Tetrahedron Letters 52 (2011) 2080–2084

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Enantioselective formal total synthesis of the *Dendrobatidae* frog toxin, (+)-pumiliotoxin B, via O-directed alkyne free radical hydrostannation

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ARTICLE INFO

*Article history:*
Available online 31 October 2010

Dedicated with fondness, respect and admiration to a master chemist, Professor Harry H. Wasserman, on the occasion of his 90th birthday

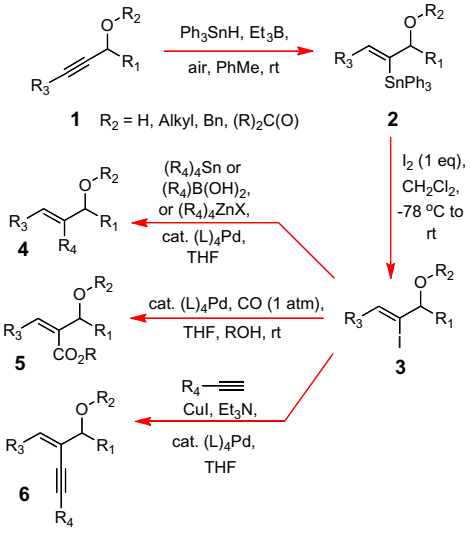
ABSTRACT

Herein we describe our application of the O-directed free radical hydrostannation of disubstituted alkylacetylenes (with $Ph_3SnH$ and $Et_3B$) to the (+)-pumiliotoxin B total synthesis problem. Specifically, we report on the use of this method in the synthesis of the Overman alkyne **8**, and thereby demonstrate the great utility of this process in a complex natural product total synthesis setting for the very first time. We also report here on a new, stereocontrolled, and highly practical enantioselective pathway to Overman's pyrrolidine epoxide partner **9** for **8**, which overcomes the previous requirement for use of preparative HPLC to separate the 1:1 mixture of diastereomeric epoxides that was obtained in the original synthesis of **9**.



In 2005,[1–3] we reported that the combination of $Ph_3SnH$ and $Et_3B$ (0.1 equiv) in toluene at room temperature was remarkably effective for performing the highly stereo- and regio-controlled O-directed free radical hydrostannation of disubstituted alkyl acetylenes to give trisubstituted vinyl triphenylstannanes of general structure **2** (Scheme 1).[1] We also noted, in these publications, that $Ph_3SnH/Et_3B$ typically out-performs $Bu_3SnH$ and various other free radical initiators, including $Et_3B$, when used in this capacity. We further demonstrated that vinyl triphenylstannanes of general structure **2** can efficiently be converted into stereodefined vinyl iodides **3** of identical geometry,[2] by iodine–tin exchange,[4] and that these intermediates can often be elaborated into different target trisubstituted alkenes **4**, **5**, and **6**, in good yield, by application of various Pd(0)-catalysed cross-coupling methods (Suzuki, Stille, Negishi, Sonogashira etc.).[2,5] Although a significant number of challenging target alkene structures were prepared via this new protocol,[2] none of these targets were natural products.[4]

In an effort to remedy this situation, and demonstrate the power of our new method for complex natural product total synthesis,[4] we decided to address the (+)-pumiliotoxin B[6] synthetic problem,[7,8] where stereocontrolled installation of the acyclic trisubstituted alkene side chain is well known to present special challenges and difficulties. In this Letter, we now document success in these efforts with our completion of a new asymmetric formal total synthesis of (+)-pumiliotoxin B by a route which intersects with Overman's elegant second-generation synthetic pathway[7b] to this compound. We note in advance that our new route not only improves on the previous technology that was available for preparing pyrrolidine epoxide **9** (which required a preparative HPLC separation to resolve a 50:50 mixture of two epoxide diastereoisomers), it also now provides Overman's advanced alkyne coupling partner **8** by a strategy that is 5 steps shorter *overall* than his 1996 route. Our new pathway to **8** is also well suited to generating novel analogues that are modified at the C(13)–C(14)-trisubstituted olefin, and at the C(11)-, C(15)- and C(16)-stereocentres.




