg, 96%) as

a yellow oil. R_f = 0.54 (hexane/EtOAc, 8:1); $[\alpha]^{25}_D$ +61.9 (c 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03–8.02 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.28–7.21 (m, 1H), 6.17 (d, *J* = 10.8 Hz, 1H), 5.49 (d, *J* = 18.0 Hz, 1H), 5.33 (s, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 3.30 (d, *J* = 9.2 Hz, 1H), 1.92 (s, 3H), 1.24 (s, 12H), 1.01 (s, 3H), 0.93 (s, 3H), 0.86 (s, 9H), –0.03 (s, 3H), –0.06 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 165.4, 145.2, 137.9, 133.3, 133.0, 130.8, 129.74 (2C), 129.70, 128.6 (2C), 83.2 (2C), 77.4, 69.4, 41.2, 26.2 (3C), 26.1, 25.04 (2C), 25.02 (2C), 22.3, 21.4, 18.5, –5.38, –5.42; IR (neat, cm^{-1}) υ_{max} 2980, 2957, 2929, 2856, 1720, 1633, 1599, 1329, 1262; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{29}H_{48}BO_5Si$ 515.3370; Found 515.3360.

Following the same experimental procedure as described for the preparation of **19b** from **21**, the previously obtained vinyl boronate (392 mg, 0.76 mmol) was converted to **27** (308 mg, 82%) as a yellow oil. R_f = 0.36 (hexane/EtOAc, 3:1) $[\alpha]^{25}_D$ +76.4 (c 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05–8.03 (m, 2H), 7.76 (s, 1H), 7.57–7.53 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.77 (s, 1H), 6.38 (dd, *J* = 13.8, 11.4 Hz, 1H), 6.23–6.10 (m, 3H), 5.69 (td, *J* = 14.4, 7.1 Hz, 1H), 3.45 (d, *J* = 6.8 Hz, 2H), 3.40 (d, *J* = 9.6 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 1.86 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), –0.02, (s, 3H), –0.05 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 165.4, 150.9, 150.4, 135.7, 133.6, 132.8, 131.9, 130.8, 129.5 (2C), 128.4 (2C), 128.3, 128.2, 126.9, 122.5, 81.7, 69.4, 40.7, 28.8, 25.8 (3C), 21.20, 21.18, 18.2, 15.7, –5.6, –5.7; IR (neat, cm^{-1}) υ_{max} 3028, 2949, 2924, 2887, 2859, 1719, 1512, 1461, 1265, 1099; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{29}H_{41}NO_4Si$ 495.2805; Found 495.2809.

(*R*,4*E*,6*E*,8*E*)-3-(Benzoyloxy)-2,2,4-trimethyl-10-(oxazol-5-yl)deca-4,6,8-trienoic acid (28).

Following the same experimental procedure as described for the preparation of **25b**, compound **27** (83 mg, 0.17 mmol) was converted to the corresponding alcohol (56 mg, 85%) as a yellow oil. R_f = 0.53 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +92.1 (c 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05–8.03 (m, 2H), 7.76 (s, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.77 (s, 1H), 6.42–6.35 (m, 1H), 6.24–6.12 (m, 3H), 5.76–5.69 (m, 1H), 5.41 (s, 1H), 3.50–3.44 (m, 3H), 3.26 (d, *J* = 11.2 Hz, 1H), 1.91 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 166.1, 150.8, 150.4, 134.7, 133.4, 133.2, 132.6,

130.2, 129.6 (2C), 129.1, 128.5 (2C), 127.8, 127.5, 122.5, 81.9, 69.4, 40.8, 28.8, 21.9, 20.4, 15.6 ; IR (neat, cm^{-1}) υ_{max} 3415, 2960, 2921, 2868, 1714, 1599, 1506, 1259, 1108; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{27}NO_4$ 381.1940; Found 381.1949.

