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The syntheses of *rac*-inthomycin A, (+)-inthomycin B and (+)-inthomycin C using a unified synthetic approach

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Abstract

The Stille coupling between a common oxazole vinyl iodide and stereodefined stannyl-diene units is described as the cornerstone of a unified synthetic route to the inthomycin family of bioactive *Streptomyces* metabolites. This procedure has been utilised to prepare (+)-inthomycin B and (+)-inthomycin C for the first time; in these examples the stereogenic centre was introduced using the Kiyooka ketene acetal/amino acid-derived oxazaborolidinone variant of the Mukaiyama aldol reaction. In addition, a convenient preparation of *rac*-inthomycin A is described based on the same strategy.

1. Introduction

Over the past twenty years a large number of complex bioactive natural products containing a methylene-interrupted oxazolyl-triene motif have been isolated from strains of *Streptomyces* sp. Oxazolomycin A **1**,[1] isolated in 1985, is the parent member of this class of antibiotics, which also includes oxazolomycins B **2** and C **3**,[2] neooxazolomycin,[3] curromycins A and B,[4] 16-methyloxazolomycin,[5] KSM-2690 A and B,[6] and lajollamycin.[7,8]

However, in the early 1990s, the groups of Omura and Zeeck discovered related compounds containing primary amides in place of the complex spirocyclic pyrrolidinone-amine-derived systems present in the oxazolomycin family.[9,10] Thus, in 1990, Omura et al. described the isolation of the *Streptomyces*-derived methylene-interrupted oxazolyl-triene **4**, which they named phthoxazolin A.[9] Then, the following year, Henkel and Zeeck studied *Streptomyces* (strain Gö 2) and reported the isolation of inthomycin A **4** (shown to possess the same structure as phthoxazolin A) together with the geometrical isomers inthomycin B **6** and C **5**.[10] Subsequently, this family was expanded when a series of novel naturally-occurring hydroxylated inthomycins were described.[11] It should be noted that although the inthomycins A–C contain the methylene-interrupted oxazolyl-triene motif present in oxazolomycin family (Fig. 1), biosynthetic studies have established that inthomycin A **4** is not an intermediate in the biosynthesis of oxazolomycin A **1**.[12]

The inthomycins have been shown to be highly specific inhibitors of cellulose biosynthesis, displaying selective in vitro antimicrobial activity against *Phytophtora parasitica* and *P. cactorum*.[9] Herbicidal activity has also been noted with radish seedlings[13] and velvet leaf[14] when treated with inthomycin A **4** after emergence; novel derivatives of inthomycin A **4** have been prepared and evaluated as herbicidal agents (leading to the discovery that the allylic alcohol is required for activity).[15] In 2004, inthomycin A **4** was also shown to inhibit the growth of prostate cancer cells.[16]

To date, there has been only one published synthesis of any member of the inthomycin family: in 1999, Henaff and

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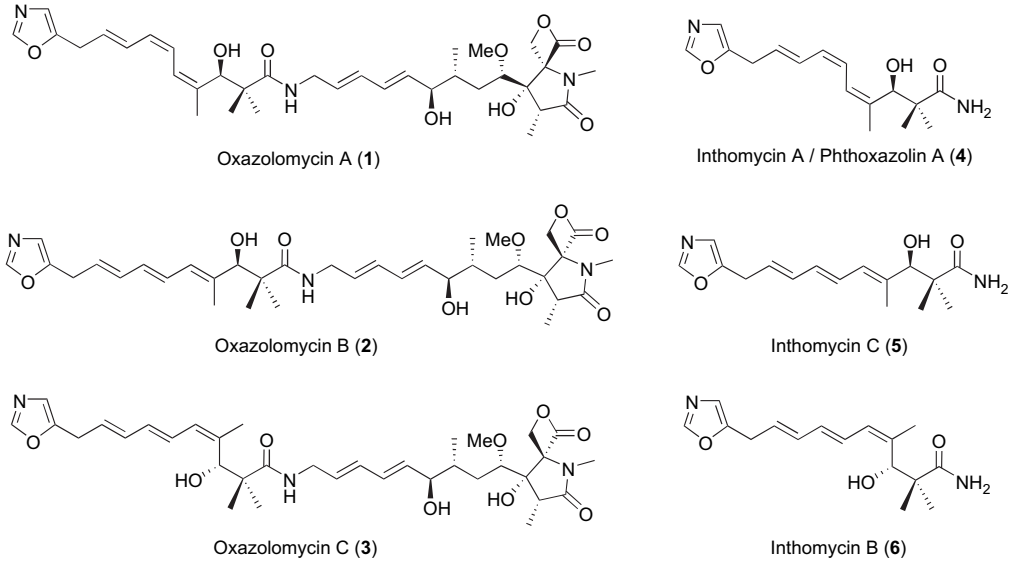
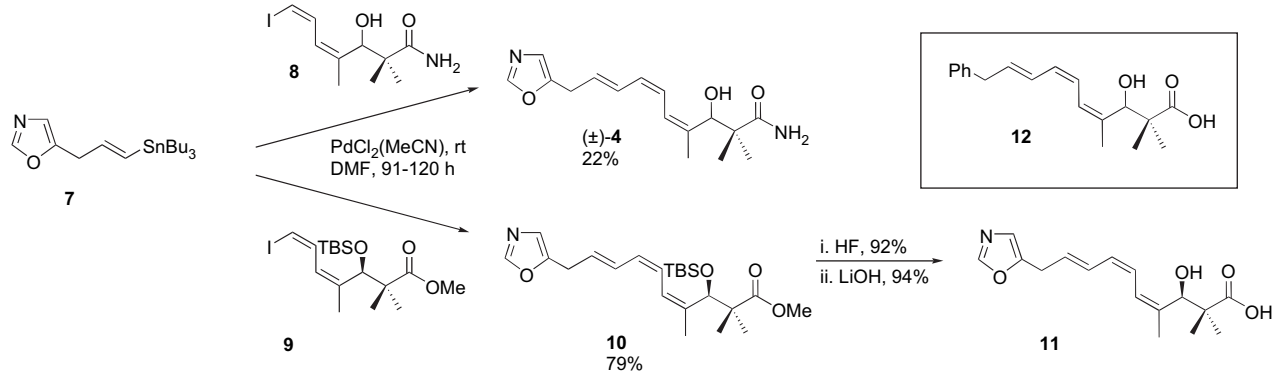


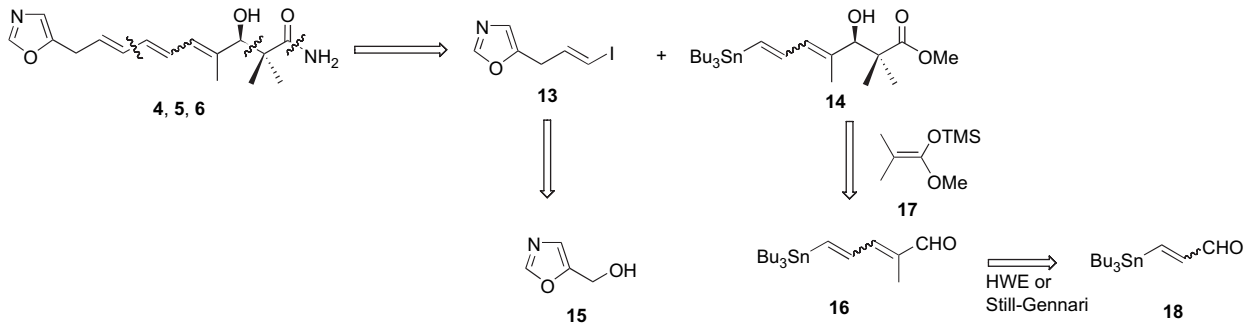
Figure 1.

Whiting reported the preparation of racemic inthomycin A **4** based on a route, which utilised the Stille coupling between oxazole vinylstannane **7** and dienyl iodide **8** as the final step (Scheme 1).[17] It should be noted that this coupling mirrored the process used earlier by Kende et al. when preparing *R*-**11** from the same oxazole vinylstannane **7** and dienyl iodide **9** (Scheme 1) during their ground-breaking enantioselective total synthesis of neooxazolomycin.[18] However, the synthetic routes were very different in terms of the construction of the vinyl iodide coupling partners: Henaff and Whiting utilised novel vinylboronate-Heck chemistry whereas Kende et al. used Sonogashira coupling with a late-stage diastereoselective Reformatsky-type condensation involving an Evans auxiliary to produce the required *R*-configured product. Nevertheless, both routes were long (10–17 steps) and low-yielding (≪3%). More recently, Moloney et al. have prepared novel analogues of the inthomycins (e.g., the racemic phenyl analogue **12**), again using Stille coupling as the cornerstone of the sequence.[19]

As part of a programme to prepare members and synthetic analogues of the oxazolomycin family,[8b] we required efficient and stereocontrolled procedures to prepare all of the inthomycins A–C and their precursor acids. Our initial approaches to inthomycin analogues[20] proved problematic and so the convergent route shown in retrosynthetic form in Scheme 2 was designed. Thus, the aim was to employ the oxazole vinyl iodide **13** as a common precursor to prepare all three inthomycins. We assumed that iodide **13** would be easily obtained from the known[18] oxazole methanol **15**. The stereodefined dienylstannanes **14** would then be required for the key Stille coupling reactions and we envisaged that they would be readily prepared from the dienals **16** via the Mukaiyama aldol reaction with ketene acetal **17**; indeed, we envisaged coupling partners **14** would be accessible in enantioenriched form by carrying out the reaction in the presence of a chiral Lewis acid as pioneered by Kiyooka.[21,22] We felt that the strength of this retrosynthetic analysis lay in the ready availability of *E*- and *Z*-3-(tributylstannyl)propenal (see later) and assumed that standard Horner–Wadsworth–Emmons or Still–Gennari methodology could be employed to convert aldehydes **18** into dienals **16** in a stereocontrolled manner. We have recently described, in communication format,[23] the successful implementation of this strategy for the preparation of (+)-inthomycin B **6**. We now report full details of the (+)-inthomycin B **6** study and the extension of this methodology to prepare (+)-inthomycin C **5** (for the first time) and *rac*-inthomycin A **4**.



Scheme 1.



Scheme 2.

2. Synthesis of (+)-inthomycin B 6

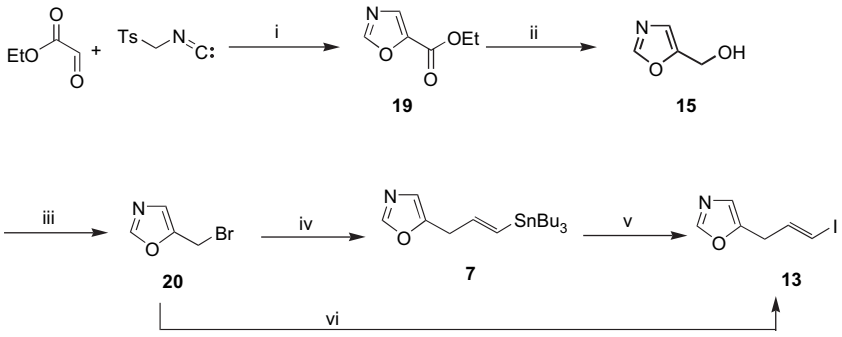
The initial objective was to develop an efficient preparation of the oxazole vinyl iodide **13**, central to the synthesis of all of the inthomycins, and van Leusen's TosMIC methodology[24] proved to be applicable on a multi-gram scale (Scheme 3). Thus, treatment of ethyl glyoxylate and TosMIC with K_2CO_3 under strictly anhydrous conditions gave oxazole **19** in 86% yield. Reduction of the ethyl ester with $NaBH_4$ cleanly afforded the primary alcohol **15** in 85% yield, which was converted into the corresponding bromide **20** using the published[18] procedure (NBS/PPh_3). The reported yield for this conversion was a moderate 44% and our initial efforts were subjected to great variability (14–45%) and efforts to prepare either the iodide or triflate corresponding to bromide **20** led to products that were too unstable to isolate. We eventually established that bromide **20** is thermally unstable and decomposes on lengthy exposure to chromatography; by purification of the crude reaction mixture using rapid filtration through a 'plug' of silica, and then ensuring that the temperature remained below 25 °C during evaporation of the solvent, bromide **20** could be isolated in a reproducible 94% yield on scales up to 6 mmol.

