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Synthesis of the C(7)−C(22) Sector of (+)-Acutiphycin via O-Directed Double Free Radical Alkyne Hydrostannation with Ph_3SnH/Et_3B, Double I−Sn Exchange, and Double Stille Coupling

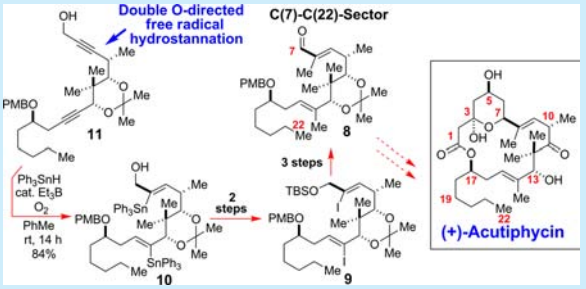
Karl J. Hale,*[ˇ] Maciej Maczka,[ˇ] Amarjit Kaur,[ˇ] Soraya Manaviazar,[ˇ] Mehrnoosh Ostovar,[‡] and Milosz Grabski[ˇ]

[ˇ]The School of Chemistry & 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

[‡]The Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom

Supporting Information

ABSTRACT: Herein a new double O-directed free radical hydrostannation reaction is reported on the structurally complex dialkyldiyne **11**. Through our use of a conformation-restraining acetal to help prevent stereocenter-compromising 1,5-H-atom abstraction reactions by vinyl radical intermediates, the two vinylstannanes of **10** were concurrently constructed with high stereocontrol using $Ph_3SnH/Et_3B/O_2$. Distannane **10** was thereafter elaborated into the bis-vinyl iodide **9** via O-silylation and double I−Sn exchange; double Stille coupling of **9**, O-desilylation, and oxidation thereafter furnished **8**.



In the preceding paper,[1] we unveiled a new total synthesis of (+)-inthomycin C, in which we documented the first successful use of the O-directed alkylacetylene free radical hydrostannation reaction with Ph_3SnH and catalytic Et_3B/O_2 for the synthetic construction of a chiral trisubstituted allylic alcohol with a geminal dimethyl substituent positioned directly next to the OH. In this accompanying *Organic Letter*, we now report on the further augmentation of that methodology, in the context of our development of a new synthetic route to the C(7)−C(22)-sector of the antitumor macrolide, (+)-acutiphycin. Specifically, we record here the first example of a new O-directed *double* free radical hydrostannation process for the simultaneous creation of two structurally distinct trisubstituted olefins within the same target molecule, a reaction that proceeds efficiently and without deleterious vinyl radical 1,5-H-atom abstraction events compromising the newly introduced stereocenters present within the C(7)−C(22) sector of the target.

(+)-Acutiphycin is a pyranylated macrolide of significant pharmaceutical interest on account of its pronounced growth inhibitory effects against human KB nasopharyngeal carcinoma *in vitro* and its ability to counteract murine Lewis lung carcinoma *in vivo*.[2] It is, however, no longer produced by the blue green alga from which it was first isolated (*Oscillatoria acutissima*), which means that all future clinical supply will have to be met by total synthesis, unless a new source of (+)-acutiphycin can be found. So far, only two total syntheses of (+)-acutiphycin have been completed: one by the team of Smith at Penn,[3a,b] the other by Jamison's group[3c,d] at MIT. Both stand out for their elegance and clever synthetic design, as well as for their excellent levels of stereocontrol. A notable asymmetric aldol approach has also been formulated by Kiyooka and Hena,[3e] alongside other noteworthy synthetic efforts from the laboratories of Miftakhov[3f] and Leger.[3g]

The two stereodefined olefins of (+)-acutiphycin present a special challenge for construction by the O-directed free radical hydrostannation method,[4] due to the fact that a conformationally unrestrained diyne of general structure **1** could give rise to a range of intermediary vinyl radicals[5] that could potentially engage in stereocenter-compromising 1,5-H-atom abstraction processes,[6] with two possible adverse outcomes shown in Scheme 1.

Given these issues, we considered that the positioning of a conformation-restraining acetal within **1** could be highly beneficial, since it would severely constrain the approach of the different vinyl radicals to the various stereocenters present within the carbon chain. A high concentration of stannane would also favor the rapid quenching of these vinyl radicals. Together, these combined tactics could be expected to promote the desired double O-directed hydrostannation event on **1** without causing a loss of stereocenter integrity from within the product.