Following the same experimental procedure as described for the preparation of the corresponding aldehyde from **25b**, the obtained alcohol (54 mg, 0.14 mmol) was converted to the corresponding aldehyde (49 mg, 12:1 isomeric mixture, 90%) as a yellow oil. R_f = 0.64 (hexane/EtOAc, 1:1); $[\alpha]^{25}_D$ +69.5 (c 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 8.02–7.98 (m, 2H), 7.76 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.76 (s, 1H), 6.37–6.12 (m, 4H), 5.74 (td, *J* = 13.7, 6.8 Hz, 1H), 3.46 (d, *J* = 7.2 Hz, 2H), 1.81 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 203.6, 165.1, 150.7, 150.4, 133.4, 133.3, 133.2, 132.9, 129.9, 129.8, 129.6 (2C), 128.5 (2C), 128.1, 127.4, 122.6, 82.1, 50.5, 28.8, 20.0, 18.1, 15.1; IR (neat, cm^{-1}) υ_{max} 3421, 3025, 2977, 2929, 2861, 1717, 1596, 1506, 1259, 1094; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{25}NO_4$ 380.1862; Found 380.1858.

Following the same experimental procedure as described for the preparation of **26b** from the corresponding aldehyde, the previously obtained aldehyde (49 mg, 0.13 mmol) was converted to **28** (45 mg, 10:1 isomeric mixture, 88%) as a yellow oil. R_f = 0.26 (hexane/EtOAc, 1.5:1); $[\alpha]^{25}_D$ +61.4 (c 1.54, $CHCl_3$); ^1H NMR (CD_3OD, 400 MHz) δ 8.07 (s, 1H), 8.02–7.99 (m, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.82 (s, 1H), 6.46–6.40 (m, 1H), 6.29–6.19 (m, 2H), 6.13 (d, *J* = 11.2 Hz, 1H), 5.80–5.73 (m, 1H), 5.59 (s, 1H), 3.49 (d, *J* = 6.8 Hz, 2H), 1.83 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) δ 179.9, 165.1, 150.8, 150.5, 133.4, 133.1, 132.9, 130.0, 129.64, 129.62 (2C), 129.3, 128.4 (2C), 127.7, 127.6, 122.4, 82.2, 47.1, 28.8, 22.5, 20.8, 15.2; IR (neat, cm^{-1}) υ_{max} 3494, 3143, 2929, 1778, 1717, 1506, 1257, 1102, 1029; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{23}H_{26}NO_5$ 396.1811; Found 396.1808.

(–)-Inthomycin C (3).

Following the same experimental procedure as described for the preparation of *O*-benzoylated **1** from **26a**, compound **28** (30 mg, 0.076 mmol) was converted to *O*-benzoylated **3** (16 mg, 8:1 isomeric mixture,

52%) as a yellow oil. R_f = 0.54 (EtOAc only); $[\alpha]^{25}_D$ +97.6 (c 0.35, $CHCl_3$); ^1H NMR (CD_3OD, 400 MHz) δ 8.06 (s, 1H), 8.03–8.01 (m, 2H), 7.61–7.57 (m, 1H), 7.48–7.44 (m, 2H), 6.82 (s, 1H), 6.45–6.39 (m, 1H), 6.28–6.17 (m, 2H), 6.12 (d, *J* = 11.0 Hz, 1H), 5.79–5.72 (m, 1H), 5.59 (s, 1H), 3.48 (d, *J* = 6.8 Hz, 2H), 1.84 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 179.8, 165.3, 151.7, 151.4, 133.7, 133.4, 133.1, 133.0, 130.1, 129.2 (2C), 129.0, 128.4 (2C), 127.6, 127.4, 121.4, 82.7, 46.8, 28.1, 21.8, 20.3, 14.5; IR (neat, cm^{-1}) υ_{max}3348, 3204, 3031, 2969, 2924, 2854, 1720, 1666, 1605, 1450, 1259, 1102; HRMS (FAB) *m*/*z*: $[M]^+$ Calcd for $C_{23}H_{26}N_2O_4$ 394.1893; Found 394.1897.