An sp^3–sp^2 Stille coupling reaction between bromide **20** and *E*-1,2-bis-(tri-*n*-butylstannyl)ethane[25] was envisaged to effect the two-carbon homologation. A range of catalysts and reaction conditions were screened to optimise the yield of **7** {$Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, Succ-$Pd(PPh_3)_2Br$, $Pd(CH_3CN)_2Cl_2$, $BnPd(PPh_3)_2Cl$, $Pd_2(dba)_3$ with $AsPh_3$ or P(2-furyl)$_3$, adding CuI or KI}. Unfortunately, given the thermal instability of bromide **20**, conditions for coupling at rt could not be found. The most reliable and reproducible procedure utilised Pd_2dba_3 (5 mol %) with freshly prepared bromide **20** in THF at reflux giving the known[17,18] vinylstannane **7** (>50%). By the use of bromide **20** in excess (1.3 equiv) the isolated yield could be improved to 66% based on the stannane (but excess **20** could not be recovered; no double coupling was seen in any of these reactions).

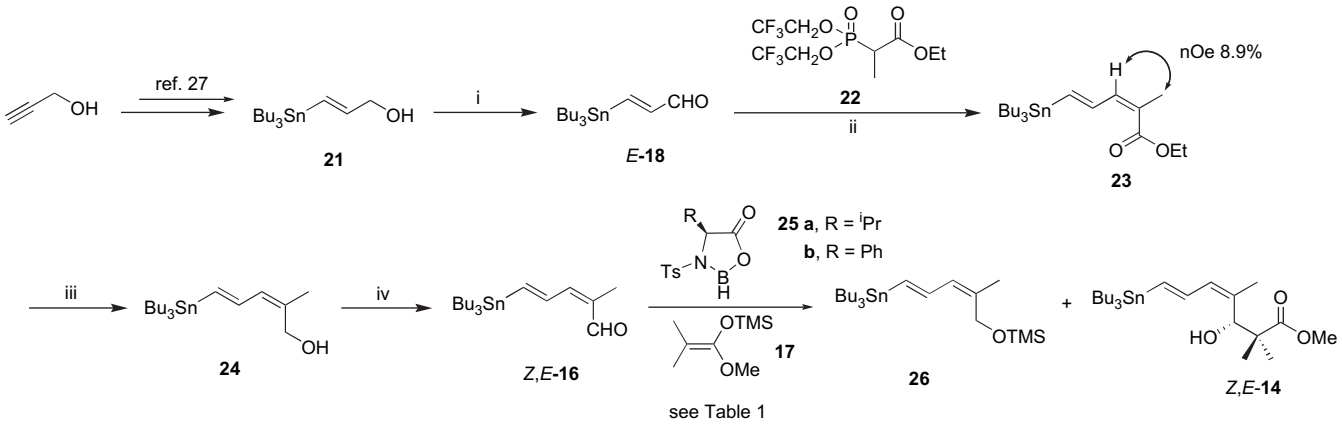
With vinylstannane **7** in hand, its conversion to the required vinyl iodide **13** proceeded smoothly using iodine in dichloromethane (86%); alternatively the coupling and iodination steps could be telescoped into a one pot process, giving iodide **13** in 46% overall yield based on bromide **20**.

The stannyl-diene *Z*,*E*-**14** required for the preparation of inthomycin B **6** was next prepared from propargyl alcohol as shown in Scheme 4. The conversion of propargyl alcohol into *E*-3-(tributylstannyl)propenal *E*-**18** was easily accomplished using a modification of Wender's procedure.[26] Thus, silylation, hydrostannylation and desilylation were accomplished as described giving alcohol **21**, but barium manganate was replaced by activated manganese dioxide producing aldehyde *E*-**18** in 92% yield (other oxidation conditions required purification by silica gel chromatography resulting in lower yields due to the acid-sensitivity of aldehyde *E*-**18**).

Reaction of *E*-**18** with ethyl 2-[bis-(2,2,2-trifluoroethoxy)-phosphoryl]propanoate **22**, under Still–Gennari conditions,[27] afforded the *Z*,*E*-diene **23** exclusively in 94% yield (Ando's reagent, ethyl 2-[bis-(phenoxy)phosphoryl]propanoate[28] gave



Scheme 3. Reagents and conditions: (i) K_2CO_3, EtOH, 80 °C, 86%; (ii) $NaBH_4$, EtOH, rt, 60 h, 85%; (iii) NBS, PPh_3, CH_2Cl_2, 0 °C, 1 h, 94%; (iv) Pd_2dba_3 (5 mol %), *E*-$Bu_3SnCH{=}SnBu_3$, THF, 80 °C, 4 h, 51%; (v) I_2, CH_2Cl_2, 0 °C, 20 min, 86%; (vi) Pd_2dba_3 (5 mol %), *E*-$Bu_3SnCH{=}SnBu_3$, THF, 80 °C, 4 h, then I_2 at 0 °C, overnight, 46%.



Scheme 4. Reagents and conditions: (i) MnO_2, CH_2Cl_2, rt, 3 d then 40 °C, 21 h, 92%; (ii) 22, 18-crown-6, KHMDS, −78 °C, 30 min, then 18, THF, −78 °C, 4.5 h, 94%; (iii) DIBAL-H, DCM, −10 °C, 1.5 h, 84%; (iv) TPAP, NMO, 4 Å molecular sieves, DCM, rt, 1.5 h, quant.

Table 1
Asymmetric Mukaiyama aldol reactions giving *Z,E*-**14**

(a) *N*-Ts-L-valine (1 equiv), BH_3·THF (1.1 equiv) (**25a**), 0 °C, 30 min then rt, 30 min, then *Z,E*-**16**, **17**, −78 °C, 45 min	*Z,E*-**14**, 50%; **26**, 38% (ee, n/d)
(b) *N*-Ts-L-valine (2 equiv), BH_3·THF (1.2 equiv) (**25a**), 0 °C to rt, overnight, then *Z,E*-**16**, **17**, −78 °C, 1.5 h	*Z,E*-**14**, 74% (64% ee)
(b) *N*-Ts-L-Phenylalanine (2 equiv), BH_3·THF (1.2 equiv) (**25b**), 0 °C to rt, overnight, then *Z,E*-**16**, **17**, −78 °C, 2.5 h	*Z,E*-**14**, 63% (60% ee)

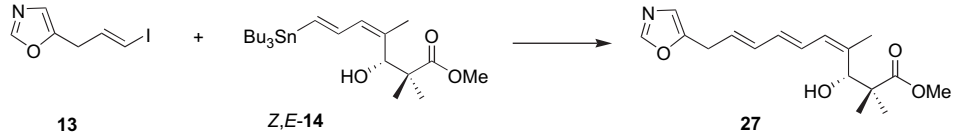
a 9:1 *Z*/*E* ratio and a modest 55% yield). The configuration of the newly formed alkene was confirmed by NOE studies as shown. A two-step reduction–oxidation sequence then afforded the highly acid sensitive aldehyde *Z,E*-**16** in 84% yield.

The asymmetric Mukaiyama–Kiyooka aldol reaction for the conversion of *Z,E*-**16** into *Z,E*-**14** was investigated next (Scheme 4, Table 1). In the initial attempt (entry a), standard Kiyooka conditions[22] were employed utilising ketene acetal **17** and the *N*-Ts-L-valine-derived oxazaborolidinone **25a** (R=^{i}Pr) at −78 °C. This procedure gave the hoped-for aldol product *Z,E*-**14** in 50% yield accompanied by the silylated reduction product **26** in 38% yield (Scheme 4). Extensive experimentation using *trans*-α-methyl-cinnamaldehyde[29] indicated that the direct reduction could be minimised by the use of an excess of *N*-Ts-L-valine (a two-fold excess compared to the borane reagent) and extending the time for oxazaborolidinone formation from 1 h to overnight. It was also found that recrystallisation of the *N*-tosyl-L-valine to constant $[\alpha]_D$ was necessary for optimum enantioselectivity. In addition, the use of an aqueous sodium bicarbonate work-up procedure gave only alcohol **14** (and no silyl ether **26**). In this way (entry b), aldol product *Z,E*-**14** was obtained in 74% yield and 64% ee {$[\alpha]_D$ +5.4 (*c* 1.07, $CHCl_3$)} (the ee was disappointing in view of the 84% ee obtained in the model studies[29]). Other oxazaborolidinones were explored without improvement although the *N*-tosyl-L-phenylalanine-derived system gave the product *Z,E*-**14** in 60% ee (entry c). The diene stereochemistry was retained in all cases as demonstrated by the isolation of a single product and inspection of the diene *J* values. Literature precedent[22] suggested that the use of *N*-tosyl-L-amino acids should produce a predominance of the required *R*-*Z,E*-**14** (as shown) and this was confirmed by Mosher's studies at a subsequent stage (see later).

The next step involved the key palladium-catalysed Stille coupling of iodide **13** with stannyl-diene *Z,E*-**14** (Table 2). A number of palladium catalysts were screened to mediate the coupling to produce triene **27** but $Pd(CH_3CN)_2Cl_2$ appeared to offer the greatest initial promise (Table 2, entries a–e). Thus (entry a), using 7 mol % of the catalyst in DMF at rt produced triene **27** in 55% yield. However, analysis of this product by ^{1}H NMR spectroscopy indicated that extensive isomerisation of the triene unit had occurred giving a mixture of inseparable stereoisomers. Attempts to minimise isomerisation by carefully degassing the solvent and excluding light failed to offer any improvement but lowering the catalyst loading (1 mol %) gave **27** with very little isomerisation although the reaction was very slow (entry b, 24 h, 37% with recovered starting materials). Retaining the low catalyst loading but raising the temperature (entry c) or using microwave acceleration (entry d) resulted in faster reactions but again isomerisation proved to be a problem. However, by keeping the reaction at 50 °C (entry e), coupling could be accomplished in quantitative yield with negligible isomerisation, the downside being the prolonged reaction time (5 d).[30] It was eventually established that the Pd(0)/CuI/CsF conditions developed by Baldwin's group[31] gave triene **27** in quantitative yield after 3 h with only trace levels of isomerisation (entry f). Stannyl by-products were effectively removed by purifying the product on flash silica doped with 10% KF[32] to afford spectroscopically pure **27**.