**Scheme 1.** Trisubstituted alkene synthesis via O-directed free radical hydrostannation.

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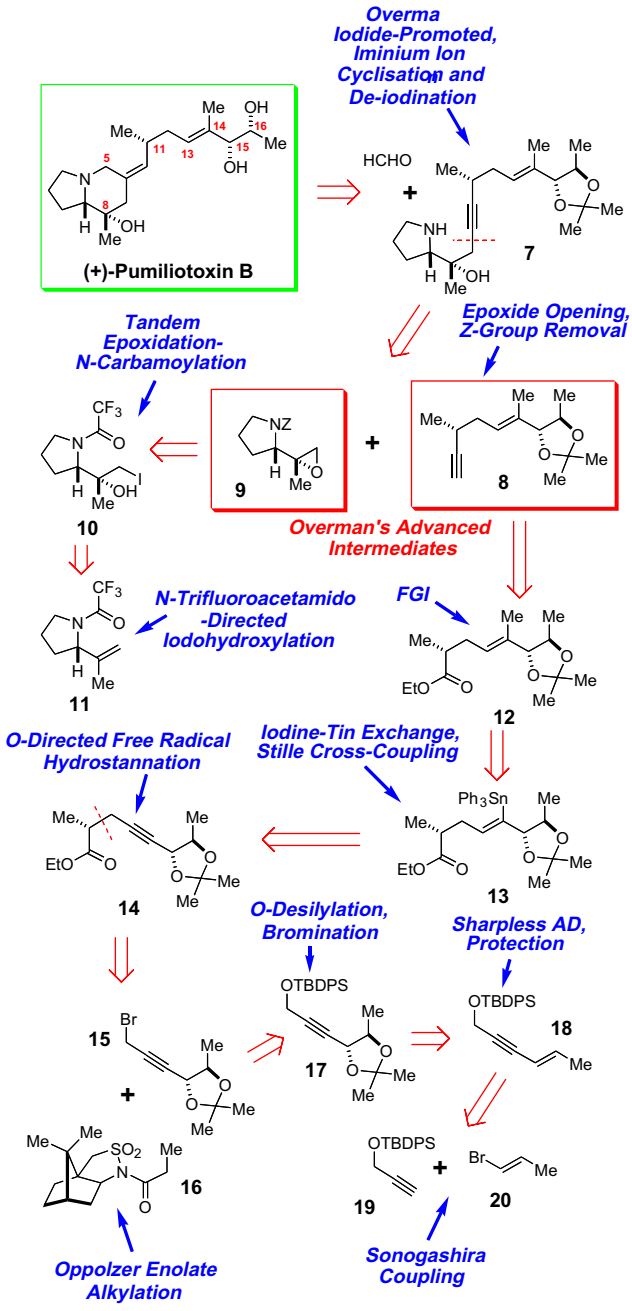
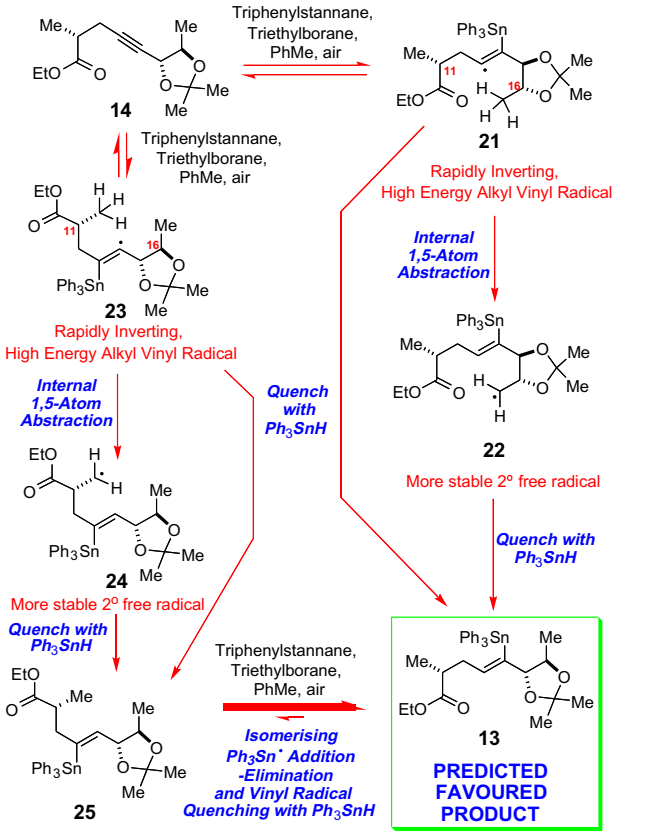
doi:10.1016/j.tetlet.2010.10.141