Following the same experimental procedure as described for the preparation of **1** from *O*-benzoylated **1**, *O*-benzoylated **3** (9.9 mg, 0.025 mmol) was converted to (–)-inthomycin C (**3**, 7.1 mg, 8:1 isomeric mixture, 98%) as a yellow oil. Pure **3** (4.2 mg, yellow oil) could be obtained after flash column chromatography on silica gel (hexane/EtOAc, 1:2). R_f = 0.43 (EtOAc only); $[\alpha]^{25}_D$ –8.3 (c 0.50, $CHCl_3$) (lit.[12d] $[\alpha]_D$ –8.4 (c 1.0, $CHCl_3$), lit.[12e] $[\alpha]_D$ –8.2 (c 1.0, $CHCl_3$), lit.[14c] $[\alpha]^{25}_D$ –4.0 (c 0.89, $CHCl_3$)); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 6.76 (s, 1H), 6.39–6.33 (m, 1H), 6.31–6.25 (m, 1H), 6.21–6.17 (m, 2H), 5.99 (d, *J* = 10.8 Hz, 1H), 5.72 (td, *J* = 13.6, 6.8 Hz, 1H), 5.64 (brs, 1H), 3.98 (s, 2H), 3.46 (d, *J* = 6.8 Hz, 2H), 1.75 (s, 3H), 1.27 (s, 3H), 1.07 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 180.9, 150.9, 150.5, 138.1, 133.5, 132.4, 128.8, 128.1, 127.5, 122.6, 83.8, 45.1, 28.9, 25.8, 21.8, 13.4; IR (neat, cm^{-1}) υ_{max} 3341, 2926, 2856, 1657, 1600, 1510, 1460, 1363, 1268, 1103, 1042, 989; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{23}N_2O_3$ 291.1709; Found 291.1715.

Associated content

Supporting Information Available

The Supporting Information is available free of charge on the ACS Publications website at DOI:

NMR and XRD analysis of Mosher ester derivatives of **13**, Chiral HPLC data for compound **13**, (*Z*)-**18** and (*E*)-**18**, Gibbs free energy calculation data of inthomycins A–C, and copies of the ^{1}H and ^{13}C NMR spectra for all new products (PDF)

CIF file for (S)-MTPA ester of **13** (CIF)

Author information

Corresponding Author

*E-mail: pennkim@snu.ac.kr

ORCID

Sanghee Kim: 0000-0001-9125-9541

Jae Hyun Kim: 0000-0001-8600-5950

Author contributions

†J.H.K. and Y.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

Acknowledgment. This work was supported by the Mid-Career Researcher Program (NRF-2019R1A2C2009905) of the National Research Foundation of Korea (NRF) grant funded by the Government of Korea (MSIP). We thank a reviewer who provided valuable suggestions on the mechanism of isomerization of (*Z*)-**18**.

References

(1) Omura, S.; Tanaka, Y.; Kanaya, I.; Shinose, M.; Takahashi, Y. Phthoxazolin, a Specific Inhibitor of Cellulose Biosynthesis, Produced by a Strain of *Streptomyces* sp. *J. Antibiot.* **1990**, *43*, 1034–1036.

(2) Tanaka, Y.; Kanaya, I.; Takahashi, Y.; Shinose, M.; Tanaka, H.; Omura, S. Phthoxazolin A, a Specific Inhibitor of Cllose Biosynthesis from Microbial Origin. I. Discovery, Taxonomy of Producing Microorganism, Fermentation, and Biological Activity. *J. Antibiot.* **1993**, *46*, 1208–1213.

(3) Omura, S. The Expanded Horizon for Microbial Metabolites–a Review. *Gene* **1992**, *115*, 141–149.

(4) (a) Kawada, M.; Yosshimoto, Y.; Minaniguchi, K.; Kumagai, H.; Someno, T.; Masuda, T.; Ishizuka, M.; Ikeda, D. A Microplate Assay for Selective Measurement of Growth of Epithelial Tumor Cells in Direct Coculture with Stromal Cells. *Anticancer Res.* **2004**, 24, 1561–1568. (b) Kawada, M.; Inoue, H.; Usami, I.; Ikeda, D. Phthoxazolin A Inhibits Prostate Cancer Growth by Modulating Tumor–Stromal Cell Interactions. *Cancer Sci.* **2009**, *100*, 150–157.

(5) Henkel, T.; Zeeck, A. Secondary Metabolites by Chemical Screening, 16. Inthomycins, New Oxazole-Trienes from *Streptomyces* sp. *Liebigs Ann. Chem.* **1991**, 367–373.