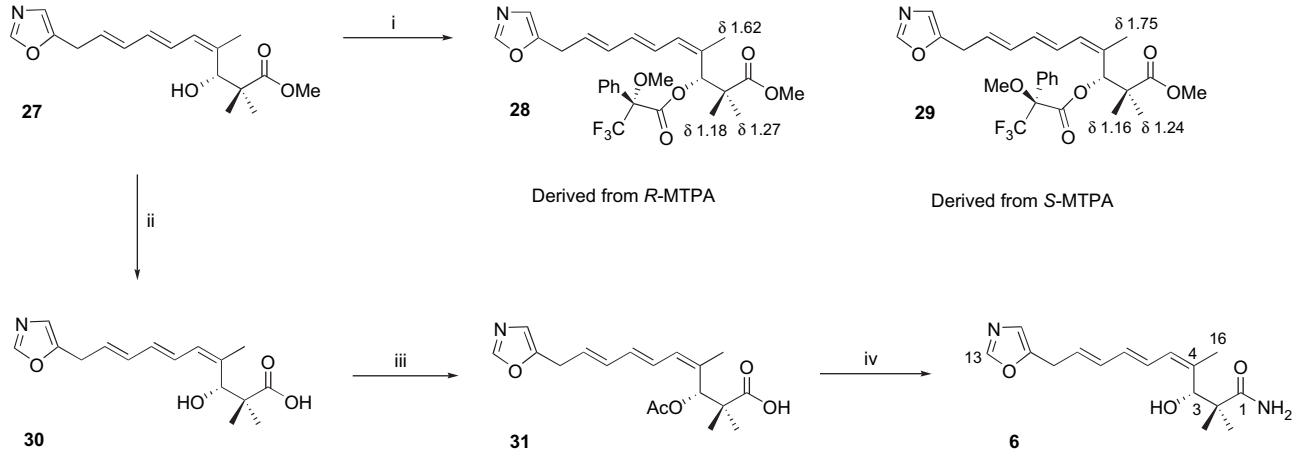
To confirm the stereochemistry of the aldol product, alcohol **27** was derivatised with both *R*- and *S*-Mosher acids.[33] Comparison of the ^{1}H NMR chemical shifts of **28** and **29** by spectroscopy (see Scheme 5) confirmed the required (and anticipated[22]) 3*R*-stereochemistry of the hydroxyl centre (and confirmed the expected mixture of diastereoisomers, ca. 80:20).

Table 2
Screening conditions for Stille coupling between **13** and *Z,E*-**14** to give **27**



Entry	Catalyst	mol %[a]	Time	Temp (°C)	Yield (%)	Isomerisation (%)
a	$Pd(CH_3CN)_2Cl_2$	7	4.5 h	rt	55	30
b	$Pd(CH_3CN)_2Cl_2$	1	24 h	rt	37[b]	Trace
c	$Pd(CH_3CN)_2Cl_2$	1	14 h	80	72	20
d	$Pd(CH_3CN)_2Cl_2$	1	7 h[c]	50	22[b]	15
e	$Pd(CH_3CN)_2Cl_2$	1	5 d[d]	50	Quant.	Trace
f	$Pd(PPh_3)_4$, CuI, CsF (2 equiv)	1	3 h	45	Quant.	Trace

[a] Reaction concentration 0.12 M in degassed DMF.
[b] Mainly recovered coupling partners.
[c] Reaction performed in a CEM microwave.
[d] If stopped after 24 h, **27** was isolated in 43% yield.



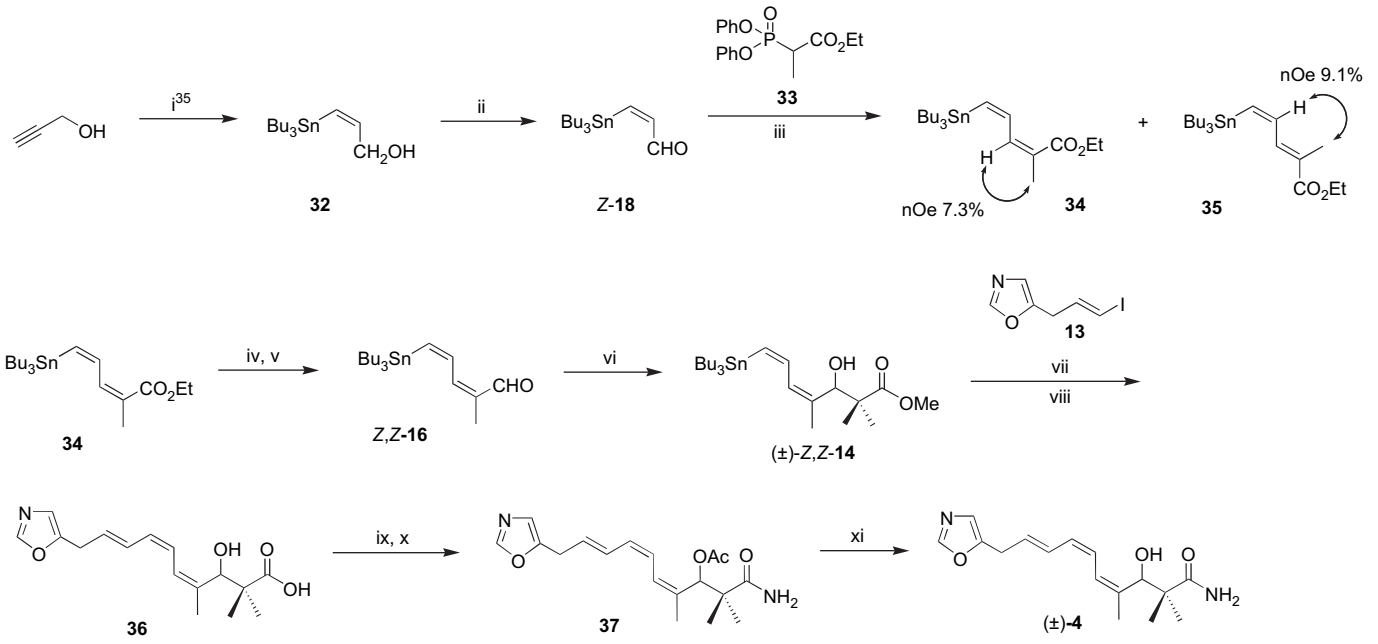
Scheme 5. Reagents and conditions: (i) MTPA-Cl, DMAP, Et_3N, DCM, 14 h, quant.; (ii) LiOH, THF–MeOH–H_2O (3:1:1), 4.5 h, 73%; (iii) (a) Ac_2O, py, rt, 14 h, (b) $NaHCO_3$ (aq), CH_2Cl_2, 8 h, rt, 62%; (iv) (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C, 3.5 h, (b) NH_4OH, rt, overnight, 50%.

In order to complete the synthesis of inthomycin B **6**, a functional group transformation of methyl ester to primary amide was required but this was complicated by the steric hindrance of the α-*gem*-dimethyl groups and the presence of a free hydroxyl group in ester **27**. Model studies[34] indicated that direct amidation was not straightforward and so methyl ester **27** was hydrolysed to the corresponding acid **30**. Disappointingly, subsequent HATU-mediated coupling with ammonia led to decomposition and no inthomycin B **6** could be isolated. After extensive experimentation, it was found that the required transformation could be accomplished by conversion to acetate **31** followed by acid activation with oxalyl chloride and then in situ treatment with ammonium hydroxide to give concomitant amide formation and acetate removal. This sequence produced inthomycin B **6** in reasonable isolated yield {$[\alpha]_D$ +19.3 (*c* 1.0, $CHCl_3$); no $[\alpha]_D$ reported in the literature}. The spectral data were consistent with those previously reported [e.g., δ_C 19.6 (C-16), 75.9 (C-3), 139.9 (C-4), 151.7 (C-13); Lit.[10] δ_C 19.6 (C-16), 75.8 (C-3), 139.9 (C-4), 151.6 (C-13)] and compound **6** was fully characterised.

Inthomycin B **6** has thus been prepared in a total of nine steps (eight flasks) from ethyl glyoxylate and dienylstannane *Z,E*-**14** (itself prepared in four steps from known aldehyde *E*-**18**) in 7% overall yield and ca. 64% ee.

3. Synthesis of inthomycin A 4

Having succeeded with the synthesis of inthomycin B, we went on to explore the preparation of inthomycin A starting from the common vinyl iodide **13** (Scheme 6). The first task was to prepare *Z*-3-(tributylstannyl)propenal *Z*-**18**, which was easily accomplished by $LiAlH_4$ reduction of propargyl alcohol then transmetallation with Bu_3SnCl[35] followed by oxidation of the resulting alcohol **32** using the Ley–Griffith TPAP procedure.[36,37] Surprisingly, reaction of aldehyde *Z*-**18** with the Still–Gennari trifluoroethoxyphosphonate **22** using the standard conditions gave mainly the *E,Z*-product **35** (*E,Z*/*Z,Z*=9:1).[37] Fortunately, on changing to the Ando phenoxy phosphonate **33**[28] the desired *Z,Z*-diene **34** was formed as the major product (*E,Z*/*Z,Z*=13:87). Reduction of this mixture allowed the *Z,Z*-isomeric alcohol to be isolated and oxidation afforded aldehyde *Z,Z*-**16** in 68% yield (*Z,Z*-**16** undergoes isomerisation readily and so has to be elaborated immediately after preparation). Application of the optimised Mukaiyama–



Scheme 6. Reagents and conditions: (i) (a) $LiAlH_4$, THF, 0 °C to rt, 26 h, (b) Bu_3SnCl, rt, 24 h, 63%;[35] (ii) TPAP, NMO, 4 Å molecular sieves, DCM, rt, 3 h, 81%; (iii) **33**, NaH, THF, −78 °C then 0 °C, 20 min, then added *Z*-**18**, −78 °C to rt, overnight, 80% (**34**:**35**=87:13); (iv) DIBAL-H, DCM, −35 °C to 0 °C, 2 h, 68%; (v) TPAP, NMO, 4 Å molecular sieves, DCM, 0 °C, 2 h, quant.; (vi) Me_2CHCO_2Me, LDA, THF, −78 °C, 25 min then *Z*,*Z*-**16**, 2 h, 83%; (vii) **13**, 5 mol % $Pd(CH_3CN)_2Cl_2$, DMF, rt, 5 h, 77%; (viii) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O, rt, 3.5 h, 92%; (ix) Ac_2O, py, rt, 20 h, then $NaHCO_3$ (aq), DCM, rt, 2 h, quant.; (x) $SOCl_2$, DMF, DCM, 0 °C to rt, 2.5 h, then NH_4OH, rt 1 h, 70%; (xi) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O, rt, 1 h, 92%.

Kiyooka conditions using the *N*-Ts-L-valine-derived oxazaborolidinone **25a**, discussed earlier, led to a complex mixture of products from which it was concluded that alkene isomerisation, aldehyde reduction and destannylation were rife.

After extensive optimisation, the highest yield of adduct *Z*,*Z*-**14** to be obtained was a disappointing 7%. The inherent instability of *Z*,*Z*-**16**, coupled with its lability under the Lewis acidic conditions, forced us to continue with a racemic synthesis utilising the lithium enolate of methyl *iso*-butyrate to form the required ester *Z*,*Z*-**14** in racemic form. Under these basic conditions the condensation was effective giving *Z*,*Z*-**14** in 83% yield.

The Stille coupling between vinyl iodide **13** and *Z*,*Z*-**14** using $Pd(CH_3CN)_2Cl_2$ (5 mol %) proceeded in 77% yield (some triene isomerisation was observed during coupling but it was <20%) and saponification gave acid **36**. Then, following the previous sequence, acetylation, acid chloride formation and quenching with ammonium hydroxide formed acetate **37** (Scheme 6). The isolation of acetate **37** provided yet another illustration of the marked differences between the different triene stereoisomers; *Z*,*E*,*E*-triene **31** underwent in situ amide formation and acetate removal whereas the acetate remained intact under these conditions with *Z*,*Z*,*E*-triene **37**. However, saponification of acetate **37** using lithium hydroxide produced racemic inthomycin A **4**. The spectral data were consistent with those previously reported[9,10] [e.g., δ_C 19.8 (C-16), 75.5 (C-3), 140.7 (C-4), 151.6 (C-13); Lit.[10] δ_C 19.8 (C-16), 75.4 (C-3), 140.6 (C-4), 151.6 (C-13)] and compound **4** was fully characterised.

