Progress in the total synthesis of inthomycins

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Abstract

The inthomycin family of antibiotics, isolated from Streptomyces strains, are interesting molecules for synthesis due to their characteristic common oxazole polyene chiral allylic β-hydroxycarbonyl fragments and significant biological activities. The full structural motif of the inthomycins is found in several more complex natural products including the oxazolomycins, 16-methyloxazolomycin, curromycins A and B, and KSM-2690. This review summarises the application of various efforts towards the synthesis of inthomycins and their analogues systematically.

Introduction

Inthomycins, alternatively known as phthoxazolins, are a class of compounds in which a methylene-interrupted oxazolyltriene unit is conjugated to a chiral β-hydroxycarbonyl center of an amide functionality. Inthomycin A ((+)-1), the first member of the inthomycin family, was isolated by Omura’s group from the strain of Streptomyces sp. OM-5714 in 1990 [1]. Then, the following year, Henkel and Zeek had reported the reisolation of inthomycin A ((+)-1) and the first isolation of inthomycin B ((+)-2) from the strain of Streptomyces sp. Gō 2, and proved inthomycin A ((+)-1) to be identical with phthoxazolin A ((+)-1) [2]. Later, the reisolation of inthomycin B ((+)-2) and inthomycin C ((−)-3) was reported by Omura’s group in 1995 [3]. Inthomycin A ((+)-1) displays moderate antifungal activity against cellulose-containing Phytophthora parasitica and Phytophthora capsici [4]. Inthomycins were reported to possess many interesting biological properties, which include the specific inhibition of the cellular biosynthesis [1,4], in vitro antimicrobial activity [4,5], and anticancer activity against human prostate cancer cell lines [6,7]. A recent study suggested that the close analogue (+)-11 of inthomycin C was found to exhibit proteasome inhibition activity [8]. The skeletal structures of inthomycins A–C (1–3) are embodied in several other naturally occurring compounds, such as neoazolomycin (4), oxazolomycins A–C (5–6) [9-14], curromycins (7) [15], and KSM-2690 (8) [16] (Figure 1). Owing to their various biological activities and characteristic closely related structural motifs, they have generated immense interest among the chemists. Over the past two decades, a wide variety of synthetic strategies have been dedicated towards the synthesis of the inthomycin class of antibiotics. An earlier report on the total synthesis of oxazolomycins provides an overview of the author’s synthetic efforts toward neoazolomycin (4), oxazolomycin A (5a), and...
related antibiotics [17]. The recent review of Lee has mainly focused on the application of copper(I) salt and fluoride-promoted Stille coupling reactions in the synthesis of bioactive molecules including inthomycins A–C (1–3) [18]. The present review provides a systematic summary of synthetic strategies for the synthesis of inthomycins and their analogues over the period of 1999 to present.

**Review**

**Synthesis**

Undoubtedly, the unique skeleton of inthomycins has acted as an inspiration for the development of new synthetic methodologies. Many methods have been developed for the synthesis of inthomycins since their first isolation in 1990 [1]. Most of the reported methods have been directed towards inthomycin C (3) due to its thermodynamically more favored 4,6,8,E,E,E-triene system. The regiochemical issues of installing the conjugated triene system, which is susceptible to cis–trans isomerization, have been longstanding problems in the area of inthomycins. The problems are more acute for the construction of enantioenriched β-hydroxycarbonyl units as evident from the recent reports [19-21]. Since the pioneering works of Henaff and Whiting [19,20], several racemic and asymmetric total syntheses of inthomycins A–C (1–3) have been carried out in many
research groups (Figure 2). However, only four synthetic strategies that lead to the total synthesis of all three members of inthomycins A–C (1–3) are available (Figure 2, route b, d, h, and i) [21-24].

The first racemic synthesis of inthomycin A ((rac)-1), alternatively known as phthoxazolin A, was reported in 1999 [19]. The key steps include i) the synthesis of intermediate dienyl iodide (rac)-20, ii) the synthesis of intermediate oxazole vinylstannane 24, and iii) the Stille coupling between oxazole vinylstannane 24 and dienyl iodide (rac)-20 as the final step. The synthesis began with alcohol (Z)-15a, which was readily prepared in 65% yield from propargyl alcohol (14) by using a copper(I)-catalyzed methyl Grignard addition followed by in situ iodinolysis. The Swern oxidation of (Z)-15a followed by immediate aldol condensation afforded racemic phenol ester (rac)-17 via aldehyde 16. However, several attempts to form enantioenriched aldol fragment 18 using both a chiral auxiliary [25-28] and catalytic asymmetric [29,30] procedures proceeded without success. Therefore, the synthesis of inthomycin A was advanced in the racemic form. Treatment of compound (rac)-17 with aqueous ammonia gave the corresponding amide (rac)-18 in 96% yield. Heck coupling between (rac)-18 and vinylboronate pinacol ester [31] using Pd(PPh3)4/Et3N conditions provided stereoselective access to dienylboronate (rac)-19a in 43% yield. A competitive Suzuki coupling was also observed with compound (rac)-19b being isolated in 35% yield [32-35]. Dienylboronate (rac)-19a was then transformed into dienyl iodide (rac)-20 by iodine monochloride addition and methoxide-mediated elimination (Scheme 1) [35]. The oxazole vinylstannane 24 was pre-