Accordingly, we selected the O-isopropylidenated enal **8** as an advanced intermediate for our proposed route (Scheme 2). It would be prepared via a multistep sequence involving *double* O-directed free radical hydrostannation on the bis-propargylically oxygenated diyne **11** with Ph_3SnH and cat. Et_3B/O_2 in PhMe. O-Silylation of **10** and retentive I−Sn exchange would thereafter ensue to furnish the bis-iodoolefin **9** ready for two-directional Stille cross-coupling with Me_4Sn. O-Desilylation and

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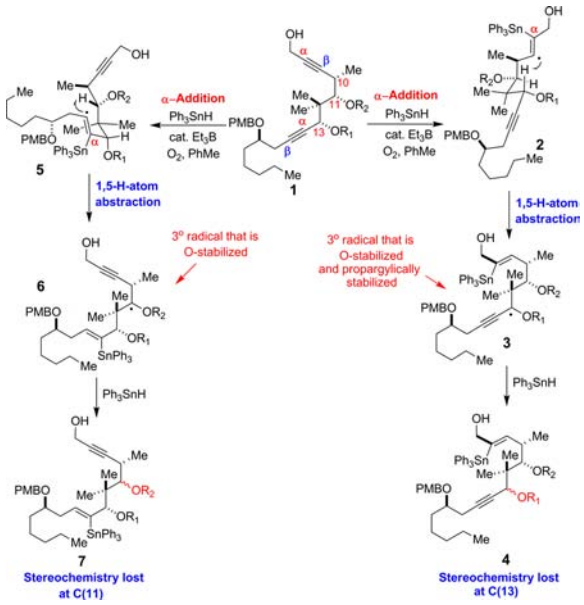
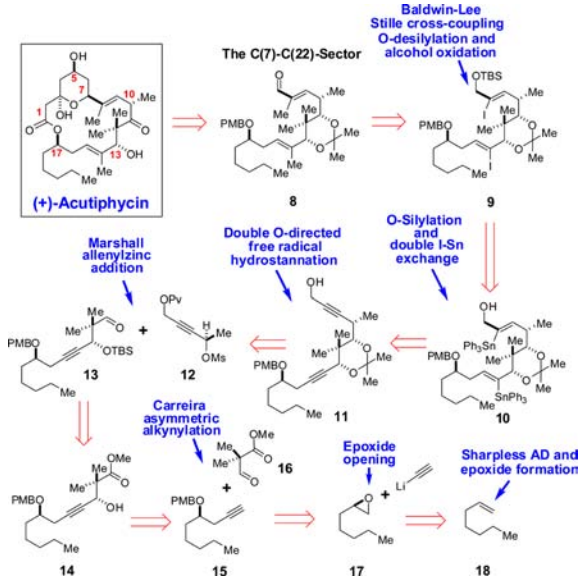
Scheme 1. Deleterious 1,5-H-Atom Transfer Events that Could *Potentially* Occur in an Acyclic Precursor 1 after α-Addition of a Ph_3Sn Radical and β-Vinyl Radical Formation



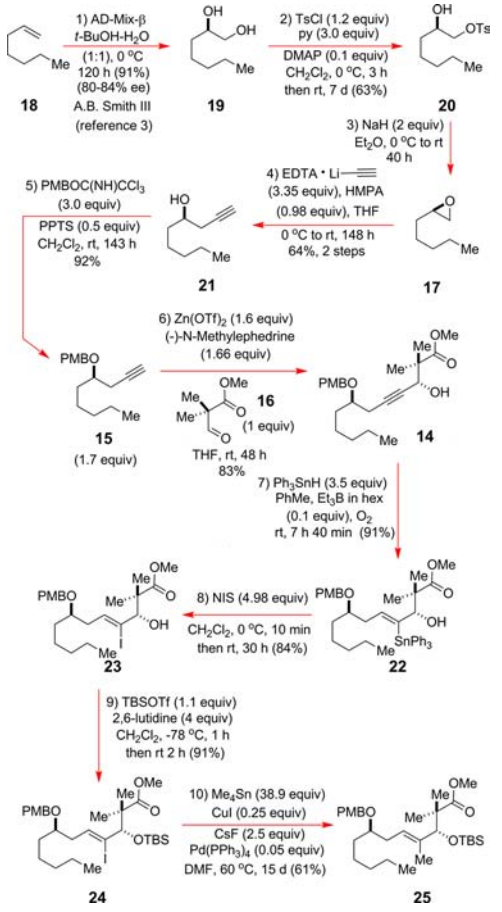
Scheme 2. Our O-Directed Double Free Radical Stannation Strategy for the C(7)−C(22) Sector of (+)-Acutiphycin