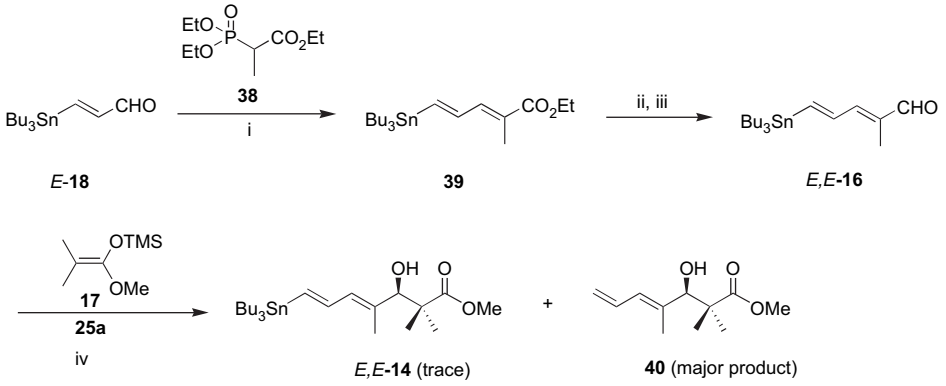
Thus, (±)-inthomycin A **4** was obtained in a total of 10 steps from ethyl glyoxylate and dienylstannane *Z*,*Z*-**14** (itself prepared in 6 steps from propargyl alcohol) in 14% overall yield, a clear improvement on other[17,18] routes.

4. Synthesis of (+)-inthomycin C 5

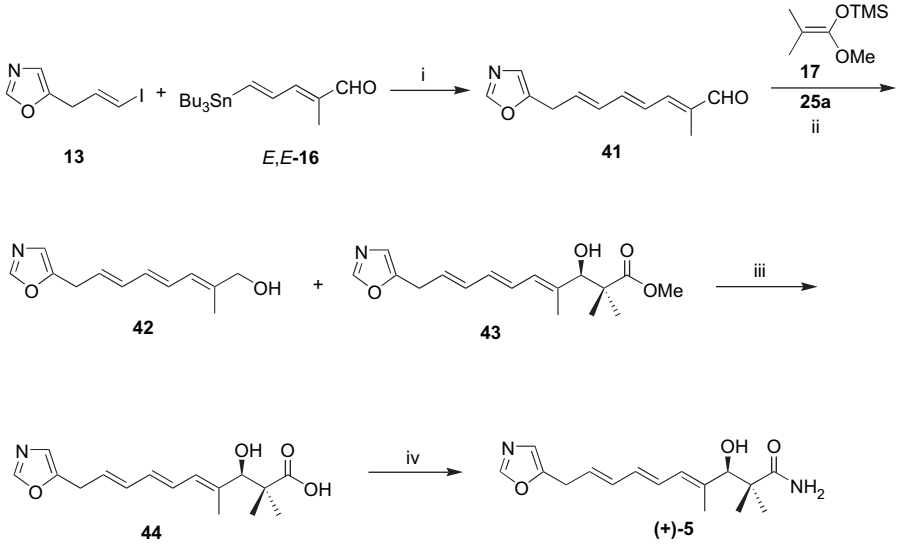
The final target was inthomycin C **5**. Using the approach outlined in Scheme 2, we proceeded to prepare the required dienylstannane *E*,*E*-**14** as shown in Scheme 7. Thus, using the aforementioned *E*-**18**, a standard *E*-selective HWE reaction with triethyl 2-phosphonopropionate **38** was employed to prepare diene **39** (*E*/*Z*=19:1, separable). DIBAL-H reduction followed by MnO_2 oxidation afforded aldehyde *E*,*E*-**16** with retention of stereochemistry (NMR spectroscopy). Utilisation of the optimised Mukaiyama–Kiyooka conditions with the *N*-Ts-L-valine-derived oxazaborolidinone **25a**, discussed earlier, gave a negligible amount of the required dienylstannane *E*,*E*-**14** but only the corresponding destannylated product **40** was obtained.

A range of reaction conditions were explored but the destannylation process could not be prevented. However, in the inthomycin C **5** case,[38] a slight variation to the original approach was devised, which ensured that the asymmetric Mukaiyama aldol reaction could still be utilised (Scheme 8). Thus, in this revised approach, Stille coupling was carried out prior to aldol homologation.

Therefore, Stille coupling of aldehyde *E*,*E*-**16** with vinyl iodide **13** using $Pd(CH_3CN)_2Cl_2$ as catalyst gave trienal **41** in 74% yield (Baldwin's conditions[31] gave no coupling in this instance). We were delighted to observe that aldehyde **41** underwent the Mukaiyama–Kiyooka aldol reaction; thus, treatment with silyl ketene acetal **14a** gave the required α-hydroxy ester **43** in 50% yield and 76% ee (as determined by Mosher ester analysis—which again confirms the *R*-stereochemistry of the major enantiomer). An excess of



Scheme 7. Reagents and conditions: (i) KHMDS, 18-crown-6, THF, −78 °C, 30 min then **38**, −78 °C to rt, overnight, 98%; (ii) DIBAL-H, DCM, −10 °C to rt, 3 h, quant.; (iii) MnO_2, DCM, rt, 2 d, quant.; (iv) *N*-Ts-L-valine, BH_3·THF, DCM, 0 °C, 5 min then rt, 25 min then −78 °C, *E*,*E*-**16** and **25a**, 3 h.



Scheme 8. Reagents and conditions: (i) 5 mol % $Pd(CH_3CN)_2Cl_2$, DMF, rt, 2 h, 74%; (ii) *N*-Ts-L-valine, BH_3·THF, DCM, 0 °C, 20 min then rt, 30 min then −78 °C, 2 h, **41** and **17**, 50% **43** (76% ee) and 43% **42**; (iii) LiOH·H_2O, THF, MeOH, H_2O, rt, 22 h, 89%; (iv) HATU, EtN^iPr_2, NH_4Cl, THF, rt, 15 h, 33%.

oxazaborolidinone **25a** was required to effect the aldol reaction, presumably due to complexation with the oxazole, and as a result competitive reduction was observed with alcohol **42** being isolated in 43% yield.

The synthesis was completed by hydrolysis of ester **43** to give acid **44** and then HATU-mediated coupling with ammonia to produce (+)-inthomycin C **5** for the first time. The spectral data were consistent with those previously reported [e.g., δ_C 13.3 (C-16), 83.9 (C-3), 140.1 (C-4), 151.8 (C-11); Lit.[10] δ_C 13.4 (C-16), 83.7 (C-3), 140.0 (C-4), 151.6 (C-11)] and compound **5** was fully characterised. The success of this direct coupling is noteworthy but the yield was modest (33%) and it was impossible to remove all traces of the tetramethyl urea by-product; it seems likely that the acetylation–acid chloride-amidation sequence used for inthomycins A and B would have given higher yields but insufficient material was available to confirm this proposal.

In summary, we have completed the first synthesis of (+)-inthomycin B **6** using a concise, convergent and stereocontrolled route with the Stille coupling of a stannyl-diene with an oxazole vinyl iodide unit, and a Mukaiyama–Kiyooka ketene acetal/amino acid-derived oxazaborolidinone procedure as its cornerstones. The same route was employed to complete a short synthesis of (±)-inthomycin A **4** and (+)-inthomycin C **5** was prepared using a slight modification in which Stille coupling was carried out prior to the Mukaiyama–Kiyooka reaction. A noteworthy feature of this study is the dramatically different reactivities observed for the different polyene stereoisomers in HWE,[23,37] Stille coupling, Mukaiyama–Kiyooka and other reactions. Although optimisation is still required, particularly in terms of the enantiocontrol of the Mukaiyama–Kiyooka processes, these synthetic routes should provide ready access to the precursor acids (**36**, **44** and **30**) required to complete the syntheses of oxazolomycins A–C **1**–**3**.

5. Experimental

5.1. General directions

Reagents and anhydrous DMF were purchased from commercial sources and were used directly without further

purification, unless specified otherwise. THF was dried with sodium and benzophenone and was distilled prior to use. Et_2O and CH_2Cl_2 were dried on an MBraun SPS Solvent Purification System. Petroleum ether refers to the fraction boiling in the range 40–60 °C. All procedures requiring inert atmospheres were performed in dry glassware under an atmosphere of nitrogen. Flash column chromatography was carried out using silica gel 35–70 mesh and the eluent specified under bellows pressure. Thin layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} pre-coated aluminium foil plates with a thickness of 250 μm, and visualised with UV light (254 nm), followed by heating after treatment with $KMnO_4$ or vanillin solutions. Infra-red spectra were recorded on a Thermo Nicolet IR100 spectrometer, as thin films between NaCl plates. Optical rotation values were recorded with a JASCO model DIP-370 digital polarimeter using sodium D line; 589 nm radiation and are expressed in units of 10^{-2} deg cm^{-2} g^{-1}. The ^1H and ^{13}C NMR spectra along with 2D experiments were recorded with a Jeol EX-400 spectrometer. The solutions were prepared in suitable deuterated solvents and referenced using residual protonated solvent or TMS. HPLC analyses were performed on Daicel columns with a chiral stationary phase as specified, using a Gilson 321 pump and 170 diode array system. Low and high field resolution chemical-ionisation (CI), electron-ionisation (EI) and electrospray-ionisation (ESI) mass spectrometry were performed with a Micromass Autospec spectrometer. High resolution molecular ions described are within ±5 ppm of the required molecular mass.

5.1.1. 5-(Bromomethyl)oxazole *20*

To a stirred solution of (oxazol-5-yl)methanol **15**[18] (0.600 g, 6.06 mmol) in DCM (30 mL) at 0 °C were added PPh_3 (1.78 g, 6.79 mmol) and *N*-bromosuccinimide (recrystallised from water, 1.21 g, 6.80 mmol). The reaction mixture was stirred at 0 °C for 1 h, then concentrated in vacuo (maintaining water bath temperature below 25 °C) and the residue directly purified by flash silica column chromatography (DCM) to provide bromide **20**[18] (0.92 g, 94%) as a colourless oil, R_f=0.56 (petroleum ether–EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 4.50 (2H, s), 7.10 (1H, s), 7.89 (1H, s); *m/z* (CI) 162 (MH^+, 100).

5.1.2. 5-[E-3-Iodo-2-propenyl]oxazole *13*

To a stirred solution of 5-(bromomethyl)oxazole **20** (1.14 g, 7.04 mmol) in degassed THF (40 mL) at rt were added *E*-1,2-bis-(tributylstannyl)ethene (4.70 g, 7.75 mmol) and Pd_2dba_3 (0.322 g, 0.35 mmol) whilst protecting the flask from light. The reaction mixture was heated at 80 °C for 4 h whereupon it was slowly cooled to 0 °C and iodine (9.62 g, 37.9 mmol) added. The resulting solution was stirred overnight, gradually warming to rt, then aqueous sodium sulfite (1 M, 30 mL) and Et_2O (60 mL) added. The layers were separated and the aqueous extracted with Et_2O (2×60 mL), the combined organic extracts dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (hexane–EtOAc 3:1) to afford compound **13** (0.76 g, 46%) as a pale yellow oil, R_f=0.23 (DCM); ν_{max} (film) 3125, 3049, 1607, 1509, 1421, 1283, 1199, 1102, 947 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.43 (2H, d, *J* 6.5), 6.26 (1H, dt, *J* 14.5, 1.5), 6.59 (1H, dt, *J* 14.5, 6.5), 6.83 (1H, s), 7.80 (1H, s); δ_C (100 MHz, $CDCl_3$) 32.5, 79.3, 123.7, 140.0, 149.4, 151.3; *m/z* (CI) 236 (MH^+, 100) [Found (CI): MH^+, 235.9576; C_6H_7NOI requires MH, 235.9572, 1.5 ppm error].