![Figure 2: Syntheses of inthomycins A–C (1–3).](image-url)
Scheme 1: The first total synthesis of racemic inthomycin A (rac)-1 by Whiting.

pared from commercially available butyne 21. The tri-n-butyltin hydride addition to 21, followed by Swern oxidation and direct oxazole formation with tosylmethyl isocyanide (TosMIC) gave the fragment 24, which was used immediately for the next step due to its high instability. Finally, the Stille cross-coupling reaction between vinylstannane 24 and dienyl iodide (rac)-20 using PdCl$_2$(CN)$_2$ and triethylamine in DMF produced racemic inthomycin A (or phthoxazolin A) (rac)-1 in 22% yield (Scheme 1).

Although the overall yield of this route was very low, this work certainly established the basis for the future enantioselective syntheses of inthomycins and related natural products.

In 2002, Moloney et al. described an efficient synthetic route using the Stille coupling reaction as the key step to accomplish the synthesis of phenyl analogues of inthomycins [36]. These triene moieties are a sub-unit of the oxazolomycin class of antibiotics. To prepare the phenyl analogue of racemic inthomycin C (rac-3), at first, the phosphonate 28 was prepared using a Claisen condensation of ethyl propionate (25) followed by methylation of 26a, treatment with bromine in acetic acid, and then triethyl phosphate. Next, compound 28 was treated with sodium hydride followed by aldehyde 29 [37] to give \((E,E)\)-dienyl stannane 30 in 50% yield. The key Stille coupling between 30 and vinyl iodide 31, prepared by Takai reaction [38] of phenylacetaldehyde, in presence of PdCl$_2$(MeCN)$_2$ produced \((E,E,E)\)-
triphenylene 32 in 84% yield. Finally, NaBH₄ reduction of 32 gave alcohol (rac)-13, in which the triene moiety is analogous to inthomycin C ((rac)-3) and oxazolomycin B (5b) (Scheme 2).

After the successful application of the Stille reaction to construct the (E,E,E)-triene system (rac)-13 in a stereoselective manner, attention was then focused on the development of an analogous strategy towards the (Z,Z,E)- and (Z,E,E)-triene systems present in oxazolomycin A (5a) and oxazolomycin C (5c), respectively. The key steps were i) synthesis of dienyl halides, ii) synthesis of the required vinylstannane and iii) Stille coupling between them (Scheme 3) [39]. The required divinyl halides 36 were prepared, starting from phenylacetaldehyde (33), by using the Takai [38] or Wittig procedures [40] as shown in Scheme 3 (68% of a 3.3:1 mixture of (E,E)/Z,E)-36b and 69% yield of a 8:1 mixture of (Z,E)/(E,E)-36a, respectively). Aldehyde 35 was then converted into dibromide 37 using PPh₃/CBr₄ followed by stereoselective palladium-catalyzed monoreduction according to the literature available protocol [41] to give vinyl bromide 38 in 76% yield (Z/E as 99:1 mixture). Iodide 15a [42] was prepared stereoselectively from propargyl alcohol following the literature procedure, and the free hydroxy group was then protected as its TBDMS ether to produce 39 in 99% yield.

The metal–halogen exchange of 39 followed by the Bu₃SnCl quench in Et₂O gave the desired stannane 40 in excellent yield (90%). Deprotection of the TBDMS ether of stannane 40 with tetra-n-butylammonium fluoride (TBAF) in THF and then subsequent Swern oxidation of the crude alcohol gave aldehyde 41 in 71% yield. The aldehyde 41 was treated with ethyl isobutyrate (42) in the presence of LDA to afford the aldol adduct (Z)-(rac)-43 in the racemic form (92% yield). The stannane (Z)-( rac-43) was then subjected to Stille coupling with iodide (E,E)-36b (3:1 mixture of stereoisomers, 3 equiv) using Pd(CH₂CN)₂Cl₂/DMF conditions to produce a 3:1 mixture of (Z,Z,E):(Z,E,E) triene products (rac)-12a and (rac)-12c in 72% yield after 10 h reaction time. After optimization, it was found that the above product ratio changed to 1:1 when the reaction was allowed to run for 24 h and only 1.3 equiv of (E,E)-36b was employed in the Stille coupling. In a similar manner, stannane (Z)-43 coupled with (Z,E)-iodide 36a (8:1 ratio of isomers, 1.3 equiv) to produce a 1:2:1 mixture of (Z,Z,E):(Z,E,E) triene products (rac)-12a and (rac)-12c in 74% yield. The stereoisomers (rac)-12a and (rac)-12c were found to be inseparable by chromatography. The isomerically pure bromide (Z)-38 was found to be inert to coupling with vinylstannane (rac)-43 under standard Stille conditions. Hydrolysis of a mixture (3:1) of (rac)-12a and (rac)-12c produced a mixture (3:1) of the corresponding acids (rac)-12b and (rac)-12d in 70% yield (Scheme 3). These trienes are analogues of oxazolomycins A (5a) and C (5c) and inthomycins A (rac-1) and B (rac-2), respectively.

