

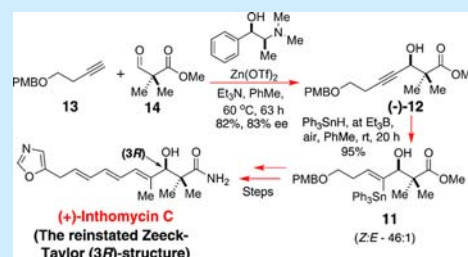
Asymmetric Total Synthesis of (+)-Inthomycin C via O-Directed Free Radical Alkyne Hydrostannation with Ph_3SnH and Catalytic Et_3B : Reinstatement of the Zeeck–Taylor (3*R*)-Structure for (+)-Inthomycin C

Karl J. Hale,* Milosz Grabski, Soraya Manaviazar, and Maciej Maczka

The School of Chemistry and Chemical Engineering and the Centre for Cancer Research and Cell Biology (CCRCB), the Queen's University Belfast, Stranmillis Road, Belfast BT9 5AG, Northern Ireland, United Kingdom

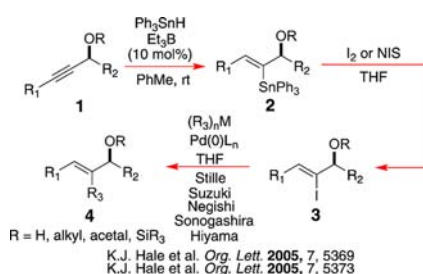
S Supporting Information

ABSTRACT: A new pathway to (+)-inthomycin C is reported that exploits an O-directed free radical hydrostannation reaction on (–)-12 and a Stille cross-coupling as key steps. Significantly, the latter process was effected on 19 where a gauche-pentane repulsive interaction could interfere. Our stereochemical studies on the alkynol (–)-12 and the enyne (+)-7 confirm that Ryu and Hatakeyama's (3*S*)-stereochemical revision of (+)-inthomycin C is invalid and that Zeeck and Taylor's original (3*R*)-stereostructure for (+)-inthomycin C is correct.



Some time ago, our group reported¹ that propargylic oxygenated dialkylacetylenes of general structure 1 (Scheme 1) typically undergo highly regio- and stereo-

Scheme 1. The O-Directed Free Radical Hydrostannation Route to Trisubstituted Alkenes with Three C–C σ -Bonds



controlled O-directed free radical hydrostannation reactions with Ph_3SnH , catalytic Et_3B , and O_2 in PhMe at rt, to give trisubstituted vinyltriphenylstannanes of general structure 2 in good-to-excellent yield. Our work followed up on, and massively augmented, a much earlier report by Willem and Gielen² that 2-methyl-3-pentyn-2-ol undergoes O-directed α -free radical hydrostannation with Ph_3SnH (1 equiv) and Et_3B (1 equiv) in dry PhMe at rt to provide (Z)-2-methyl-3-triphenylstannyl-3-pentene-2-ol, as the sole reaction product in 67% yield. Unfortunately, the latter workers never reported the successful conversion of their vinyltriphenylstannane product into a representative target alkene, and it was left to our group to show that vinyltriphenylstannanes of this sort can efficiently be transformed into target trisubstituted alkenes 4 by I–Sn exchange and transition-metal-catalyzed cross-coupling.³ As a consequence, the O-directed free radical hydrostannation of

dialkylacetylenes with Ph_3SnH and catalytic Et_3B has now become a stereocontrolled olefination method of genuine synthetic worth.^{1,3,4}

As well as providing many sophisticated examples of stereodefined trisubstituted olefin synthesis via this approach,^{1,3} we subsequently went on to employ it for a new and fully stereocontrolled formal total synthesis of the frog alkaloid, (+)-pumiliotoxin B,⁴ by a route which greatly improved and shortened the original pathway⁵ to this molecule. Our (+)-pumiliotoxin B paper⁴ also presented our expanded thoughts on the highly complex mechanism⁶ of this novel hydrostannation reaction, which is not a simple process by any means,⁷ but one that operates through a complex radical mechanism in which there are multiple competing Ph_3Sn radical addition/elimination and vinylstannane isomerization events all occurring concurrently and cooperatively,⁶ with the result that α -triphenylstannylated alkenes of general structure 2 eventually predominate over time.