(6) Takahashi, K.; Kawabata, M.; Uemura, D. Structure of Neooxazolomycin, an Antitumor Antibiotic. *Tetrahedron Lett.* **1985**, *26*, 1077–1078.

(7) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D. Structure of Oxazolomycin, a Novel β-Lactone Antibiotic. *Tetrahedron Lett.* **1985**, *26*, 1073–1076.

(8) Kanzaki, H.; Wada, K.; Nitoda, T.; Kawazu, K. Novel Bioactive Oxazolomycin Isomers Produced by *Streptomyces Albus* JA3453. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 438–442.

(9) (a) Ryu, G.; Hwang, S.; Kim, S.-K. 16-Methyloxazolomycin, a New Antimicrobial and Cytotoxic Substance Produced by a *Streptomyces* sp. *J. Antibiot.* **1997**, *50*, 1064–1066. (b) Ryu, G.; Kim, S.-K. Absolute Stereochemistry Determination of 16-Methyloxazolomycin Produced by a *Streptomyces* sp. *J. Antibiot.* **1999**, *52*, 193–197.

(10) Ogura, M.; Nakayama, H.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. Structure of a New Antibiotic Curromycin A Produced by a Genetically Modified Strain of *Streptomyces Hygroscopicus*, a Polyether Antibiotic Producing Organism. *J. Antibiot.* **1985**, *38*, 669–673.

(11) Otani, T.; Yoshida, K.; Kubota, H.; Kawai, S.; Ito, S.; Hori, H.; Ishiyama, T.; Oki, T. Novel Triene-β-lactone Antibiotics, Oxazolomycin Derivative and Its Isomer, Produced by *Streptomyces* sp. KSM-2690. *J. Antibiot.* **2000**, *53*, 1397–1400.

(12) For selected examples of inthomycin C synthesis, see: (a) Senapati, B. K.; Gao, L.; Lee, S. I.; Hwang, G.-S.; Ryu, D. H. Highly Enantioselective Mukaiyama Aldol Reactions Catalyzed by a Chiral Oxazaborolidinium Ion: Total Synthesis of (–)-Inthomycin C. *Org. Lett.* **2010**, *12*, 5088–5091. (b) Souris, C.; Frebault, F.; Patel, A.; Audisio, D.; Houk, K. N.; Maulide, N. Stereoselective Synthesis of Dienyl-Carboxylate Building Blocks: Formal Synthesis of Inthomycin C. *Org. Lett.* **2013**, *15*, 3242–3245. (c) Hale, K. J.; Grabski, M.; Manaviazar, S.; Maczka, M. Asymmetric Total Synthesis of (+)-Inthomycin C via O-Directed Free Radical Alkyne Hydrostannation with Ph_3SnH and Catalytic Et_3B: Reinstatement of the Zeeck–Taylor (3*R*)-Structure for (+)-Inthomycin C. *Org. Lett.* **2014**, *16*, 1164–1167. (d) Hale, K. J.; Hatakeyama, S.; Urabe, F.; Ishihara, J.; Manaviazar, S.; Grabski, M.; Maczka, M. The Absolute Configuration for Inthomycin C: Revision of Previously Published Work with a Reinstatement of the (3*R*)-Configuration for (–)-Inthomycin C. *Org. Lett.* **2014**, *16*, 3536–3539. (e) Balcells, S.; Haughey, M. B.; Walker, J. C. L.; Josa-Cullere, L.; Towers, C.; Donohoe, T. J. Asymmetric Total Synthesis of (–)-(3*R*)-Inthomycin C. *Org. Lett.* **2018**, *20*, 3583–3586.

(13) For synthesis of inthomycin A or B, see: (a) Hénaff, N.; Whiting, A. A Convergent Stereoselective Total Synthesis of Racemic Phthoxazolin A. *Org. Lett.* **1999**, *1*, 1137–

1139. (b) Hénaff, N.; Whiting, A. Highly Stereoselective Palladium Catalysed Cross-Coupling Approaches to the Total Synthesis of Phthoxazolin A. *Tetrahedron* **2000**, *56*, 5193–5204. (c) Webb, M. R.; Donald, C.; Taylor, R. J. K. A General Route to the *Streptomyces*-Derived Inthomycin Family: the First Synthesis of (+)-Inthomycin B. *Tetrahedron Lett.* **2006**, *47*, 549–552.