In 2006, R. J. K. Taylor and co-workers reported the first total synthesis of inthomycin B ((+)-2) using a Stille coupling of a stannyl-diene with an oxazole vinyl iodide unit followed by a Kiyooka ketene acetal/amino acid-derived oxazaborolidinone.

Scheme 2: Moloney’s synthesis of the phenyl analogue of inthomycin C ((rac)-3).
procedure as its cornerstones (Scheme 4) [43]. In the beginning, oxazole 45 was prepared in good yield (86%) by treating ethyl glyoxylate with tosyl methyl isocyanate (TosMIC) in the presence of K$_2$CO$_3$ at 80 °C [44]. The reduction of the ethyl ester of 45 followed by NBS treatment gave unstable bromide 46 [45], which was immediately coupled to (E)-1,2-bis(tri-$n$-butylstannyl)ethene (47) using catalytic Pd$_2$dba$_3$ in refluxing THF to produce iodide 48 in 46% yield. The coupling partner (Z,E)-(+)–54 was prepared enatioselectively from the known (E)-3-(tributylstannyl)propenal (49) [46] using a four-step sequence. Treatment of 49 with the Still–Gennari bis-trifluoroethoxy phosphonate reagent 50 proceeded stereoselectively to give ester 51 in excellent yield (94%). Subsequent DIBAL-H reduction of ester 51 followed by tetrapropylammonium perruthenate (TPAP) oxidation afforded aldehyde (Z,E)-(+)–52 as a single isomer in 83% yield over two steps. The asymmetric aldol reaction aldehyde (Z,E)-(+)–52 with silyl ketene acetal 53 in the presence of oxazaborolidinone derived from N-tosyl-ʟ-valine and BH$_3$·THF generated the desired alcohol (Z,E,E)-(+)–54 in 74% yield and 64% ee. Next, a wide range of catalysts/conditions were screened for the crucial Stille coupling between iodide 48 and (Z,E)-(+)–54 to overcome the problems of isomerization of the (Z,E,E)-triene unit of the desired products. Finally, PdCl$_2$(MeCN)$_2$ (1 mol %) in DMF was found to smoothly deliver the required triene (+)–55 in quantitative yield. After many unsuccessful attempts of direct conversion of methyl ester (+)–55 into the corresponding primary amide, acetylation of acid 56a followed by acid chloride formation of acetate 56b and in situ ammonium hydroxide treatment was found to be fruitful to produce inthomycin B (+)–2 in reason-

![Scheme 3: Moloney's synthesis of phenyl analogues of inthomycins A (rac-1) and B (rac-2).](image-url)
able yield (Scheme 4). This synthetic route introduced the chiral entry to any member of the inthomycin family for the first time.

In 2008, R. J. K. Taylor and co-workers described a unified synthetic route to the inthomycin family [21]. The developed procedure has been utilized successfully to prepare racemic inthomycin A ((rac)-1) and inthomycin C ((+)-3) (Scheme 5 and Scheme 6). The previously reported procedure [20,45] was modified to improve the yield of inthomycin A ((rac)-1) by replacing the Stille coupling partners. The required (Z, Z)-3-(tributylstannyl)propenal (57) was easily accomplished by LiAlH₄ reduction of propargyl alcohol (14) and then transmetallation with Bu₃SnCl followed by oxidation of the resulting alcohol using the Ley-Griffith TPAP procedure [47,48]. Treatment of aldehyde 57 with the Ando phenoxy phosphonate 58a [49] gave the desired (Z, Z)-diene 59 as the major product (59/60 = 87:13).

DIBAL-H reduction of 59 allowed the isolation of (Z, Z)-isomeric alcohol followed by subsequent oxidation produced aldehyde (Z, Z)-61. After extensive unsuccessful efforts to produce enantiopure aldol fragment (Z, Z)-62 using the N-tosyl-L-valine-derived oxazaborolidinone, the racemic synthesis of (Z, Z)-(rac)-62 was achieved by utilizing the lithium enolate of methyl isobutyrate. Stille coupling of (Z, Z)-(rac)-62 with vinyl iodide 48 in the presence of Pd(CH₂CN)₂Cl₂ in DMF proceeded smoothly to give the corresponding ester (triene isomerization was less than 20% during coupling), which was then converted into acid derivative (rac)-63 by saponification. Finally, the acid derivative (rac)-63 was subjected to undergo acetylation, acid...
Scheme 5: R. J. K. Taylor’s total synthesis of racemic inthomycin A (rac)-1.

chloride formation, and quenching with ammonium hydroxide to produce amide derivative (rac)-64 in 70% yield. Finally, saponification of acetate (rac)-64 using lithium hydroxide gave racemic inthomycin A (rac)-1 in 14% overall yield (Scheme 5).