As part of our group's ongoing effort to further define the synthetic scope and applications⁸ of this new olefination method, we recently became interested in establishing its utility for the creation of chiral trisubstituted allylic alcohols with a β -quaternary carbon center; structural motifs that can be found in the anticancer natural products (+)-inthomycin C⁹ and (+)-acutiphycin¹⁰ (Figure 1). Of course, by employing the O-directed free radical hydrostannation process to create such systems, we naturally recognized that we would be forced to confront the potentially troublesome cross-coupling of an organometallic with an electronically unactivated (Z)-trisubsti-

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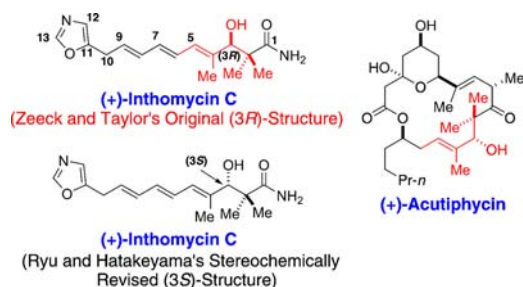


Figure 1. (+)-Inthomycin C and (+)-acutiphycin.

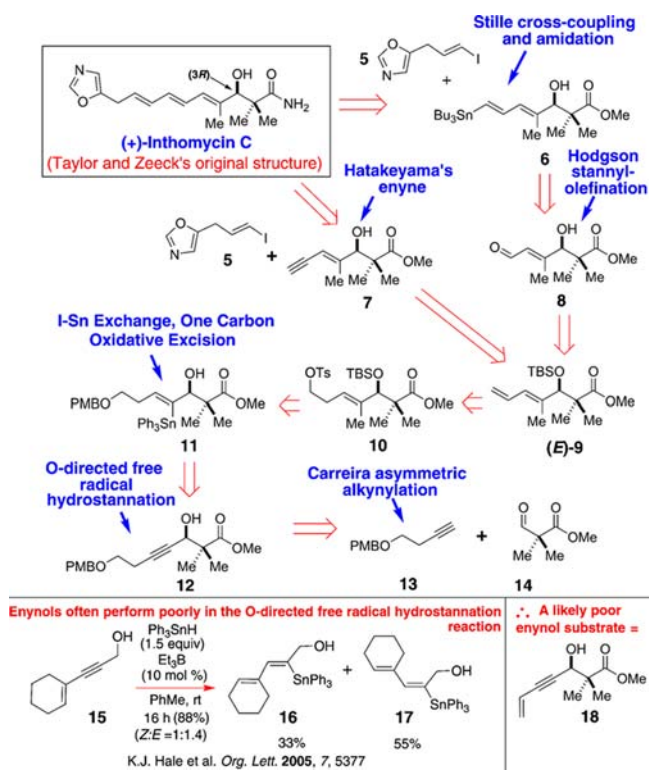
tuted vinyl iodide in which *multiple* gauche-pentane repulsive interactions could potentially thwart the key oxidative addition and reductive elimination steps, reactions for which no prior literature precedent existed, as far as we could tell.

With this in mind, we now present a new and highly successful application of the O-directed free radical alkyne hydrostannylation reaction with Ph_3SnH and catalytic Et_3B in PhMe at rt^1 in the total synthesis of (+)-inthomycin C; an antineoplastic natural product first synthesized by Professor R. J. K. Taylor and his team in 2008,¹¹ and later resynthesized in opposite enantiomeric form by Ryu¹² and Hatakeyama,¹³ by different routes. The latter workers appeared to find a stereochemical flaw in the originally assigned (3R)-stereostructure for (+)-inthomycin C (the Zeek–Taylor structure, as we now term it), revising it to the (3S)-configurational stereoisomer shown in Figure 1, but to us, this stereochemical revision of Ryu¹² and Hatakeyama¹³ looked potentially unsafe, since neither team had unambiguously verified the absolute stereochemistry of the chiral starting materials that they had employed in their respective syntheses.

Our retrosynthetic analysis of the original Zeek–Taylor (3R)-stereoisomer for (+)-inthomycin C is outlined in Scheme 2. It was conceived around the observation that enynols such as **15** generally give rise to poor *Z/E*-selectivity in the O-directed free radical hydrostannylation reaction with Ph_3SnH and catalytic Et_3B in PhMe at rt .⁶ This suggested that we would almost certainly encounter extremely poor stereoselectivity in the hydrostannylation of **18** en route to diene (*E*)-**9** (Scheme 2). Given that we wished for (*E*)-**9** to serve as an advanced intermediate in our proposed route, we thus elected to prepare it from the tosylate **10** by E2 elimination, accessing the latter from the corresponding alcohol, which itself would be obtained from the vinyltriphenylstannane **11**. In turn, **11** would be secured from the O-directed free radical hydrostannylation of **12** with $\text{Ph}_3\text{SnH}/\text{cat. Et}_3\text{B}/\text{O}_2$. We envisioned obtaining the alkynol **12** by asymmetric alkynylation of **14** with alkyne **13**, using Carreira's methodology.¹⁴ Diene (*E*)-**9** would thereafter be taken forward to Ryu's claimed (3R)-dienylstannane **6**¹² and Hatakeyama's postulated (3R)-enyne **7**¹³ to complete formal and eventually full total syntheses of (+)-inthomycin C, assuming that the Zeek–Taylor absolute stereostructure was indeed correct.