(14) (a) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. The Syntheses of *rac*-Inthomycin A, (+)-Inthomycin B and (+)-Inthomycin C Using a Unified Synthetic Approach. *Tetrahedron* **2008**, *64*, 4778–4791. (b) Yoshino, M.; Eto, K.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Organocatalytic Asymmetric Syntheses of Inthomycins A, B and C. *Org. Biomol. Chem.* **2012**, *10*, 8164–8174. (c) Kumar, M.; Bromhead, L.; Anderson, Z.; Overy, A.; Burton, J. W. Short, Tin-Free Synthesis of All Three Inthomycins. *Chem. Eur. J.* **2018**, *24*, 16753–16756.

(15) For total synthesis of oxazolomycin family members, see: (a) Kende, A. S.; Kawamura, K.; DeVita, R. J. Enantioselective Total Synthesis of Neooxazolomycin. *J. Am. Chem. Soc.* **1990**, *112*, 4070–4072. (b) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Total Synthesis of Neooxazolomycin. *Angew. Chem. Int. Ed.* **2007**, *46*, 6703–6705. (c) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S.

Total Synthesis of Oxazolomycin A. *Org. Lett.* **2011**, *13*, 5398–5401. (d) Kim, J. H.; Kim, I.; Song, Y.; Kim, M. J.; Kim, S. Asymmetric Total Synthesis of (+)-Neooxazolomycin Using a Chirality-Transfer Strategy. *Angew. Chem. Int. Ed.* **2019**, *58*, 11018–11022.

(16) (a) Hale, K. J.; Xiong, Z.; Wang, L.; Manaviazar, S.; Mackle, R. Carreira Alkynylations with Paraformaldehyde. A Mild and Convenient Protocol for the Hydroxymethylation of Complex Base-Sensitive Terminal Acetylenes via Alkynylzinc Triflates. *Org. Lett.* **2015**, *17*, 198–201. (b) Jandeleit, B.; Li, Y.; Gallop, M. A.; Zerangue, N.; Virsik, P. A.; Fischer, W.-N. Masked Carboxylate Neopentyl Sulfonyl Ester Cyclization Release Prodrugs of Acamprosate, Composition Therof, and Methods of Use. US 200969419, A1, 2009.

(17) Huynh, T. N. T.; Retailleau, P.; Denhez, C.; Nguyen, K. P. P.; Guillaume, D. Regioselective Synthesis of 3,4,5-Trisubstituted 2-Aminofurans. *Org. Biomol. Chem.* **2014**, *12*, 5098–5101.

(18) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of α,β-Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119,* 8738–8739. (b) Welsch, T.; Tran, H.-A.; Witulski, B. Total Syntheses of the Marine Illudalanes Alcyopterosin I, L, M, N, and C. *Org. Lett.* **2010**, *12*, 5644–5647.

(19) (a) Murakami, Y.; Yoshida, M.; Shishido, K. Diastereoselective Construction of Chiral Building Blocks for the Synthesis of Indole Alkaloids Using an Intramolecular Heck Reaction. *Tetrahedron Lett.* **2009**, *50*, 1279–1281. (b) Morra, N. A.; Pagenkopf, B. L. Gram Scale Synthesis of the C(18)−C(34) Fragment of Amphidinolide C. *Org. Lett.* **2011**, *13*, 572–575.

(20) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. Chiral Synthesis via Organoboranes. 14. Selective Reductions. 41. Diisopinocampheylchloroborane, an Exceptionally Efficient Chiral Reducing Agent. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546. (b) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. Chiral Synthesis via Organoboranes. 34. Selective Reductions. 47. Asymmetric Reduction of Hindered α,β-Acetylenic Ketones with B-Chlorodiisopinocampheylborane to Propargylic Alcohols of Very High Enantiomeric Excess. Improved Workup Procedure for the Isolation of Product Alcohols. *J. Org. Chem.* **1992**, *57*, 2379–2386.