The total synthesis of inthomycin C ((+)-3) was achieved by using a Stille coupling between (E,E)-67 and vinyl iodide 48 followed by directed asymmetric aldol reaction under Mukaiyama–Kiyooka aldol reaction conditions (Scheme 6). Initially, (E)-3-(tributylstannyl)propenal (65) was converted into (E,E)-diene 66 (E/Z = 19:1, separable) using the standard (E)-selective Horner–Wadsworth–Emmons (HWE) reaction. DIBAL-H reduction of ester 66 followed by MnO₂ oxidation produced aldehyde (E,E)-67 stereoselectively. Unfortunately, attempted enantioselective aldol reactions of (E,E)-67 with silylketene acetal 53 using N-tosyl-l-valine-derived oxazaborolidinone 68 gave a negligible amount of the required dienylstan-
nane (E,E)-69 with a significant amount of destannylation product 70. The destannylation process could not be prevented even after a range of reaction conditions were tested. Thus, this approach was revised and the key Stille coupling was carried out before the introduction of the asymmetric aldol fragment (Scheme 6). Therefore, the key Stille coupling of aldehyde (E,E)-67 with vinyl iodide 48 in the presence of PdCl₂(CH₃CN)₂ gave (E,E,E)-trienal 71 in 74% yield. The trienal 71 underwent asymmetric aldol reaction in the presence of oxazaborolidinone derivative 68 and silyl ketene acetal 53 to produce the required α-hydroxy ester (+)-11 in 50% yield and 76% ee ((R)-stereochemistry of the major enantiomer). A competitive reduction of 71 was also observed to produce alcohol 72 in 43% yield. Finally, hydrolysis of the ester (+)-11 followed by hexafluorophosphate azabenzotriazole tetramethyl uranium (HATU)-mediated coupling with ammonia gave inthomycin C ((+)-3) in 33% yield, containing inseparable tetracyclolurea as byproduct (ca. 20%).
In 2010, Senapati, Ryu et al. [50] described the first total synthesis of naturally occurring inthomycin C ((−)-3) in excellent yield and enantiopurity by employing a cationic oxazaborolidinium-catalyzed asymmetric Mukaiyama aldol reaction and Stille coupling as the key steps (Scheme 7). Treatment of compound 75 with tetra-n-butylammonium fluoride (TBAF) in THF at −78 °C and the resulting solution was carefully allowed to warm to 0 °C to give the desired alcohol ((E,E)-69) in 86% yield and 93% ee with only trace amounts of the corresponding destannylated product, a major disadvantage of R. J. K. Taylor’s synthesis of (+)-inthomycin C, ((+)-3, see Scheme 6, compound 70) [21]. Next, the key Stille coupling reaction of dienylstannane ((E,E)-69) with oxazole vinyl iodide 48 using Pd(PPh$_3$)$_4$/CsF/Cul conditions [51,52] gave ester (+)-11 in 85% yield. The ester (+)-11 was then hydrolyzed with lithium hydroxide to give the corresponding acid (+)-73 in 90% yield. The transformation of acid (+)-73 to acetate (+)-76 using acetic anhydride in pyridine followed by acid activation with oxalyl chloride and then in situ treatment with 28% ammonium hydroxide afforded amide (−)-77 in 90% yield. Finally, deacetylation of (−)-77 using lithium hydroxide produced (−)-inthomycin C (−)-3 in 80% yield with high enantiopurity (Scheme 7).

In 2012, Hatakeyama and co-workers reported a unified strategy for the asymmetric total syntheses of inthomycin A (++-1), inthomycin B (+-2), and inthomycin C ((−)-3), starting with an organocatalytic asymmetric [2+2] cycloaddi-
Scheme 7: The first total synthesis of naturally occurring inthomycin C ((–)-3) by Ryu et al.

The vinyl iodide (Z,Z)-(+)–84 was coupled to stannane 24, using the Mee–Lee–Baldwin (MLB) protocol [51, 52], to afford (+)-86. Finally, removal of TBS protection followed by functional group modifications, compound (+)-86 was transformed into inthomycin A ((+)-1). Similarly, the coupling between vinyl iodide 85a and stannane 24 produced triene (+)-88. Subsequently, compound (+)-55 was transformed into inthomycin B ((+)-2, Scheme 9).

For the synthesis of inthomycin C ((–)-3), Hatakeyama et al. prepared (E)-aldehyde 78 starting from propargyl alcohol 14 via (E)-iodo alcohol 15a. The β-lactone (+)-79a was converted to enantioenriched vinyl iodides (+)-84 and 85a separately. Thus, methanolation of (+)-79a provided (–)-80a which was methylated using methyl iodide and lithium disopropylamide (LDA) to produce (–)-81a in 84% yield. Desilylation of (–)-81a followed by tert-butyl(dimethyl)silyl (TBS) protection of (–)-82a gave ester (+)-83. Compound (+)-83 was converted to (Z,Z)-(+)–84 by using iodination and a diimide reduction as reported previously [56]. Similarly, the treatment of (–)-83 with in situ-generated Schwartz’s reagent from zirconocene dichloride and DIBAL-H followed by iodine to produce an inseparable 6:1 mixture of (Z,E)-iododiene 85a and its 6-iodo-isomer 85b in 82% yield (Scheme 8).

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For the synthesis of inthomycin C ((–)-3), Hatakeyama et al. prepared (E)-aldehyde 78 starting from propargyl alcohol 14 via (E)-iodo alcohol 15b. Treatment of (E)-78 with propionyl chloride, LiClO4, and diisopropylethylamine in the presence of quinidine TMS ether (TMSQD) according to Nelson’s procedures [53-55] provided the enantioenriched β-lactone (–)-79b in 85% yield. The desired terminal acetylene (–)-82b was synthesized from β-lactone (–)-79b following a three-step sequence as shown in Scheme 10. Subsequent stannylation followed by iodination converted compound (–)-82b to an inseparable 7:1 mixture of (E,E)-iododiene (+)-89a, and its 6-iodo isomer 89b in
Scheme 8: Preparation of $E,E$-iododiene (+)-84 and $Z,E$-iododiene 85a.