5.1.3. Ethyl 2Z,4E-2-methyl-5-(tributylstannyl)-2,4-pentadienoate *23*

To a stirred mixture of 18-crown-6 (0.384 g, 1.45 mmol) and ethyl 2-[bis-(2,2,2-trifluoroethoxy)phosphoryl]propanoate **22**[27] (0.153 g, 0.44 mmol) in THF (6 mL) was added KHMDS ([0.5 M in toluene]; 0.83 mL, 0.42 mmol) at −78 °C. The solution was stirred for 30 min at −78 °C, before the addition of *E*-3-(tributylstannyl)propen-1-al *E*-**18**[26] (0.120 g, 0.35 mmol) in THF (4 mL). The reaction mixture was stirred for 4.5 h at −78 °C, then allowed to warm to rt, quenched with a saturated solution of NH_4Cl (2 mL) and diluted with Et_2O (25 mL). The layers were separated, the organic layer washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash silica column chromatography (DCM) to afford compound **23** (0.140 g, 94%) as a pale yellow oil, R_f=0.78 (petroleum ether–EtOAc, 20:1); ν_{max} (neat) 2927, 1710, 1617, 1462, 1375, 1241, 1191, 1124, 999 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82–0.98 (18H, m), 1.20–1.38 (6H, m), 1.40–1.56 (6H, m), 1.97 (3H, s), 4.23 (2H, q, *J* 7.0), 6.39 (1H, d, *J* 10.5), 6.53 (1H, d, *J* 18.5), 7.52 (1H, dd, *J* 18.5, 10.5); δ_C (100 MHz, $CDCl_3$); 9.7, 13.8, 14.4, 20.8, 27.4, 29.3, 60.4, 124.9, 142.3, 142.9, 143.6, 167.8; *m/z* (CI) 431 (MH^+, 9), 390 (38), 373 (37), 308 (100),139 (36) [Found (CI): MH^+, 427.1974; $C_{20}H_{39}O_2Sn$ requires MH, 427.1967, 1.6 ppm error].

5.1.4. 2Z,4E-2-Methyl-5-(tributylstannyl)-2,4-pentadien-1-ol *24*

To a stirred solution of ester **23** (0.432 g, 1.01 mmol) in DCM (10 mL) at −10 °C was added DIBAL-H ([1.0 M in toluene]; 3.0 mL, 3.0 mmol). The reaction was stirred at −10 °C for 1.5 h, then quenched with methanol (5 mL), the cool bath removed and the mixture stirred for 5 min before adding potassium-sodium tartrate (20% in water, 5 mL). The resulting emulsion was vigorously stirred for 2 h, then the layers separated and the aqueous extracted with DCM (3×25 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash silica column chromatography (petroleum ether–EtOAc, 9:1) to afford compound **24** (0.326 g, 84%) as a colourless oil, R_f=0.33 (petroleum ether–EtOAc, 9:1); ν_{max} (neat) 3326, 2925, 2851, 1462, 1376, 1006 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82–0.98 (15H, m), 1.22–1.38 (6H, m), 1.40–1.56 (6H, m), 1.88 (3H, s), 4.30 (2H, d, *J* 5.5), 5.95 (1H, d, *J* 10.5), 6.19 (1H, d, *J* 18.5), 6.80 (1H, dd, *J* 18.5, 10.5); δ_C (100 MHz, $CDCl_3$) 9.7, 13.9, 21.5, 27.4, 29.3, 62.0, 131.6, 134.3, 135.6, 141.6; *m/z* (EI) 331 (M^+–Bu, 100), 177 (41), 137 (55), 81 (66) [Found (EI): M–Bu, 327.1069; $C_{14}H_{27}OSn$ requires M–Bu, 327.1079, 3.1 ppm].

*5.1.5. 2Z,4E-2-Methyl-5-(tributylstannyl)-2,4-pentadien-1-al Z,E-**16***

To a stirred solution of alcohol **24** (0.043 g, 0.11 mmol) in DCM (1.5 mL) at rt was added 4 Å molecular sieves (0.050 g), 4-methylmorpholine-*N*-oxide (0.020 g, 0.17 mmol) and tetrapropylammonium perruthenate (0.004 g, 0.01 mmol). The reaction mixture was stirred at rt for 1.5 h, then passed through a plug of alumina (deactivated with 6% H_2O; eluting DCM), to afford compound *Z,E*-**16** (0.043 g, quant.) as a colourless oil, R_f=0.30 (petroleum ether–Et_2O, 30:1); ν_{max} (neat) 2959, 2926, 1683, 1261, 1111, 1018, 802 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82–0.98 (15H, m), 1.22–1.38 (6H, m), 1.40–1.56 (6H, m), 1.84 (3H, s), 6.72 (1H, d, *J* 18.5), 6.88 (1H, d, *J* 11.0), 7.50 (1H, dd, *J* 18.5, 11.0), 10.35 (1H, s); δ_C (100 MHz, $CDCl_3$) 9.8, 13.8, 16.3, 27.4, 29.2, 133.4, 138.7, 146.9, 148.0, 190.9; *m/z* (CI) 387 (MH^+, 84), 346 (28), 329 (48), 308 (96), 291 (59), 95 (100) [Found (CI): MH^+, 383.1705; $C_{18}H_{35}OSn$ requires MH, 383.1705, 0.1 ppm error].

*5.1.6. Methyl 3R,4Z,6E-3-hydroxy-2,2,4-trimethyl-7-(tributylstannyl)-4,6-heptadienoate Z,E-**14***

To stirred solution of *N*-tosyl-L-valine[39] (0.565 g, 2.08 mmol) in DCM (8.5 mL) at 0 °C was added a solution of BH_3·THF (1.0 M in THF, 1.40 mL, 1.40 mmol). The mixture was slowly warmed to rt and stirred for 18 h then cooled to −78 °C and aldehyde *Z,E*-**16** (0.400 g, 1.04 mmol) in DCM (2 mL) added. After 5 min 1-methoxy-2-methyl(trimethylsiloxy)propene **17** (0.42 mL, 2.07 mmol) was added and the resulting solution stirred at −78 °C for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and allowed to warm to rt. DCM (50 mL) was added, the layers were separated and the aqueous extracted with DCM (3×50 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (petroleum ether–EtOAc, 9:1) to afford compound *Z,E*-**14** (0.428 g, 84%, 64% ee, see text) as a colourless oil, $[\alpha]_D^{21}$ +5.4 (*c* 1.07, $CHCl_3$), R_f=0.24 (petroleum ether–EtOAc, 9:1); ν_{max} (film) 3502, 2957, 2927, 2872, 2853, 1727, 1464, 1377, 1259, 1192, 1136, 1053, 987 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.73–1.02 (15H, m), 1.15 (3H, s), 1.27 (3H, s), 1.19–1.38 (6H, m), 1.40–1.52 (6H, m), 1.72 (3H, s), 3.30 (1H, d *J* 6.5), 3.71 (3H, s), 4.80 (1H, d, *J* 6.5), 6.01 (1H, d, *J* 10.5), 6.15 (1H, d, *J* 18.5), 6.77 (1H, dd, *J* 18.5, 10.5); δ_C (100 MHz, $CDCl_3$) 9.7, 13.8, 19.2, 21.1, 24.7, 27.4, 29.3, 47.0, 52.3, 75.3, 133.9, 134.2, 134.5, 142.0, 178.5; *m/z* (CI) 489 (MH^+, 48), 431 (76), 308 (79), 291 (80), 181 (51), 95 (100) [Found (CI): MH^+, 485.2385; $C_{23}H_{45}O_3Sn$ requires MH, 485.2386, 0.2 ppm error].

*5.1.7. Methyl 3R,4Z,6E,8E-3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatrienoate **27***

To a stirred solution of stannane *Z,E*-**14** (0.043 g, 0.09 mmol) in degassed DMF (1 mL) at rt was added iodide **13** (0.023 g, 0.10 mmol) and then nitrogen bubbled through the solution (to further degas) for 30 min. To the solution were added CsF (0.027 g, 0.18 mmol), $Pd(PPh_3)_4$ (0.001 g, 0.9 μmol) in degassed DMF (0.1 mL) and CuI (0.0017 g, 0.009 mmol). The reaction mixture was heated at 45 °C for 3 h in the dark, cooled to rt and purified directly by flash silica column chromatography doped with 10% KF (petroleum ether–Et_2O, 1:1). DMF was still present, thus DCM (10 mL) and H_2O (10 mL) were added, the layers separated and the aqueous extracted once with DCM (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to afford compound **27** (0.027 g, quant.) as an amorphous yellow foam, $[\alpha]_D^{21}$ +57.9 (*c* 0.80, $CHCl_3$), R_f=0.34 (petroleum ether–EtOAc 1:1); ν_{max} (film) 3419, 3136, 2981, 2951, 1726, 1511, 1471, 1435, 1260, 1192, 1140, 1055, 912 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, s), 1.27 (3H, s), 1.75 (3H, s), 3.48 (2H, d, *J* 7.0), 3.72 (3H, s), 4.71 (1H, s), 5.73 (1H, dt, *J* 14.5, 6.5), 6.03 (1H, d, *J* 11.5), 6.10–6.23 (2H, m), 6.43 (1H, dd, *J* 13.5, 11.5), 6.79 (1H, s), 7.79 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.6, 21.1, 24.5, 29.0, 46.9, 52.4, 75.2, 122.6, 127.3, 128.0, 130.3, 131.8, 133.5, 137.0, 150.6, 150.9, 178.5; *m/z* (EI) 305 (M^+, 1), 269 (8), 204 (100), 102 (29), 82 (39), 57 (22), 41 (32) [Found (EI): M^+ 305.1637; $C_{17}H_{23}NO_4$ requires M, 305.1627, 3.4 ppm error].

*5.1.8. 3R,4Z,6E,8E-3-Hydroxy-2,2,4-trimethyl-10(oxazol-5-yl)-4,6,8-decatrienoic acid **30***

To a stirred solution of ester **27** (0.023 g, 0.08 mmol) in THF (0.6 mL), methanol (0.2 mL), water (0.2 mL) at rt was added lithium hydroxide monohydrate (0.013 g, 0.31 mmol). The reaction mixture was stirred for 14 h, then concentrated in vacuo and Et_2O (5 mL) and water (5 mL) added. The layers were separated and the aqueous washed once with Et_2O (5 mL). The aqueous layer was acidified to pH 1–2 with aq HCl (0.3 M) and extracted with Et_2O (2×20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to afford compound **30** (0.020 g, 91%) as an amorphous yellow foam, $[\alpha]_D^{22}$ +26.0 (*c* 0.60, $CHCl_3$), R_f=0.39 (EtOAc–methanol, 9:1); ν_{max} (film) 3398, 3135, 2925, 1707, 1512, 1467, 1263, 1124, 1052, 991 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, s), 1.30 (3H, s), 1.79 (3H, s), 3.47 (2H, d, *J* 7.0), 4.74 (1H, s), 5.72 (1H, dt, *J* 14.5, 7.0), 6.02 (1H, d, *J* 11.0), 6.10–6.21 (2H, m), 6.42 (1H, dd, *J* 13.5, 11.5), 6.81 (1H, s), 7.87 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.5, 20.9, 25.1, 28.9, 46.1, 74.9, 122.0, 127.2, 127.8, 130.5, 132.0, 133.6, 136.8, 150.9, 151.3, 181.7; *m/z* (ESI) 290 ($M-H^+$, 100) [Found (ESI): $M-H^+$, 290.1397; $C_{16}H_{21}NO_4$ requires M–H, 290.1398, 0.4 ppm].

*5.1.9. 3R,4Z,6E,8E-3-Acetoxy-2,2,4-trimethyl-10(oxazol-5-yl)-4,6,8-decatrienoic acid **31***

To a stirred solution of acid **30** (0.037 g, 0.13 mmol) in pyridine (1 mL) was added acetic anhydride (0.12 mL, 1.27 mmol) at rt. The solution was stirred for 22 h, concentrated in vacuo, DCM (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) added, then the biphasic reaction mixture stirred vigorously at rt for 8 h. The layers were separated, the aqueous acidified to pH 1–2 with aq HCl (2.9 M) and extracted with DCM (3×10 mL). The combined organic extracts were dried

over $MgSO_4$, filtered and concentrated in vacuo to afford compound **31** (0.026 g, 62%) as a yellow oil, $[\alpha]_D^{21}$ +50.8 (*c* 1.30, $CHCl_3$), R_f=0.57 (EtOAc); ν_{max} (film) 3354, 2925, 1739, 1708, 1655, 1510, 1373, 1237, 1042 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, s), 1.28 (3H, s), 1.79 (3H, s), 2.06 (3H, s), 3.49 (2H, d, *J* 7.0), 5.73 (1H, dt, *J* 14.5, 7.0), 5.98 (1H, s), 6.09 (1H, d, *J* 11.5), 6.14 (1H, dd, *J* 14.5, 10.5), 6.24 (1H, dd, *J* 14.5, 10.5), 6.56 (1H, dd, *J* 14.5, 11.5), 6.82 (1H, s), 7.82 (1H, s); *m/z* (EI) 333 (M^+, 7), 204 (100), 82 (28), 43 (61) [Found (EI): M^+, 333.1575; $C_{18}H_{23}NO_5$ requires M, 333.1576, 3.6 ppm error].