oxidation would subsequently provide **8**. Carreira asymmetric alkynylation[7] between **15** and **16** and Marshall asymmetric allenylzinc addition[8] between aldehyde **13** and the *O*-mesylate **12**[8b] were thereafter envisioned for the obtention of **11**.

Initially we decided to carry out a model study to help establish whether the alkynol **14** would undergo O-directed free radical hydrostannation with Ph_3SnH and catalytic Et_3B/O_2 with good regio- and stereocontrol. I−Sn exchange and Stille cross-coupling were subsequently envisaged for securing **25** (Scheme 3). Success in this endeavor would not only give us a good indication of whether our proposed double O-directed free radical hydrostannation strategy would be likely to create **10** stereoselectively but also provide us with a viable synthetic

Scheme 3. Our O-Directed Free Radical Hydrostannation Strategy for the C(12)−C(24) Sector of (+)-Acutiphycin



alternative, in the event of the desired double hydrostannation event later faltering.

Accordingly, we commenced our synthesis of **14** with the preparation of terminal epoxide **17** (Scheme 3). For this, we exploited Smith's excellent Sharpless AD protocol on 1-heptene[3a,b] to obtain the diol **19**, which was shown to be of 80−84% ee by Mosher ester NMR analysis, a protocol that concurrently confirmed the absolute configuration of **19**. The latter was then selectively O-tosylated to obtain **20**, which was converted through to **17** by treatment with NaH in Et_2O. Due to the high volatility of this epoxide, it was generally found best to use it crude for the subsequent epoxide ring-opening step with the lithium acetylide−EDTA complex in THF/HMPA, which provided the volatile homopropargylic alcohol **21** in 64% yield for the two steps. Compound **21** was thereafter protected with PMB-trichloroacetimidate, and the alkyne **15** was used for a Carreira asymmetric alkynylation with the β-aldehydo ester **16**.[1] The latter reaction proceeded cleanly and with high stereocontrol to deliver **14** as essentially a single, diastereomerically pure, compound in 79% yield after SiO_2 flash chromatography, which removed the minor diastereomer that inevitably arose from the use of an alkyne of 80−84% ee. Mosher ester analysis of the (*R*)- and (*S*)-MTPA acid esters confirmed the absolute stereochemistry of the newly induced asymmetric center, showing it to be fully in accord with the predictions of the Carreira stereochemical model,[7] so reinforcing the earlier work done on (+)-inthomycin C.[1] The propargylic alcohol **14** was thereafter subjected to O-directed