Scheme 9: Hatakeyama's total synthesis of inthomycin A (+)-1 and inthomycin B (+)-2.
Scheme 10: Hatakeyama’s total synthesis of inthomycin C ((–)−3).
Scheme 11: Maulide’s formal synthesis of racemic inthomycin C ((rac)-3).
Hale’s synthesis of dienylstannane (+)-69 and enyne (+)-82b intermediates.

Smoothly converted into a 5.9:1 mixture of inthomycin C ((+)\(-3\)) and another isomer via a three-step sequence (Scheme 13).

Unfortunately, further purification of (+)-3 could not be achieved at the end and the [\(\alpha\)]D value obtained for the 5.9:1 mixture of inthomycin C ((+)\(-3\)) was \(-8.4\) (c 1.0, CHCl\(_3\)). The observed [\(\alpha\)]D value was lower in magnitude compared to that of Ryu’s [50] and Hatakeyama’s synthesis [22] and opposite in sign with R. J. K. Taylor’s synthesis [21]. On the other hand, the specific rotation value of the newly synthesized fragment (+)-82b (see Scheme 12) had a similar magnitude but opposite in sign to that reported by Hatakeyama previously [22]. Thus, the absolute stereochemical assignment of enyne (+)-82b was revised as (3R), which contradicted Hatakeyama’s postulated (3S) configuration of enyne (−)-82b (Scheme 10) [22]. Hence, this new total synthesis has claimed to reinstate the originally formulated Zeeck–Taylor (3R)-stereostructure [2,21] for inthomycin C (+)-3, R. J. K. Taylor’s total synthesis (Scheme 6) and disputes Ryu and Hatakeyama’s (3S)-stereocchemical revision of inthomycin C (+)-3 (See Scheme 7 and Scheme 10).
Soon after, a subsequent collaboration between the Hale and Hatakeyama groups demonstrated that inthomycin C ((+)-3) has (3R)- and not (3S)-stereochemistry [57]. Careful reappraisal of the previously published work [21,22,50,60] now strongly recommends that the R. J. K. Taylor, Ryu, Hatakeyama, and Hale teams all have synthesized (3R)-inthomycin C ((+)-3), despite their discrepant $\alpha_D$ values. All the disputes and anomalies regarding the specific rotation values of the common intermediate 82b and the synthetic (3R)-inthomycin C described by Hale and others were finally resolved in this work. Subsequently, the Hatakeyama team converted their authentic (+)-82 into the (R)- and (S)-MTPA Mosher esters which provided well-matched NMR data to Hale’s previous synthesis [60]. Upon further purification using flash chromatography, the Hatakeyama team re-examined their $\alpha_D$ data for the authentic (3R)-enynol 82b which had been stored in their laboratory and it was found that (3R)-82b had a $\alpha_D$ of +12.2 (c 0.95, CHCl$_3$). This specific rotation was well consistent with the +12.6 (c 0.71, CHCl$_3$) value as reported by the Hale group previously for (3R)-inthomycin C ((–)−3) (Scheme 14). Although this new value was much lower in magnitude compared to previous reports (−41.5 (c 0.1, CHCl$_3$)) [22] by the same group, it was much closer to Hale’s report [60] for a 5.9:1 mixture of inthomycin C (−8.4 (c 1.0, CHCl$_3$)) (see Scheme 13). Meanwhile, the Hale group transformed the resynthesized inthomycin C ((–)−3) into the corresponding (R)- and (S)-MTPA ester derivatives 106 and 107, respectively (Scheme 14). Based on the corrected specific rotation value of inthomycin C ((−)-3) and re-investigation of their (R)- and (S)-MTPA esters, Hale and Hatakeyama jointly concluded that Ryu and others had indeed synthesized (3R)-inthomycin C ((+)−3).

Two years later, Reddy and co-workers accomplished enantioselective formal syntheses of both inthomycins C ((+)−3) and inthomycin C ((−)-3) using Hatakeyama’s enynol intermediate 82b (Scheme 15) [66]. The synthesis commenced with the benzylation of (R)-pantolactone 108a to produce (+)-109a in 85% yield. Next, treatment of (+)-109a with $N,O$-dimethylhydroxylamine hydrochloride, and an excess of MeMgBr followed by immediate TBS ether formation produced (+)-110a in 82% yield over 2 steps. Wittig olefination of (+)-110a with phosphonate 111 furnished the desired (E)-(+)−112a, which was then converted into Hatakeyama’s enynol (−)-82b using a four-step sequence to complete the formal synthesis of inthomycin C ((−)-3). The spectroscopic data as well as the $\alpha_D$ value of the present compound (−)-82b were well-matched with that published previously [22,60]. Similarly, (S)-pantolactone 108b was transformed into enyl (−)-82b by following the same procedures as described for (−)-82b to accomplish the formal synthesis of inthomycin C ((−)-3).
In 2018, Donohoe et al. demonstrated a tin-free, short and efficient total synthesis of inthomycin C (−)-3 by comprising the three key steps of C–C bond-forming reactions: i) a vinylogous Mukaiyama aldol reaction, ii) an olefin cross-metathesis reaction, and iii) an asymmetric Mukaiyama–Kiyooka aldol reaction (Scheme 16 and Scheme 17) [8]. The total synthesis was initiated with the preparation of two alkenes precursors (rac)-118 and 121. The tiglic aldehyde 115 was converted into silyl
enol ether 116 followed by treatment with acetal 117 using a vinylogous Mukaiyama aldol reaction to produce the desired aldehyde (rac)-118 in 81% yield. Meanwhile, the TIPS protection of oxazole 119 and then subsequent lithiation at the C-5 position and quenching in situ with allyl bromide furnished oxazole derivative 121 in 90% yield (Scheme 16).