5.1.10. Inthomycin B **6**

To a stirred solution of acid **31** (0.014 g, 0.04 mmol) in DCM (0.5 mL) at 0 °C was added oxalyl chloride (6 μL, 0.07 mmol) and a drop of DMF. The reaction mixture was stirred for 3.5 h slowly warming to rt, then NH_4OH (35% ammonia, 1 mL) was added. The resulting solution was stirred at rt overnight, diluted with DCM (5 mL) and water (5 mL) added. The layers were separated, the aqueous extracted with DCM (3×10 mL), the combined organic extracts washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (chloroform–methanol, 12:1) to afford the (+)-inthomycin B **6** (0.006 g, 50%) as an amorphous foam, $[\alpha]_D^{22}$ +19.3 (*c* 1.00, $CHCl_3$), R_f=0.47 (chloroform–methanol, 9:1); ν_{max} (film) 3342, 2923, 2852, 1732, 1659, 1652, 1601, 1511, 1375, 1242, 1106, 1046, 990 cm^{-1}; UV (methanol) λ_{max} (ε)=200 nm (14,000), 266 nm (27,000), 275 nm (33,600), 286 nm (27,400) $mol^{-1}\,dm^3\,cm^{-1}$; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, s), 1.36 (3H, s), 1.81 (3H, s), 3.48 (2H, d, *J* 6.5), 4.04 (1H, d, *J* 5.5), 4.61 (1H, d, *J* 5.5), 5.52 (1H, br s), 5.74 (1H, dt, *J* 14.0, 6.5), 6.02 (1H, d, *J* 11.5), 6.11–6.25 (2H, m), 6.27 (1H, br s), 6.42 (1H, dd, *J* 14.0, 11.5), 6.80 (1H, s), 7.79 (1H, s); δ_H (400 MHz, acetone-d_6) 1.06 (3H, s), 1.28 (3H, s), 1.78 (3H, s), 3.51 (2H, d, *J* 6.5), 4.64 (1H, s), 5.78 (1H, dt, *J* 15.0, 6.5), 5.99 (1H, d, *J* 11.5), 6.15 (1H, dd, *J* 14.5, 10.5), 6.28 (1H, dd, *J* 15.0, 10.5), 6.42 (1H, br s), 6.62 (1H, dd, *J* 14.5, 11.5), 6.83 (1H, s), 7.04 (1H, br s), 8.01 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.3, 21.8, 26.3, 29.0, 44.6, 76.0, 122.7, 127.6, 127.6, 130.2, 132.1, 133.4, 137.7, 150.6, 150.9, 181.2; δ_C (100 MHz, acetone-d_6) 19.6, 22.2, 26.4, 27.5, 45.3, 75.9, 123.2, 128.3, 129.0, 129.9, 132.3, 134.2, 139.9, 151.7, 151.8, 181.1; *m/z* (CI) 291 (MH^+, 15), 273 (70), 204 (94), 186 (32), 133 (28), 105 (100), 88 (77), 52 (46) [Found (CI): MH^+, 291.1706; $C_{16}H_{23}N_2O_3$ requires MH, 291.1709, 1.1 ppm error]. This data was consistent with the (sparse) data available in the literature.[10]

5.1.11. 3-(Tributylstannyl)-2Z-propen-1-al Z-**18**

To a stirred solution of 3-(tributylstannyl)-(2*Z*)-propen-1-ol **32**[35] (0.095 g, 0.27 mmol) in DCM (4 mL) were added 4 Å molecular sieves (0.10 g), 4-methylmorpholine-*N*-oxide (0.048 g, 0.41 mmol) and tetrapropylammonium perruthenate (0.005 g, 0.01 mmol). The reaction was stirred at rt for 3 h then concentrated in vacuo. The residue was purified by flash silica column chromatography (petroleum ether–EtOAc, 20:1) to afford compound *Z*-**18** (0.076 g, 81%) as a colourless oil, R_f=0.69 (petroleum ether–EtOAc, 9:1), ν_{max} (film) 2957, 2923, 2871, 2852, 1691, 1550, 1463, 1377, 1188, 1073, 1023, 928 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, t, *J* 7.0), 1.05 (6H, m), 1.31 (6H, m), 1.50 (6H, m), 6.98 (1H, dd, *J* 12.5, 7.0), 7.69 (1H, d, *J* 12.5), 9.50 (1H, d, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 12.0, 14.3, 27.8, 29.6, 146.2, 163.6, 195.3; *m/z* (CI) 364 (MNH_4^+, 66), 347 (MH^+, 77), 308 (48), 289 (98) [Found (CI): MNH_4^+, 360.1662; $C_{15}H_{34}NOSn$ requires MNH_4, 360.1658, 1.2 ppm error].

5.1.12. Ethyl 2Z,4Z-2-methyl-5-(tributylstannyl)-2,4-pentadienoate **34**

To a stirred suspension of sodium hydride (60% in mineral oil, 0.165 g, 4.13 mmol) in THF (40 mL) at −78 °C was added ethyl 2-[bis-(phenoxy)phosphoryl]propanoate[28] **33** (1.59 g, 4.76 mmol). The reaction mixture was warmed to 0 °C and stirred for 20 min, then recooled to −78 °C and a solution of aldehyde *Z*-**18** (1.10 g, 3.18 mmol) in THF (10 mL) was added via cannula. The stirred solution was slowly warmed to rt overnight, water (15 mL) and Et_2O (250 mL) added, the layers separated and the aqueous extracted with Et_2O (3×40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (petroleum ether–ether, 20:1) to afford compounds **34** and **35** (1.09 g, 80%) as an inseparable mixture (87:13) as a colourless oil, R_f=0.30 (petroleum ether–EtOAc, 20:1); ν_{max} (film) 2957, 2926, 1713, 1463, 1374, 1320, 1239, 1200, 1123, 1072, 1025 cm^{-1}; *m/z* (CI) 431 (MH^+, 6), 308 (100), 291 (31) [Found (CI): MH^+, 427.1968; $C_{20}H_{39}O_2Sn$ requires MH, 427.1967, 0.1 ppm error].

NMR data for **34**: δ_H (400 MHz, $CDCl_3$) 0.85–1.00 (18H, m), 1.22–1.38 (6H, m), 1.45–1.55 (6H, m), 1.98 (3H, s), 4.23 (2H, q, *J* 7.0), 6.28 (1H, d, *J* 11.5), 6.46 (1H, d, *J* 13.0), 7.89 (1H, dd, *J* 13.0, 11.5); δ_C (100 MHz, $CDCl_3$) 10.6, 13.7, 14.3, 21.1, 27.2, 29.1, 60.4, 127.2, 141.9, 142.7, 143.2, 167.6.

NMR data for **35**: δ_H (400 MHz, $CDCl_3$) 0.81–1.09 (15H, m), 1.22–1.37 (9H, m), 1.41–1.62 (6H, m), 1.97 (3H, s), 4.21 (2H, q, *J* 7.0), 6.63 (1H, d, *J* 11.0), 7.11 (1H, d, *J* 11.0), 7.34 (1H, dd, *J* 11.0, 11.0); δ_C (100 MHz, $CDCl_3$) 10.8, 13.8, 14.4, 21.8, 27.3, 29.3, 60.6, 128.0, 140.4, 141.6, 145.8, 168.6.

5.1.13. 2Z,4Z-2-Methyl-5-(tributylstannyl)-2,4-pentadien-1-al Z,Z-**16**

(a) To a stirred solution of inseparable esters **34** and **35** (1.09 g, 2.54 mmol) in DCM (40 mL) at −35 °C was added DIBAL-H (1.0 M in DCM, 7.6 mL, 7.6 mmol). The solution was stirred for 2 h, warming from −35 °C to 0 °C, quenched with methanol (10 mL), warmed to rt and stirred for a further 50 min. After this time an aqueous solution of potassium-sodium tartrate (20%, 30 mL) was added and the mixture stirred overnight. The phases were partitioned and the aqueous extracted with DCM (4×60 mL), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified

by flash silica column chromatography (petroleum ether–EtOAc, 9:1) to afford (2*Z*,4*Z*)-2-methyl-5-(tributylstannyl)-2,4-pentadien-1-ol (0.670 g, 68%) as a colourless oil, R_f=0.36 (petroleum ether–Et_2O, 5:1); ν_{max} (film) 3360, 2958, 2927, 1463, 1001, 908 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, t, *J* 7.5), 0.92–0.96 (6H, m), 1.24–1.36 (6H, m), 1.46–1.57 (6H, m), 1.90 (3H, s), 4.29 (2H, d, *J* 6.0), 5.84 (1H, d, *J* 11.0), 6.07 (1H, d, *J* 12.5), 7.33 (1H, dd, *J* 12.5, 11.0); δ_C (100 MHz, $CDCl_3$) 10.4, 13.7, 21.7, 27.3, 29.1, 61.7, 130.8, 134.2, 137.7, 140.8; *m/z* (EI) 331 ($[M-Bu]^+$, 1), 251 (61), 177 (37), 137 (63), 121 (35), 81 (36), 57 (40), 41 (100) [Found (EI): M^+–Bu, 327.1071; $C_{14}H_{27}OSn$ requires M–Bu, 327.1079, 2.6 ppm error].

(b) To a stirred solution of (2*Z*,4*Z*)-2-methyl-5-(tributylstannyl)-2,4-pentadien-1-ol (0.161 g, 0.42 mmol) in DCM (4 mL) at 0 °C were added 4 Å molecular sieves (0.10 g), 4-methylmorpholine-*N*-oxide (0.073 g, 0.62 mmol) and tetrapropylammonium perruthenate (0.014 g, 0.04 mmol). The mixture was stirred for 2 h, then passed through a plug of alumina (deactivated with 6% water; eluting DCM), to afford compound *Z*,*Z*-**16** (0.160 g, quant.) as a pale yellow oil, R_f=0.76 (petroleum ether–EtOAc, 20:1); ν_{max} (film) 2958, 2927, 2872, 2854, 1680, 1658, 1464, 1378, 1072, 909 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, t, *J* 7.0), 0.98–1.02 (6H, m), 1.27–1.36 (6H, m), 1.48–1.62 (6H, m), 1.87 (3H, s), 6.69 (1H, d, *J* 12.5), 6.79 (1H, d, *J* 12.0), 8.01 (1H, dd, *J* 12.5, 12.0), 10.36 (1H, s); δ_C (100 MHz, $CDCl_3$) 10.7, 13.7, 16.6, 27.2, 29.1, 135.1, 138.2, 146.8, 147.6, 190.9; *m/z* (CI) 387 (MH^+, 23), 308 (100) [Found (CI): MH^+, 383.1698; $C_{18}H_{35}OSn$ requires MH, 383.1705, 1.9 ppm error].