(21) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-Field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for

the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nat. Protoc.* **2007**, *2*, 2451–2458.

(22) Corey, E. J.; Katzenellenbogen, J. A. Stereospecific Synthesis of Trisubstituted and Tetrasubstituted Olefins. Conjugate Addition of Dialkylcopper-Lithium Reagents to α,β-Acetylenic Esters. *J. Am. Chem. Soc.* **1969**, *91*, 1851–1852.

(23) For selected examples of methyl cuprate addition, see: (a) Smith, A. B.; Barbosa, J.; Wong, W.; Wood, J. L. Total Syntheses of (+)-Trienomycins A and F via a Unified Strategy. *J. Am. Chem. Soc.* **1996**, *118*, 8316–8328. (b) Liu, Y.; Feng, G.; Wang, J.; Wu, J.; Dai, W.-M. Synthesis of Two Diastereomers of Iriomoteolide-1a via a Tunable Four-Module Coupling Approach Using Ring-Closing Metathesis as the Key Step. *Synlett* **2011**, *12*, 1774–1778. (c) Mahapatra, S.; Carter, R. G. Exploiting Hidden Symmetry in Natural Products: Total Syntheses of Amphidinolides C and F. *J. Am. Chem. Soc.* **2013**, *135*, 10792−10803.

(24) (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. Total Synthesis of (–)-Stemospironine. *Org. Lett.* **2001**, *3*, 2721–2724. (b) Korner, M.; Hiersemann, M. Enantioselective Synthesis of the C8−C20 Segment of Curvicollide C. *Org. Lett.* **2007**, 9, 4979–4982.

(25) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. NMR Spectroscopic Investigation of the Adducts Formed by Addition of Cuprates to Ynoates and Ynones: Alkenylcuprates or Allenolates? *Chem. Eur. J.* **1998**, *4*, 2051–2058.

(26) The role of the O-silyl protection in inducing *E* selectivity was previously reported, see ref 24.

(27) Coombs, J. R.; Zhang, L.; Morken, J. P. Synthesis of Vinyl Boronates from Aldehydes by a Practical Boron–Wittig Reaction. *Org. Lett.* **2015**, *17*, 1708–1711.

(28) The enantiomeric purity of the obtained product remained unchanged under the studied reaction conditions.

(29) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. Stereoselective Hydrogenolysis of 1,1-Dibromo-1-alkenes and Stereospecific Synthesis of Conjugated (*Z*)-Alkenyl Compounds. *J. Org. Chem.* **1998**, *63*, 8965–8975.

(30) For selected examples of *Z* to *E* isomerization of α,β-unsaturated aldehyde, see: (a) Sonye, J. P.; Koide, K. On the Mechanism of DABCO-Catalyzed Isomerization of γ-Hydroxy-α,β-alkynoates to γ-Oxo-α,β-(*E*)-alkenoates. *Org. Lett.* **2006**, *8*, 199–202. (b) Castagnolo, D.; Botta, L.; Botta, M. Alkyne-Enol Ether Cross-Metathesis in the Presence of $CuSO_4$: Direct Formation of 3-Substituted Crotonaldehydes in Aqueous Medium. *J. Org.*

Chem. **2009**, *74*, 3172–3174. (c) Vidali, V. P.; Mitsopoulou, K. P.; Dakanali, M.; Demadis, K. D.; Odysseos, A. D.; Christou, Y. A.; Couladouros, E. A. An Unusual Michael-Induced Skeletal Rearrangement of a Bicyclo[3.3.1]nonane Framework of Phloroglucinols to a Novel Bioactive Bicyclo[3.3.0]octane. *Org. Lett*. **2013**, *15*, 5404–5407. (d) Marzo, L.; Luis-Barrera, J.; Mas-Ballesté, R.; Ruano, J. L. G.; Alemán, J. Stereodivergent Aminocatalytic Synthesis of *Z*- and *E*- Trisubstituted Double Bonds from Alkynals. *Chem. Eur. J.* **2016**, *22*, 16467–16477.

(31) See the Supporting Information for Gibbs free energy calculation data for inthomycins A–C.