An attempted cross-metathesis reaction of 121 with alkene fragment (rac)-118 in the presence of Grubbs II (G-II) catalyst under optimized conditions produced (rac)-122 in 57% yield. After exhaustive experimentation, demethoxylation of (rac)-122 was achieved to produce (E,E,E)-aldehyde 123 predominantly in an 8:1 mixture of diastereoisomers. Then, the key aldol reac-
tion of 123 with silyl enol ether 53 under optimized Mukaiyama–Kiyooka conditions, followed by TIPS deprotection, afforded adduct (3R)-(+)-11 in 63% yield and with 94% ee. Ester hydrolysis followed by acetylation of (3R)-(+)-11 produced acid derivative (+)-76 [50] in 87% yield. Finally, compound (+)-76 underwent amidation and deacetylation to give an 11:1:1 mixture of geometrical isomers of inthomycin C ((−)-3) in 77% yield over two steps (Scheme 17) [50]. The (3R) stereochemistry of (−)-3 was confirmed by MTPA ester derivatization, which supports the recent work by Hale and Hatakeyama [57].

Recently, Burton’s group developed some efficient and tin-free total syntheses of all three inthomycins A–C ((+)-1, (+)-2, and (−)-3) using a Suzuki or Sonogashira cross-coupling of the (E)- or (Z)-alkenyl iodides 130 with the dienylboronic ester 128 as key step (Schemes 18–22). Initially, (E)-pent-2-en-4-yn-1-ol (124) was smoothly converted into the desired bromide derivative 125 [67] in two simple steps. The bromide 125 was then reacted with pre-lithiated oxazole derivative 120 [68,69] under optimized conditions to produce coupled product 126. The selective deprotection of the TMS group of 126 was found to be extremely challenging. The commonly used conditions provided the allene as a major product instead of the desired product. Ultimately, the mono-desilylated product 127 was obtained in 85% yield by using sodium sulfide in a mixture of THF and water. Next, the zirconium-catalyzed hydroboration of the terminal acetylene in 127 gave (E,E)-128 in good yield and with complete stereocontrol (Scheme 18).

To accomplish the key Suzuki coupling of dienylboronic ester 128, the necessary alkynyl iodides (Z)- and (E)-130 were prepared from the propargyl alcohol (14) in good yields using a four-step sequence such as Negishi’s (Z) and (E)-stereoselective isomerization of the terminal alkyne followed by iodinolysis [19,70,71], oxidation to the corresponding aldehydes and enantioselective Kiyooka–Mukaiyama aldol reaction followed by TES protection of the resulting alcohols (Scheme 19).

For the synthesis of inthomycin B ((+)-2), a Suzuki coupling reaction between (E,E)-128 and (Z)-(+)-130a was performed in the presence of palladium(II) acetate, triphenylphosphine, and aqueous sodium carbonate to give (E,E,Z)-triene (+)-131 selectively in 64% yield. Treatment of triene (+)-131 with HF·pyridine in acetonitrile [22] gave double silyl deprotected triene (+)-132 which was then converted into inthomycin B ((+)-2) via aminolysis of the corresponding pentafluorophenyl ester (+)-133. The synthetic inthomycin B ((+)-2) showed well-matched spectroscopic properties with that of both natural and synthetic inthomycin B (Scheme 20) [2,22,43].

For the synthesis of inthomycin C ((−)-3), the Suzuki coupling between the dienylboronate (E,E)-128 and the (E)-(−)-130b was carried out under optimized conditions to produce the (E,E,E)-triene derivative (+)-134 in 65% yield (Scheme 21). Then, compound (+)-134 was converted smoothly into inthomycin C ((−)-3) by following the similar sequence of reactions as described for the synthesis of inthomycin B ((+)-2, see Scheme 20).

Having been successful in the synthesis of inthomycins B ((+)-2) and C ((−)-3), a significant effort was given to the synthesis of inthomycin A ((−)-1). In the beginning, conversion of enyne 127 to the corresponding (Z,E)-dienylboronic ester 128 was investigated in the presence of rhodium(I)-catalyzed anti-selective hydroboration [72] under several conditions. Unfortunately, the yield of the desired (Z,E)-128 was found to be poor (<40%). Therefore, enyne 127 was selected as a coupling reagent for the Suzuki coupling reaction. The synthesis of inthomycin A ((−)-1) was achieved by following the established methodology (Scheme 22).