Based upon Carreira's stereochemical model for asymmetric alkynylation,¹⁴ for which no violation has yet been reported, we used $\text{Zn}(\text{OTf})_2$ (0.3 equiv), Et_3N (0.93 equiv), and (–)-*N*-methyl ephedrine (0.4 equiv) to mediate the reaction of **13** with **14** in PhMe at 60°C , a process that took just over 2.5 days to reach completion, and which cleanly led to the alkynol (–)-**12** in 82% yield and 83% ee (Scheme 3). The absolute stereochemistry of (–)-**12** was confirmed by Mosher ester configurational analysis,¹⁵ which indicated that the stereo-

Scheme 2. Our Retrosynthetic Planning for (3R)-(+)-Inthomycin C

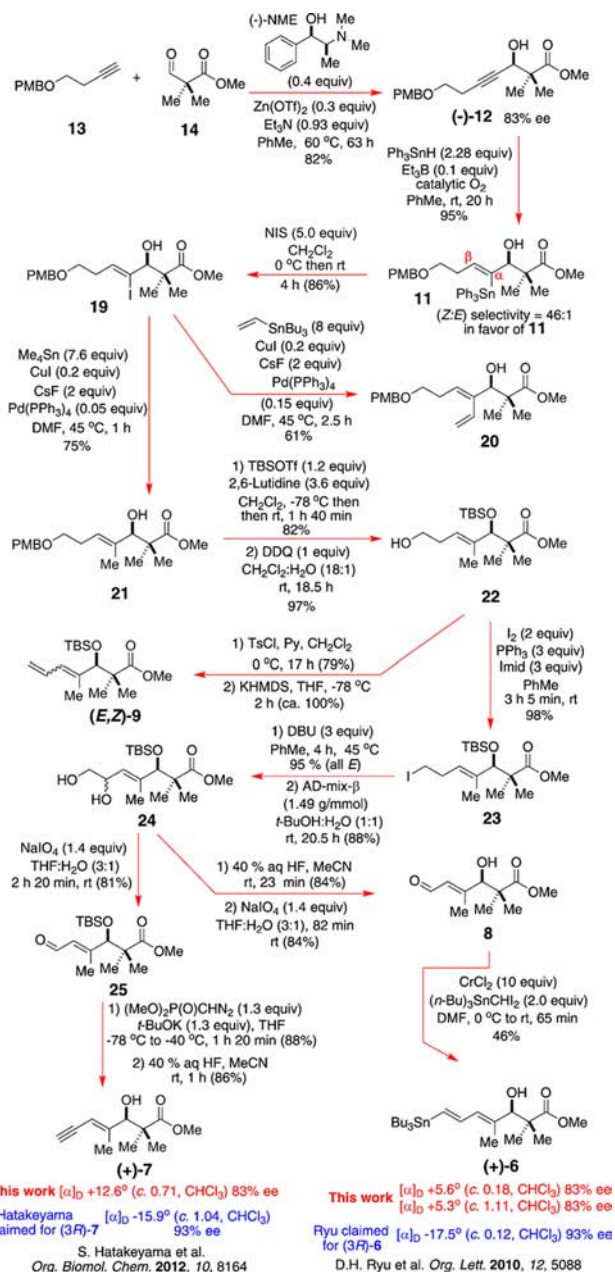


chemical outcome was as depicted, and in complete accord with Carreira's model.¹⁴ Specifically, the resonance from the propargylic methylene of the (*R*)-MTPA ester derived from (–)-**12** was +0.0327 ppm (*ca.* 13.1 Hz) more shielded than that for the corresponding (*S*)-MTPA ester in CDCl_3 which, according to the *modified* Mosher ester configurational mnemonic of Riguer,¹⁵ was strongly indicative of (*R*)-absolute stereochemistry for the C(3)-alcohol in **12** (see the Supporting Information (SI)).