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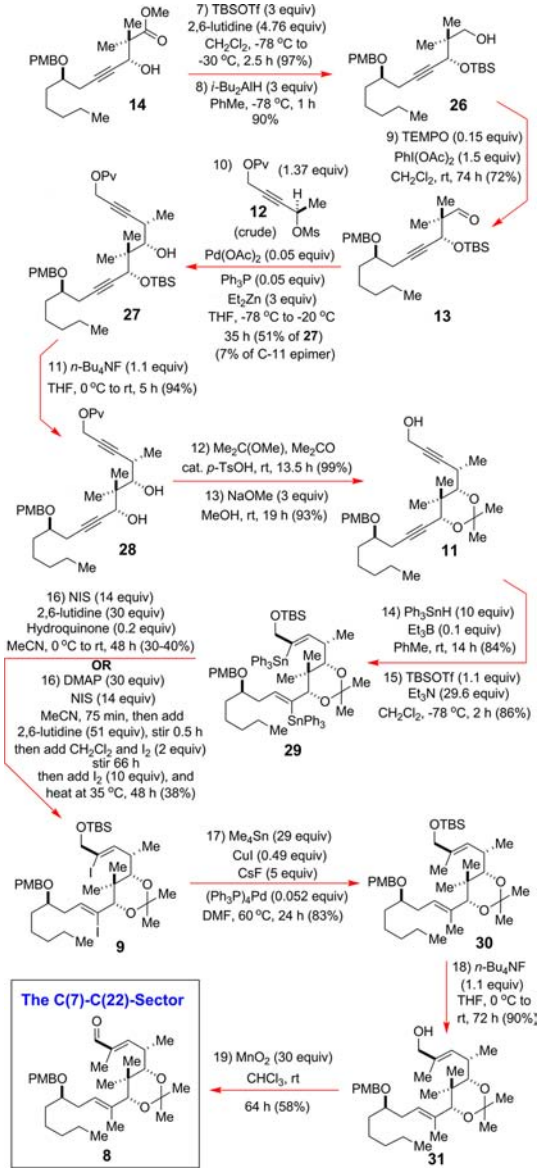
free radical hydrostannation with Ph_3SnH and catalytic Et_3B/O_2 in PhMe for 7 h 40 min;[4a,5] it provided the (*Z*)-configured vinyltriphenylstannane **22**, which smoothly engaged in I−Sn exchange[4b,9] to give **23** in 84% yield. While it proved difficult to estimate the precise level of stereo- and regiocontrol that had manifested itself in the hydrostannation step by NMR, due to **22** giving rise to rotamers,[10] following I−Sn exchange with *N*-iodosuccinimide (NIS) in CH_2Cl_2,[4b] the regio- and stereocontrol could be seen to be near total. Again, very minor rotameric equilibria were evident for **23**. However, unlike with **22**, the effects were now not sufficiently severe to prevent a reliable stereochemical estimate of hydrostannation performance. Following O-silylation, **24** was subjected to the Baldwin−Lee CsF/CuI variant of the Stille cross-coupling conditions with Me_4Sn,[11] which successfully converted it into **25** in 61% yield, albeit, after the reactants had been heated in DMF at 60 °C for the rather lengthy period of 15 days! It will be noted that **24** and **25** both had identical mobilities on TLC, which made reaction progress extremely difficult to monitor. Nevertheless, after multielution TLC, **24** and **25** could be distinguished by their differing colors upon staining with anisaldehyde/H_2SO_4 stain. In our experience, TLC behavior of this sort is quite common for this type of Stille coupling, and we now alert the community to this fact.

With the viability of the aforementioned chemistry established, we now embarked on the double O-directed hydrostannation strategy that we had retrosynthetically mapped out in Scheme 2. This initially entailed us O-silylating alcohol **14** (Scheme 4), reducing the O-silylated ester to the alcohol **26** and oxidizing the latter to the aldehyde **13** with iodosobenzene diacetate and TEMPO.[12] This set up a Pd(0)-mediated Marshall allenylzinc addition[8] for the obtention of **27**. Although two products were invariably formed in this process, **27** always predominated. The reaction also never usually reached completion, but it did come quite close on a number of occasions. Following SiO_2 flash chromatography, **27** could typically be isolated pure in 51% yield, alongside a 7% yield of the diastereomeric C(11)-alcohol epimer. The O-silylated ether **27** was next treated with TBAF to obtain the 1,3-diol **28**, which was O-acetalated. O-Depivaloylation subsequently afforded the propargylic alcohol **11** in 84% overall yield for the three steps. Alkynol **11** underwent double O-directed free radical hydrostannation over 14 h to give the bisvinylstannane **10** as the primary reaction product in 84% yield. Once more, accurate evaluation of the level of diastereoselectivity that had manifested itself at this stage was thwarted by the existence of a complex rotameric equilibrium induced by the combined presence of the hydroxymethyl and Ph_3Sn subunits. Our attempts at implementing the I−Sn exchange reaction on **10** also gave rise to problems. Nevertheless, after O-silylation, I−Sn exchange could eventually be accomplished on **29** with NIS[4b] in MeCN, *in the presence of 2,6-lutidine*[13] and catalytic hydroquinone. It gave rise to the desired bis-vinyl iodide **9** as essentially a single compound in 40% yield, which suggested that the hydrostannation event had proceeded with very high regio- and stereocontrol, as is now customary for these reactions.[5,9] Another set of highly useful I−Sn exchange conditions that we identified utilized NIS/I_2/2,6-lutidine and DMAP in $MeCN/CH_2Cl_2$ at 35−40 °C to bring about the same transformation. The conversion of **29** into **9** is by far the most complex I−Sn exchange ever performed on a vinyltriphenylstannane substrate, and the 30−40% yield of **9** that was obtained by both methods essentially translates to a 55−63%