Scheme 18: Synthesis of dienylboronic ester (E,E)-128.
partner for the key Sonogashira reaction of alkenyl iodide (Z)-(+)\textsuperscript{130a} to construct the required (Z,Z,E)-triene for completion of the inthomycin A ((+)\textsuperscript{1} synthesis. Fortunately, the alkenyl iodide (Z)-(+)\textsuperscript{130a} coupled smoothly with enyne \textsuperscript{127} in the presence of Pd(PPh\textsubscript{3})\textsubscript{4}, Cu, and triethylamine to give (+)-(+)\textsuperscript{135} in 62% yield. The double desilylation of compound (+)-(+)\textsuperscript{135} using HF-pyridine in acetonitrile afforded (–)-\textsuperscript{136} in 91% yield. The semi-hydrogenation of (–)-\textsuperscript{136} to produce the
desired (Z,Z,E)-triene (+)-87 was challenging under a variety of conditions, and eventually, it was achieved by the use of the Zn(Cu/Ag) couple in methanol [73]. Finally, the methyl ester (+)-87 was readily transformed into inthomycin A ((+)-1) via pentafluorophenyl ester (+)-137 by the same reaction sequence as described for inthomycin B ((+)-2) in Scheme 20. In this route, the synthetic inthomycin A ((+)-1) was contaminated with a small amount (<10%) of inthomycin B ((+)-2, Scheme 22).

Very recently, Kim et al. [24] developed a unified strategy to access all the three isomers of inthomycins A–C ((+)-1, (+)-2, and (−)-3) by using a common intermediate (Z)-143a and an oxazole-derived vinylstannane 24 or vinyl iodide 48 (Schemes 23–26). The synthesis started with the preparation of TBS-protected hydroxy pivalic acid 138 [74], following the literature procedure. The acid 138, when submitted to the reaction with oxalyl chloride followed by a CuI-catalyzed nucleophilic alkyne addition of methyl propiolate, provided ynone 139 in 86% yield.

Scheme 21: Burton's total synthesis of inthomycin C ((−)-3).

Scheme 22: Burton's total synthesis of inthomycin A ((+)-1).
over two steps. When compound 139 was treated with (+)-diisopinocampheylchloroborane (DIPCl) [75,76] at room temperature and the resulting mixture was processed as in the usual manner using diethanolamine, the expected alcohol (−)-140 was obtained in 93% ee and 72% yield. Compound (−)-140 was further transformed to the corresponding Mosher’s esters and their NMR and X-ray crystallographic data were well-matched with the (R)-stereostructure of (−)-140 [77,78]. The hydroxy

![Scheme 23: Synthesis of common intermediate (Z)-(−)-143a.](image)

![Scheme 24: Synthesis of (Z)-and (E)-selective fragments (+)-145a–c.](image)
group of (−)-140 was protected as benzoate to give (−)-141 in good yield. Next, the benzoate-protected ynoate (−)-141 was converted into aldehyde (Z)-(+)−143a by employing a copper-catalyzed methylation of the alkyne moiety to the corresponding enoate (Z)-(+)−142 followed by an ester reduction–oxidation sequence using DIBAL-H and TPAP (Scheme 23).

The aldehyde (Z)-(+)−143a was the common intermediate for the synthesis of (E)- or (Z)-selective vinyl boronates or vinyl halides (+)−145 to accomplish total syntheses of all inthomycins A–C ((+)−1, (+)−2 and (−)−3, see Scheme 25 and Scheme 26).

With the key intermediate (Z)-(+)−143a in hand, it was transformed into (E)-vinylboronate (+)−145b in perfect stereoselectivity by using the recently developed boron-Wittig reaction with bis[(pinacolato)boryl]methane (144) [79]. By applying the Corey–Fuchs dibromoolefination and followed by Pd-catalyzed hydrogenolysis under Uenishi’s conditions [80], compound (Z)-(+)−143a delivered the bromodiene (Z,Z)-(+)−145a in good yield and stereoselectivity. Isomerization of (Z)-(+)−143a to (E)-(+)−143b was carried out successfully using sterically hindered base DBU or DABCO. Treatment of (E)-(+)−143b with 144 using the boron-Wittig reaction [79] afforded the desired (E,E)-vinylboronate (E,E)-(+)−145c in 96% yield (Scheme 24).

Scheme 25: Kim’s total synthesis of inthomycins A (+)-1 and B (+)-2.
Followed by the successful access to (Z)- and (E)-selective isomers of (+)-145a-c, further exploration to the incorporation of a triene unit of inthomycins was investigated. The PEPPSI-iPr-catalyzed [58] Stille cross-coupling between vinyl bromide (ZZ)-(+)145a and (E)-vinylstannane 24 [43] proceeded without significant isomerization to give (4Z,6Z,8E)-triene (+)-146a, a subunit of inthomycin A ((+)-1). Meanwhile, the Suzuki–Miyaura coupling of vinylboronate (ZE)-(+)145b with the known (E)-oxazole iodide 48 [43] was performed successfully to afford geometrically pure (4Z,6E,8E)-triene (+)-146b in 85% yield following the synthesis of inthomycin B ((+)-2). Careful deprotection of silyl ether of (+)-146a with HF-pyridine in THF/pyridine delivered alcohol (+)-147a. Next, the Swern oxidation of the resulting alcohol (+)-147a followed by Pinnick oxidation afforded the acid (+)-148a. Finally, the EDCI-mediated amidation of unstable acid (+)-148a followed by debenzoylation produced inthomycin A ((+)-1). Similarly, compound (+)-146b was converted into inthomycin B ((+)-2) (Scheme 25).