With the stereochemical integrity of **12** duly established, we submitted it to our O-directed free radical hydrostannylation procedure, to obtain **11** as the major component of a 46:1 mixture of (*Z/E*)- α -stannylated geometric isomers in excellent yield (95%). The purified vinylstannane **11** was subsequently reacted with excess *N*-iodosuccinimide (5.0 equiv) in CH_2Cl_2 to give **19** in 86% yield with complete retention of olefin geometry. Next, we examined whether **19** would undergo Stille cross-coupling with Me_4Sn successfully, and eventually we found that it did, as long as Baldwin and Lee's CsF/CuI -promoted conditions¹⁶ were employed with catalytic $\text{Pd}(\text{PPh}_3)_4$ in DMF at 45°C for 1 h. Following due optimization, **21** was eventually procured in 75% yield. Vinyl iodide **19** was also transformed into the diene **20** in 61% yield, to show the wider scope and applicability of the method.

Returning now to the problem at hand, the hydroxyl group of **21** was next protected as a TBS-ether, and the pendant PMB group was detached with DDQ. Initially **22** was O-tosylated under standard conditions to obtain **10** in 79% yield. An E2 elimination was then attempted with KHMDs in THF at -78°C , but this caused scrambling of the trisubstituted olefin geometry, presumably due to the reaction being of the E1cb manifold. Fortunately, this problem could soon be rectified by performing the elimination on the iodide **23** with 1,8-

Scheme 3. Our Formal Synthesis of (+)-Inthomycin C that Intersects with Ryu's Claimed Dienylstannane 6 and the Claimed Enyne 7 of Hatakeyama



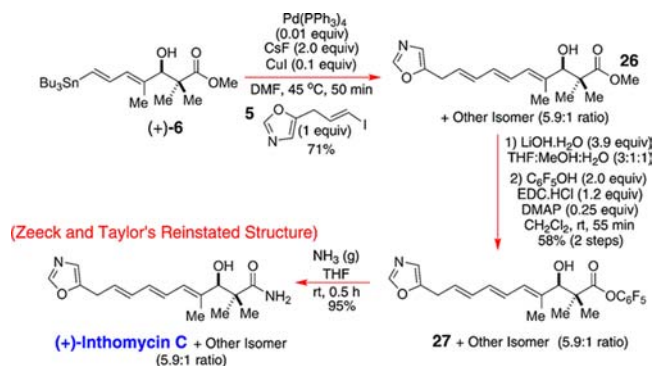
diazabicycloundec-7-ene (DBU) (3 equiv) in PhMe at 45 °C for 3 h. Under these conditions, the classical E2-elimination proceeded cleanly to give the desired (*E*)-diene **9** exclusively in 95% yield.

Because of the significant steric bulk of the TBS-protecting group, it proved possible to perform a very clean and highly regioselective dihydroxylation on (*E*)-**9** with Sharpless' AD-mix- β reagent.¹⁷ It afforded a mixture of stereoisomers **24**, from which the TBS-group could be successfully removed. Thereafter, the resulting triol had its terminal diol cleaved with aqueous NaIO_4 in THF to produce the stereodefined enal **8** in 84% yield. A Hodgson vinylstannation¹⁸ was next performed on **8** to secure Ryu's claimed advanced intermediate **6**, whose $[\alpha]_D$ value was found to be $+5.3^\circ$ (c 1.11 in CHCl_3). Significantly, the NMR spectral values for (+)-**6** correlated well with those

reported by Ryu and co-workers for (–)-**6**,¹² but clearly our $[\alpha]_D$ was of opposite sign and a much lower magnitude than that recorded by Ryu and his team ($[\alpha]_D -17.5^\circ$ (c 0.12 CHCl_3)).¹² Since our previous modified Mosher ester analysis had supported the absolute stereochemical assignment that we had made for the Carreira product **12**, we concluded that (+)-**6** must have (3*R*)-stereochemistry, which meant that we had completed a formal total synthesis of the Zeck–Taylor^{9a,11} stereostructure for (+)-inthomycin C. Ryu and co-workers had clearly prepared the enantiomeric (3*S*)-stereostructure.

However, to help put things beyond any doubt at all, we decided to examine Ryu's reported CsF/CuI-mediated Stille cross-coupling of vinyl iodide **5** with enantiomeric (+)-**6** (Scheme 4).¹²

Scheme 4. Our Reinvestigation of the Ryu Cross-coupling of 5 with (+)-6 and Our New Simplified Endgame for Securing the Total Synthesis of (+)-Inthomycin C