5.1.14. Methyl 4*Z*,6*Z*-3-hydroxy-2,2,4-trimethyl-7-(tributylstannyl)-4,6-heptadienoate (±)-*Z*,*Z*-**14**

To a stirred solution of diisopropylamine (290 μL, 2.07 mmol) in THF (10 mL) at −78 °C was added *n*-butyllithium (2.30 M in hexanes; 0.77 mL, 1.78 mmol). The solution was stirred for 30 min then methyl *iso*-butyrate (203 μL, 1.78 mmol) was added. This was allowed to stir at −78 °C for a further 25 min, then a solution of aldehyde *Z*,*Z*-**16** (0.570 g, 1.48 mmol) in THF (10 mL) was added to the reaction mixture over 3 min. The reaction mixture was stirred at −78 °C for 2 h, then saturated aqueous NH_4Cl (10 mL) was added and the solution allowed to warm to rt. The layers were separated and the aqueous extracted with Et_2O (3×40 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford a yellow oil. The crude product was purified by flash silica column chromatography (petroleum ether–EtOAc, 20:1 to 10:1) to afford the title compound (±)-*Z*,*Z*-**14** (0.597 g, 83%) as a colourless oil, R_f=0.44 (petroleum ether–EtOAc, 20:1); ν_{max} (film) 3488, 2956, 2925, 2854, 1725, 1461, 1377, 1260, 1193, 1135, 1051 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85–0.96 (15H, m), 1.16 (3H, s), 1.22–1.37 (9H, m), 1.44–1.56 (6H, m), 1.75 (3H, s), 3.30 (1H, d, *J* 6.5), 3.72 (3H, s), 4.81 (1H, d, *J* 6.5), 5.92 (1H, d, *J* 11.0), 6.05 (1H, d, *J* 12.5), 7.29 (1H, dd, *J* 12.5, 11.0); δ_C (100 MHz, $CDCl_3$) 10.6, 13.8, 19.5, 21.1, 24.7, 27.4, 29.3, 47.0, 52.4, 75.1, 133.4, 134.4, 136.7, 141.4, 178.6; *m/z* 489 (MH^+, 17), 387 (50), 331 (37), 308 (100), 291 (48), 181 (39), 95 (32), 71 (43) [Found (CI): MH^+, 485.2388; $C_{23}H_{45}O_3Sn$ requires MH, 485.2386, 0.4 ppm error].

5.1.15. 4*Z*,6*Z*,8*E*-3-Hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatrienoic acid **36**

(a) A flask containing a stirred solution of iodide **13** (0.027 g, 0.11 mmol) and stannane (±)-*Z*,*Z*-**14** (0.050 g, 0.10 mmol) in degassed DMF (0.5 mL) at rt was evacuated, then flushed with nitrogen three times. $Pd(CH_3CN)Cl_2$ (0.0012 g, 0.005 mmol) was added, the flask stirred at rt in the dark for 5 h, then saturated NH_4Cl (5 mL) and EtOAc (10 mL) were added and the layers separated. The aqueous was extracted with EtOAc (3×10 mL) and the combined organic extracts washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (petroleum ether–EtOAc, 2:1) to afford methyl (4*Z*,6*Z*,8*E*)-3-hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatrienoate (0.024 g, 77%) as a pale yellow oil, R_f=0.23 (petroleum ether–EtOAc, 2:1); (400 MHz, $CDCl_3$) 1.15 (3H, s), 1.26 (3H, s), 1.79 (3H, s), 3.51 (2H, d, *J* 7.0), 3.71 (3H, s), 4.76 (1H, s), 5.77 (1H, dt, *J* 15.0, 7.0), 5.94 (1H, dd, *J* 11.5, 11.0), 6.20 (1H, dd, *J* 12.0, 11.0), 6.44 (1H, d, *J* 12.0), 6.64 (1H, dd, *J* 15.0, 11.5), 6.80 (1H, s), 7.79 (1H, s); *m/z* (CI) 306 (MH^+, 5), 216 (37), 209 (29), 192 (42), 183 (45), 148 (26), 112 (100), 100 (38). The data for this compound were consistent with those published.[18]

(b) To a stirred solution of the ester from part (a) (0.076 g, 0.25 mmol) in THF (1.5 mL), methanol (0.5 mL) and water (0.5 mL) at rt was added lithium hydroxide monohydrate (0.031 g, 0.75 mmol). The reaction mixture was stirred for 3.5 h, concentrated in vacuo and the residue dissolved in water (5 mL). The aqueous layer was extracted with Et_2O (5 mL), acidified to pH 4 with aq HCl (1.5 M) and extracted with EtOAc (4×10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to afford compound **36** (0.067 g, 92%) as a pale yellow oil, R_f=0.38 (EtOAc); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, s), 1.33 (3H, s), 1.85 (3H, s), 3.53 (2H, d, *J* 7.0), 4.80 (1H, s), 5.78 (1H, dt, *J* 14.5, 7.0), 5.97 (1H, dd, *J* 11.5, 11.0), 6.20 (1H, dd, *J* 12.0, 11.0), 6.46 (1H, d, *J* 12.0), 6.65 (1H, dd, *J* 14.5, 11.5), 6.84 (1H, s), 7.87 (1H, s); *m/z* (ESI) 290 (MH, 100). The data for this compound were consistent with those published.[18]

5.1.16. 4*Z*,6*Z*,8*E*-3-Acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatriene amide **37**

(a) To a stirred solution of acid **36** (0.052 g, 0.18 mmol) in pyridine (1 mL) was added acetic anhydride (0.15 mL, 1.58 mmol) at rt. The solution was stirred for 20 h, concentrated in vacuo and the residue passed through a plug of flash silica eluting with EtOAc. The filtrate was concentrated in vacuo and the resulting yellow oil dissolved in DCM (5 mL). Saturated $NaHCO_3$ (4 mL) was added and the reaction mixture vigorously stirred at rt for 2 h, then acidified to pH 1 with aq HCl (2.9 M). The aqueous was extracted with DCM (4×10 mL), the organic extracts combined, washed with brine

(5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford (4*Z*,6*Z*,8*E*)-3-acetoxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatrienoic acid (0.060 g, quant.) as an amorphous yellow powder, R_f=0.48 (EtOAc); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, s), 1.27 (3H, s), 1.82 (3H, s), 2.05 (3H, s), 3.51 (2H, d, *J* 7.0), 5.77 (1H, dt, *J* 14.5, 7.0), 5.96–6.02 (2H, m), 6.36 (1H, dd, *J* 12.0, 11.0), 6.51 (1H, d, *J* 12.0), 6.63 (1H, dd, *J* 14.5, 11.5), 6.82 (1H, s), 7.84 (1H, s); *m/z* (EI) 333 (M^+, 7), 204 (100), 82 (28), 43 (61).

(b) To a stirred solution of the acid from part (a) (0.010 g, 0.03 mmol) in DCM (0.5 mL) at 0 °C were added thionyl chloride (3.5 μL, 0.05 mmol) and a drop of DMF. The reaction mixture was stirred for 2.5 h slowly warming to rt, then NH_4OH (35% ammonia, 1 mL) was added. The resulting solution was stirred at rt for 1 h, diluted with DCM (5 mL) and water (5 mL) added. The layers were separated, the aqueous extracted with DCM (3×10 mL), the combined organic extracts washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (EtOAc) to afford compound **37** (0.007 g, 70%) as a yellow oil, R_f=0.44 (DCM–methanol, 9:1); ν_{max} (film) 2977, 2928, 1735, 1674, 1603, 1509, 1372, 1241, 1029 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, s), 1.23 (3H, s), 1.82 (3H, s), 2.10 (3H, s), 3.52 (2H, d, *J* 7.0), 5.54 (1H, br s), 5.79 (1H, dt, *J* 14.5, 7.0), 5.85 (1H, s), 5.99–6.04 (2H, m), 6.36 (1H, dd, *J* 12.0, 11.0), 6.50 (1H, d, *J* 12.0), 6.62 (1H, dd, *J* 14.5, 11.5), 6.82 (1H, s), 7.81 (1H, s); δ_C (100 MHz, $CDCl_3$) 20.6, 21.1, 21.8, 25.0, 29.2, 46.3, 76.9, 122.4, 124.1, 126.9, 128.3, 129.1, 129.1, 133.1, 150.8, 151.0, 169.5, 178.1; *m/z* (EI) 332 (M^+, 8), 204 (81), 87 (86), 43 (100) [Found (EI): M^+ 332.1735, $C_{18}H_{24}N_2O_4$; requires M, 332.1736, 0.3 ppm error].

5.1.17. Inthomycin A **10**

To a stirred solution of amide **37** (0.007 g, 0.02 mmol) in THF (0.3 mL), methanol (0.1 mL) and water (0.1 mL) at rt was added lithium hydroxide monohydrate (0.002 g, 0.04 mmol). The reaction mixture was stirred for 1 h, concentrated in vacuo and the residue dissolved in water (5 mL). The aqueous was acidified to pH 1 with aq HCl (1 M) and extracted with DCM (5×5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the title compound **10** (0.006 g, 92%) as an amorphous yellow powder, R_f=0.31 (DCM–methanol, 9:1); ν_{max} (film) 3334, 2921, 2851, 1660, 1600, 1511, 1464, 1378, 1262, 1107, 1043, 910 cm^{-1}; UV (methanol) λ_{max} (ε)=202 nm (25,300), 266 nm (24,900), 275 nm (29,200), 286 nm (22,700) $mol^{-1}\,dm^3\,cm^{-1}$; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, s), 1.36 (3H, s), 1.84 (3H, s), 3.52 (2H, d, *J* 7.0), 4.64 (1H, s), 5.58 (1H, br s), 5.78 (1H, dt, *J* 15.0, 7.0), 5.95 (1H, dd, *J* 11.5, 11.0), 6.20 (1H, dd, *J* 12.0, 11.0), 6.29 (1H, br s), 6.42 (1H, d, *J* 12.0), 6.65 (1H, dd, *J* 15.0, 11.5), 6.80 (1H, s), 7.80 (1H, s); δ_H (400 MHz, acetone-d_6) 1.06 (3H, s), 1.28 (3H, s), 1.83 (3H, s), 3.56 (2H, d, *J* 6.5), 4.67 (1H, s), 5.24 (1H, br s), 5.82 (1H, dt, *J* 15.0, 6.5), 5.96 (1H, dd, *J* 11.5, 11.0), 6.32 (1H, dd, *J* 12.0, 11.0), 6.38 (1H, br s), 6.48 (1H, d, *J* 12.0), 6.79 (1H, dd, *J* 15.0, 11.5), 6.84 (1H, s), 8.01 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.6, 21.8, 26.3, 29.2, 44.7, 75.5, 122.7, 123.8, 125.0, 128.3, 128.3, 128.8, 138.5, 150.6, 150.9, 181.2; δ_C (100 MHz, acetone-d_6) 19.8, 22.2, 26.4, 29 (masked by solvent peak), 45.4, 75.5, 123.2, 124.7, 125.0, 128.4, 129.0, 129.8, 140.7, 151.6, 151.7, 181.1; *m/z* 290 (M^+, 3), 204 (28), 87 (100) [Found (EI): M^+, 290.1633; $C_{16}H_{22}N_2O_3$ requires M, 290.1630, 0.8 ppm error]. These data were consistent with those previously published.[9,10]

5.1.18. 2E,4E-2-Methyl-5-(tributylstannyl)-2,4-pentadien-1-al E,E-**16**

(a) To a stirred solution of ethyl (2*E*,4*E*)-2-methyl-5-(tributylstannyl)-2,4-pentadienoate **39**[40] (0.433 g, 1.01 mmol) in DCM (10 mL) at −10 °C was added DIBAL-H ([1.0 M in toluene]; 3.0 mL, 3.0 mmol). The solution was stirred for 3 h slowly warming to rt, then methanol (5 mL) was added and the reaction mixture stirred for 15 min. An aqueous solution of potassium-sodium tartrate (20%, 5 mL) was added, the resulting suspension stirred overnight then filtered through Celite® washing with DCM (50 mL). Water (30 mL) was added, the layers separated and the aqueous extracted with DCM (2×50 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford (2*E*,4*E*)-2-methyl-5-(tributylstannyl)-2,4-pentadien-1-ol (0.408 g, quant.) as a colourless oil, R_f=0.21 (petroleum ether–EtOAc, 10:1); δ_H (400 MHz, $CDCl_3$) 0.85–0.94 (15H, m), 1.26–1.37 (6H, m), 1.46–1.58 (6H, m), 1.84 (3H, s), 4.08 (2H, d, *J* 6.0), 6.06 (1H, d, *J* 10.5), 6.26 (1H, d, *J* 18.5), 6.77 (1H, dd, *J* 18.5, 10.5); *m/z* (EI) 331 ($M-Bu^+$, 98), 291 (36), 275 (71), 235 (42), 219 (56), 177 (82), 137 (100), 121 (71), 81 (51).