To complete the total synthesis of inthomycin C ((−)-3), a cross-coupling between (E,E)-(+)145c and vinyl iodide 48 was carried out to produce (4E,6E,8E)-triene (+)-146c in 82% yield. Utilizing the same sequence as applied to the synthesis of inthomycins A–B from (+)-146a and (+)-146b, respectively (see Scheme 25), the triene (+)-146c was successfully converted into an 8:1 mixture of inthomycin C ((−)-3) and another minor isomer in good overall yield after the final step (Scheme 26). The spectroscopic data and specific rotation values of the three inthomycins A–C ((+)-1, (+)-2, and (−)-3) were consistent with those reported previously [8,23,57]. The absolute configurations of inthomycins A–C ((+)-1, (+)-2, and (−)-3) were reconfirmed as 3R by assigning the (R)-stereocchemical descriptor for the common intermediate (−)-140, which supports the recent work of Hale and Hatakeyama [57].

**Conclusion**

This review highlighted reports on the various synthetic efforts for both the formal and total synthesis of racemic and enantiopure inthomycins A–C (1–3). These compounds have three key structural features: an oxazole ring, a triene system, and an amide moiety with a chiral, hydroxylated carbon at the β-position. These interesting structures accompanied by their promising biological activities and the lack of natural sources have made inthomycins an attractive target in the synthetic organic community to work intensively in this area. The synthesis of simple looking inthomycins is challenging due to the unusually interposed functional groups and isomerizable double bonds in the conjugated triene moiety. Various stereoselective cross-coupling reactions such as Stille, Suzuki, or Sonogashira or

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\text{Scheme 26: Completion of total synthesis of inthomycin C ((−)-3) by Kim.}
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Suzuki–Miyaura have been utilized to construct the geometrically distinctive polyene systems of inthomycins A–C (1–3). The elegant work of R. J. K. Taylor [21,43], Ryu [50], Donohoe [57], and Burton [23] demonstrated the power of the Mukaiyama–Kiyooka aldol reactions to install the asymmetric center of inthomycins. Alternatively, Hatakeyama and Kim’s groups employed an asymmetric β-lactone synthesis and an asymmetric ynone reduction protocol for the construction of the stereogenic center of inthomycins, respectively [22,24]. Despite these recent advances, the development of novel methods for the regio- and stereocontrolled synthesis of inthomycins, inthomycin-embedded natural products, and their synthetic analogues with better biological outcomes is of strategic importance and being continued for further discovery.

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References
1. Omura, S.; Tanaka, Y.; Kanaya, I.; Shinose, M.; Takahashi, Y. J. Antibiot. 1990, 43, 1034–1036. doi:10.1764/antibiotics.43.1034
2. Henkel, T.; Zeek, A. Liebigs Ann. Chem. 1991, 367–373. doi:10.1002/jlac.199119910164
3. Shiomori, K.; Arai, N.; Shinose, M.; Takahashi, Y.; Yoshida, H.; Iwabuchi, J.; Tanaka, Y.; Omura, S. J. Antibiot. 1995, 48, 714–719. doi:10.1764/antibiotics.48.714
4. Tanaka, Y.; Kanaya, I.; Takahashi, Y.; Shinose, M.; Tanaka, H.; Omura, S. J. Antibiot. 1993, 46, 1208–1213. doi:10.1764/antibiotics.46.1208
5. Omura, S. Gene 1992, 115, 141–149. doi:10.1016/0378-1119(92)90552-z
6. Kawada, M.; Inoue, H.; Usami, I.; Ikeda, D. Cancer Sci. 2009, 100, 150–157. doi:10.1111/j.1349-7006.2008.00996.x
7. Kawada, M.; Yoshimoto, Y.; Minamiguchi, K.; Kumagai, H.; Someno, T.; Masuda, T.; Ishizuka, M.; Ikeda, D. Anticancer Res. 2004, 24, 1561–1568.
8. Balcells, S.; Haughey, M. B.; Walker, J. C. L.; Josa-Culleré, L.; Towers, C.; Donohoe, T. J. Org. Lett. 2018, 20, 3583–3586. doi:10.1021/acs.orglett.8b01370
9. Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. Tetrahedron Lett. 1985, 26, 1077–1078. doi:10.1016/s0040-4099(00)88516-2
10. Kawai, S.; Kawabata, G.; Kobayashi, A.; Kawazu, K. Agric. Biol. Chem. 1989, 53, 1127–1133. doi:10.1016/bb1961.53.1127
11. Mori, T.; Takahashi, K.; Kashibabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. Tetrahedron Lett. 1985, 26, 1073–1076. doi:10.1016/s0040-4099(00)88515-0