While reasonably efficient in terms of chemical yield, it did not proceed with complete stereocontrol (Scheme 4). Rather, in our hands, it furnished a 5.9:1 mixture of triene stereoisomers, in which the desired product **26** predominated; the precise constitution of this other undesired triene component has yet to be determined, but this loss of stereocontrol was not mentioned by Ryu.¹² Unfortunately, it proved extremely difficult to separate this minor (but still significant) stereoisomer from **26** by multielution preparative TLC, without also encountering *prohibitive* reductions in yield. Indeed, our very best efforts at doing this only managed to produce **26** as the major component of a 17.1:1 mixture with considerable material sacrifice (see the SI for this set of NMR spectra). So, initially, in order to be able to go forward with a satisfactory amount of material, we decided to proceed with a partially separated sample that consisted of approximately a 9:1 mixture of isomers. This was subjected to ester hydrolysis with aqueous LiOH in THF, and the resulting acid was transformed into **27**, whose purity could be further enriched to 9.7:1 in favor of **27** by preparative TLC. Upon treatment with dry NH_3 in THF, the latter was then very smoothly converted into a 9.7:1 mixture of (+)-inthomycin C and another isomer (see the SI for our NMR spectra). Unfortunately, because of the high chemical instability of the inthomycins (a fact already documented by Whiting in his elegant route to (±)-inthomycin A¹⁹), we found that our purified mixture of (+)-inthomycin C and this isomeric triene contaminant (ca. 9.7:1) decomposed within several weeks of storage in the refrigerator under N_2 , before we had the opportunity to record its $[\alpha]_D$ value!

We therefore repeated the Ryu coupling¹² of **5** with (+)-**6** to reobtain the 5.9:1 mixture enriched in **26** (see the SI), and

without separation (to avoid material losses), we duly took this forward through the same reaction sequence in the hope that purification could be effected at the end, by SiO₂ flash chromatography. Unfortunately, it could not, and the $[\alpha]_D$ value that we obtained for the 5.9:1 mixture of (+)-inthomycin C, contaminated with this inseparable stereoisomeric triene component, was -8.4° (c 1.0 CHCl₃ [Lit. for (+)-inthomycin C + 20% tetramethylurea = $+25.9^\circ$ (c 0.27 CHCl₃) (Taylor¹¹); Lit. for pure (–)-inthomycin C reports an $[\alpha]_D = -34.33^\circ$ (c 0.1 CHCl₃) (Ryu¹²) and an $[\alpha]_D = -41.5^\circ$ (c 0.1 CHCl₃) (Hatakeyama¹³)]. We attribute the low negative $[\alpha]_D$ value observed for our final (3R)-(+)-inthomycin C sample to the deleterious presence of this other unidentified triene component, which arises from use of the Ryu cross-coupling method.¹²

Given all of these difficulties and possible ambiguities, we decided to convert diol **24** into Hatakeyama's claimed (–)-inthomycin C intermediate, (–)-**7**¹³ (see Scheme 3), to complete an alternate formal total synthesis,²⁰ and although we did observe an excellent spectral match with the NMR data quoted by Hatakeyama,¹³ we found that the optical rotation of our sample of **7** (prepared in 80–86% ee) was of opposite sign ($[\alpha]_D = +12.6^\circ$ (c 0.71 CHCl₃)) to the value quoted by Hatakeyama in his paper for a molecule of allegedly the same (3R)-absolute stereochemistry [Lit. $[\alpha]_D = -15.09^\circ$ (c 1.04 CHCl₃)¹³]. We therefore prepared the (R)- and (S)-MTPA esters of (+)-**7** and used the modified Mosher method¹⁵ to independently confirm our (3R)-absolute stereochemical assignment (see the SI for more information). The combined $[\alpha]_D$ data for (+)-**6** and (+)-**7**, and our unambiguous determination of their (3R)-absolute configurations, have therefore led us to conclude that Hatakeyama¹³ and Ryu¹² must have synthesized (–)-inthomycin C with (3S)-stereochemistry, rather than the (3R)-stereochemistry that they claimed. Zeeck and Taylor's original assignment^{9,11} of (3R)-stereochemistry for (+)-inthomycin C is therefore correct, and Taylor's total synthesis does indeed deliver the (+)-(3R)-stereostructure as he reported.

Clearly, our new total synthesis of (+)-inthomycin C has furnished valuable new Mosher ester and optical rotation evidence that reinstates the originally formulated Zeeck–Taylor (3R)-stereostructure⁹ for (+)-inthomycin C and Taylor's total synthesis. Our work has also proven the great synthetic worth of the O-directed free radical hydrostannation process with Ph₃SnH and catalytic Et₃B in PhMe for the synthetic construction of challenging chiral trisubstituted allylic alcohol motifs possessing a β-geminal dimethyl substituent. Further work in this direction, in the context of a future projected (+)-acutiphycin total synthesis, will be reported in the paper that follows.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR, IR, and mass spectra can be found in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: k.j.hale@qub.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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