(b) To a stirred solution of (2*E*,4*E*)-2-methyl-5-(tributylstannyl)-2,4-pentadien-1-ol (0.064 g, 0.16 mmol) in DCM (2 mL) at rt was added manganese dioxide (0.140 g, 1.63 mmol). The solution was vigorously stirred at rt for 2 d, diluted with DCM (20 mL) and filtered through Celite® washing with DCM (50 mL). The filtrate was concentrated in vacuo to afford compound *E*,*E*-**16** (0.064 g, quant.) as a pale yellow oil, R_f=0.71 (hexane–Et_2O, 30:1); ν_{max} (film) 2956, 2926, 2871, 2852, 1677, 1619, 1464, 1395, 1377, 1354, 1237, 1159, 998 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, t, *J* 7.5), 0.98 (6H, t, *J* 8.0), 1.29–1.36 (6H, m), 1.50–1.57 (6H, m), 1.88 (3H, s), 6.75 (1H, d, *J* 9.0), 6.97 (1H, d, *J* 18.5), 7.04 (1H, dd, *J* 18.5, 9.0), 9.44 (1H, s); δ_C (100 MHz, $CDCl_3$) 9.5, 9.8, 13.7, 27.2, 29.2, 135.9, 141.4, 149.6, 150.2, 195.7; *m/z* (EI) 329 ($M-Bu^+$, 72), 273 (60), 217 (77), 95 (100) [Found (EI): $M-Bu^+$, 329.0929; $C_{14}H_{25}O^{120}Sn$ requires M–Bu, 329.0927, 0.5 ppm error].

5.1.19. 2E,4E,6E-2-Methyl-8-(oxazol-5-yl) 2,4,6-octatrienal **41**

Nitrogen was bubbled through a solution of iodide **13** (0.048 g, 0.20 mmol) and stannane *E*,*E*-**16** (0.072 g, 0.19 mmol) in degassed DMF (3 mL) for 30 min. $Pd(CH_3CN)_2Cl_2$ (0.002 g, 0.008 mmol) was added and the reaction mixture stirred at rt in the dark for 2 h. Saturated NH_4Cl

(5 mL) and EtOAc (10 mL) were then added, the layers separated and the aqueous extracted with EtOAc (3×10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated in vacuo, then the resulting orange oil purified by flash silica column chromatography (petroleum ether–EtOAc, 1:1 to EtOAc) to afford compound **41** (0.028 g, 74%) as a yellow oil, R_f=0.43 (petroleum ether–EtOAc, 1:1); ν_{max} (film) 3131, 2956, 2928, 1680, 1613, 1510, 1464, 1366, 1257, 1226, 1101, 991, 964 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.86 (3H, s), 3.56 (2H, d, *J* 6.5), 6.03 (1H, dt, *J* 15.5, 6.5), 6.33 (1H, dd, *J* 15.5, 9.0), 6.62–6.65 (2H, m), 6.82–6.86 (2H, m), 7.82 (1H, s), 9.45 (1H, s); δ_C (125 MHz, $CDCl_3$) 9.9, 29.3, 123.2, 127.5, 133.0, 133.3, 138.2, 140.5, 148.1, 150.9, 194.9; *m/z* (CI), 204 (MH^+, 100%) [Found (CI): MH^+, 204.1022; $C_{12}H_{14}O_2N$ requires MH, 204.1025, 1.1 ppm error].

5.1.20. Methyl 3R,4E,6E,8E-3-hydroxy-2,2,4-trimethyl-10(oxazol-5-yl)-4,6,8-decatrienoate **43**

To a stirred solution of *N*-L-tosyl-valine (0.352 g, 1.30 mmol) in DCM (5 mL) at 0 °C was added a solution of BH_3·THF (1.0 M in THF, 1.18 mL, 1.18 mmol), the mixture was stirred at 0 °C for 20 min, and then rt for 30 min. The solution was cooled to −78 °C and aldehyde **41** (0.120 g, 0.59 mmol) in DCM (1 mL) was added followed by 1-methoxy-2-methyl(trimethylsiloxy)propene (0.14 mL, 0.71 mmol). The reaction mixture was stirred at −78 °C for 2 h, a buffer solution (pH 6.865, 8 mL) added and the suspension slowly warmed to rt. The organic layers were separated, the aqueous layer extracted with DCM (3×20 mL), the organic extracts combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash silica column chromatography (petroleum ether–EtOAc 2:1) to afford compound **43** (0.090 g, 50%, 76% ee established by Mosher ester derivatisation) as a yellow oil, $[\alpha]_D^{22}$ +5.2 (*c* 1.55, $CHCl_3$), R_f=0.35 (hexane–EtOAc, 1:1); ν_{max} (film) 3402, 2981, 2951, 1728, 1512, 1468, 1435, 1257, 1132, 989 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, s), 1.21 (3H, s), 1.74 (3H, s), 3.19 (1H, br s), 3.49 (2H, d, *J* 7.0), 3.71 (3H, s), 4.17 (1H, s), 5.76 (1H, dt, *J* 13.5, 7.0), 6.02 (1H, d, *J* 11.0), 6.15–6.25 (2H, m), 6.37 (1H, dd, *J* 13.5, 11.0), 6.78 (1H, s), 7.77 (1H, s); δ_C (67.9 MHz, $CDCl_3$) 14.3, 21.1, 24.1 (CH_3), 29.2, 47.3, 52.5, 82.6, 122.9, 127.7, 128.4, 128.9 (2×CH), 132.5, 133.8, 137.6, 150.8, 178.5; *m/z* (CI), 306 (MH^+, 22%), 288 (100), 204 (27), 192 (17), 183 (10), 112 (24) [Found (CI): MH^+, 306.1706; $C_{17}H_{23}O_4N$ requires 306.1705, 0.4 ppm error].

5.1.21. 3R,4E,6E,8E-3-Hydroxy-2,2,4-trimethyl-10-(oxazol-5-yl)-4,6,8-decatrienoic acid **44**

To a stirred solution of ester **43** (0.033 g, 0.11 mmol) in THF (1.5 mL), methanol (0.5 mL) and water (0.5 mL) was added lithium hydroxide hydrate (0.014 g, 0.32 mmol) at rt and the solution stirred for 22 h. The reaction mixture was concentrated in vacuo and the residue partitioned between EtOAc (15 mL) and NaOH (1 M, 5 mL). The layers were separated, the aqueous layer acidified to pH 3–4 with aq HCl (2 M) and extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford compound **44** (0.028 g, 89%) as an orange oil, $[\alpha]_D^{20}$ +17.1 (*c* 0.82, $CHCl_3$), R_f=0.45 (EtOAc); ν_{max} (film) 3406, 3136, 2980, 2926, 1714, 1263, 1130, 990 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, s), 1.24 (3H, s), 1.77 (3H, s), 3.48 (2H, d, *J* 7.0), 4.17 (1H, s), 5.73 (1H, dt, *J* 13.5, 7.0), 6.03 (1H, d, *J* 11.0), 6.18–6.23 (2H, m), 6.38 (1H, dd, *J* 13.5, 11.5), 6.80 (1H, s), 7.85 (1H, s); δ_C (100 MHz, $CDCl_3$) 13.9, 20.7, 24.4, 28.9, 46.5, 82.4, 122.1, 127.3, 128.2, 129.0, 132.5, 133.7, 137.2, 150.8, 151.2, 181.6; *m/z* (ESI) 290 ($\{M-H\}^+$, 100) [Found (ESI): $M-H^+$, 290.1395; $C_{16}H_{20}NO_4$ requires MH, 290.1398, 0.8 ppm error].

5.1.22. Inthomycin C **5**

To a stirred solution of acid **44** (0.015 g, 0.05 mmol) in THF (1 mL) were added EtN^iPr_2 (27 μL, 0.15 mmol), HATU (0.029 g, 0.08 mmol) and NH_4Cl (0.005 g, 0.09 mmol). The reaction mixture was stirred for 15 h at rt, then partitioned between Et_2O (10 mL) and aq HCl (0.3 M, 10 mL). The layers were separated, the aqueous extracted with Et_2O (3×10 mL) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified twice by flash silica column chromatography (EtOAc) to afford compound (+)-**5** (0.004 g, 27%) containing inseparable tetramethyl urea (ca. 20%) as a yellow oil, $[\alpha]_D^{21}$ +25.9 (*c* 0.27, $CHCl_3$), R_f=0.41 (EtOAc); ν_{max} (film) 3345, 2925, 2855, 1658, 1511, 1465, 1381, 1109, 991 cm^{-1}; UV (methanol) λ_{max} (ε)=203 nm (53,900), 271 nm (18,400), 276 nm (19,600), 290 nm (15,500), $mol^{-1}\,dm^3\,cm^{-1}$; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, s), 1.31 (3H, s), 1.79 (3H, s), 3.49 (2H, d, *J* 6.5), 4.01 (1H, s), 5.51 (1H, br s), 5.75 (1H, dt, *J* 14.0, 6.5), 6.02 (1H, d, *J* 11.0), 6.18–6.27 (3H, m), 6.39 (1H, dd, *J* 13.5, 11.0), 6.80 (1H, s), 7.80 (1H, s); δ_H (400 MHz, acetone-d_6) 1.07 (3H, s), 1.21 (3H, s), 1.76 (3H, s), 3.52 (2H, d, *J* 7.0), 4.01 (1H, s), 5.79 (1H, dt, *J* 14.5, 7.0), 6.03 (1H, d, *J* 11.5), 6.20–6.33 (3H, m), 6.48 (1H, dd, *J* 14.0, 11.5), 6.83 (1H, s), 6.95 (1H, br s), 8.00 (1H, s); δ_C (100 MHz, $CDCl_3$) 13.5, 21.8, 25.8, 29.0, 45.1, 83.9, 122.7, 127.6, 128.2, 129.0, 132.5, 133.6, 138.0, 150.6, 150.6, 180.8; δ_C (100 MHz, acetone-d_6) 13.3, 22.5, 25.6, 29 (masked by solvent peak), 45.6, 83.9, 122.7, 128.4, 128.7, 129.1, 132.7, 134.2, 140.1, 151.2, 151.8, 180.6; *m/z* (EI) 290 (M^+, 2), 204 (29), 87 (100) [Found (EI): M^+, 290.1631; $C_{16}H_{22}N_2O_3$ requires M, 290.1630, 0.2 ppm error]. This data was consistent with the (sparse) data available in the literature.[10]

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29. These model studies were based on the following transformation:

I

The *R*- and *S*- enantiomers of **I** were separated using HPLC with a Daicel Chiralcel OD column, eluting with 9:1 hexane–isopropanol. Variation of solvent, stoichiometry of reagents, times and temperatures gave ee's in the range 53–84% (with yields generally in the 80–90% range). The optimum ee was obtained using the L-valine-derived oxazaborolidinone **25a** (84% ee) but the L-phenylalanine-derived oxazaborolidinone **25b** was also effective giving **I** in 82% ee.
30. Copper thiophene carboxylate-induced coupling (Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748–2749) was investigated to avoid the presence of palladium. However, this procedure gave triene **27** in only 20% yield with complete isomerisation.
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I (R = Me, H) **II**

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