Scheme 4. Our Conformationally Restricted O-Directed Double Free Radical Hydrostannation Route to the C(7)−C(22) Sector of (+)-Acutiphycin



yield for each respective vinylstannane I−Sn cleavage step, which is not bad at all when one considers the high degree of steric hindrance around both alkenes in the bis-vinyltriphenylstannane **29**, a factor which, in this rather *unusual* instance, required multiple phenyl groups to be cleaved from around the central Sn-atoms, to allow the desired electrophilic cleavages of the vinyl-Sn bonds to proceed satisfactorily to produce **9**. This requirement to cleave *multiple* more sterically accessible Ph−Sn bonds before vinyl iodide formation could occur almost certainly accounted for why such a large excess of the *N*-iodosuccinimide/2,6-lutidine or the NIS/I_2/2,6-lutidine/DMAP was needed to bring about this overall conversion. Our study of this reaction also highlighted the critical role played by 2,6-lutidine (and DMAP) in bringing these proceedings to a successful conclusion. In this regard, I_2 alone in CH_2Cl_2 caused extensive decomposition when applied on **29**, an outcome that contrasted sharply with the many successful I−Sn exchanges that we[4b,9] and others[14] have

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performed on less hindered vinyltriphenylstannane substrates. Possibly, I_2 alone cleaves the *syn*-1,3-acetal without the lutidine or DMAP present.

All of these issues notwithstanding, the fact that this I−Sn exchange could eventually be accomplished allowed us to investigate the double Stille cross-coupling of vinyl diiodide **9** with Me_4Sn. Fortunately, this reaction proceeded successfully when it was conducted under the Baldwin−Lee conditions[11] with CuI, catalytic $(Ph_3P)_4Pd$, and CsF as additives in DMF at 60 °C over 24 h. The bis-olefin **30**, so formed, was produced in 83% yield. Again minor rotamers could be observed in its ^1H NMR spectra. O-Desilylation of **30** was thereafter accomplished with commercial TBAF in THF to give the alcohol **31**. Oxidation of **31** with MnO_2 in $CHCl_3$ subsequently completed our pathway to the enal **8**. Overall, these two transformations proceeded in 52% combined yield. Efforts are currently underway to use **8** to help us complete a new total synthesis of (+)-acutiphycin, and further results will be reported as and when additional progress is made.

However, of significance for now, the present work has demonstrated, for the very first time, that it is possible to perform a *double* O-directed free radical hydrostannation on a nonsymmetric, bis-propargylically oxygenated, dialkyl-diyne to predictably set two structurally distinct trisubstituted vinyltriphenylstannanes within the same molecule, with very high stereo- and regiocontrol. We have also shown the viability of doing two-directional I−Sn exchange and double Stille cross-coupling in complex highly crowded systems that possess acid-sensitive functionality. We have additionally revealed the occasional need to cleave off *multiple* more sterically accessible phenyl groups from a Ph_3Sn moiety, in order to effect an I−Sn exchange in a vinyltriphenylstannane where the constituent C=C double bond experiences a high degree of steric hindrance, as was the case here for **9**. As such, we have greatly expanded the synthetic utility of the O-directed free radical hydrostannation reaction with Ph_3SnH/cat. Et_3B. We have also laid down important markers for the future application of this reaction in total synthesis. In particular, we have devised an effective acetal-tethering tactic for preventing deleterious stereocenter-compromising 1,5-H-atom abstraction events from destroying the chirality present within acyclic vinylstannane products. Clearly, by applying the Ph_3SnH/cat. Et_3B O-directed alkyne free radical hydrostannation process on highly challenging target molecules such as (+)-acutiphycin and (+)-inthomycin C,[1] we have gained new strategic insights into how to deploy this powerful and mechanistically complex[5] reaction in other even more challenging synthetic situations heretoforth.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and copies of the ^1H and ^{13}C NMR spectra. 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.

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