**Scheme 2.** Our retrosynthetic analysis for (+)-pumiliotoxin B.



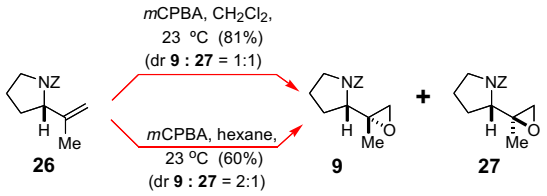

**Scheme 3.** Some of the mechanistic events[3] that would be likely to be operating in the O-directed hydrostannation of **14** with $Ph_3SnH$ and $Et_3B$.

As soon as one retrosynthetically dissects the structure of alkyne **8** (Scheme 2) and one moves forward towards the propargylic acetal **14**, one can very soon see that this alkyne is perfectly set up for application of the O-directed free radical hydrostannation process. In this regard, one must remember that this is a mechanistically complex reaction,[3] in which the triphenylstannyl radical is capable of *reversibly* adding to *either* alkyne carbon to generate two individual, transient, highly reactive, vinylic radicals at either C-atom of the original alkyne structure. Moreover, once generated, these rapidly-inverting, high energy, vinyl radicals can frequently engage in internal 1,5-H-atom abstraction events at appropriately positioned carbons.[4]

In the case of alkyne **14** (Scheme 3), the two potential vinylic radical 1,5-H-atom abstraction sites would be at the methyl groups attached to C(11) and C(16), and the resulting secondary carbon radicals **22** and **24** would then almost certainly be rapidly quenched by the excess stannane that would be present in the reaction mixture. Thus, for **14**, it was our belief that none of the newly incorporated stereocentres in the chain would ever be put at risk by applying the O-directed free radical hydrostannation process. Moreover, because the propargylic O-atom of **14** should be capable of satisfactorily coordinating to the mildly Lewis acidic $Ph_3Sn$ radical, as well as the stannane itself, we considered that these combined events would greatly favour triphenyltin radical addition to the α-carbon of **14** (based upon our many past experiences) and this, along with the multiple $Ph_3Sn^{\cdot}$ addition–elimination/isomerisation pathways that are known to operate[3] in these reactions, led us to predict that the formation of **13** would ultimately be favoured.

Thereafter, we believed that **13** (Scheme 2) would be capable of being converted into the desired vinylic iodide by tin–iodine exchange[2] which, if successful, would allow a subsequent Stille cross-coupling reaction with tetramethylstannane to complete the final elaboration of the trisubstituted olefin **12** (Scheme 2). Conversion of the ester **12** into the terminal alkyne **8** would then complete our intersection with Overman's second-generation route to (+)-pumiliotoxin B, which has a truly superb end-game.[7b]

With respect to introducing the C(11)-Me substituent of **8**, we favoured an Oppolzer-type alkylation[9] between **16** and the activated propargylic bromide **15** to achieve this objective, due to the improved nucleophilicity of such metal enolates compared with their Evans *N*-acyl oxazolidinone counterparts. A logical way of installing the two O-stereocentres in **15** would be to perform a Sharpless AD reaction[10] on the eneyne **18**, and then to effect a series of standard functional group interconversions, but this particular option would obviously require a potentially very challenging Sonogashira coupling to be effected between **19** and **20**.




**Scheme 4.** Overman's preparation of chiral epoxide **9**.

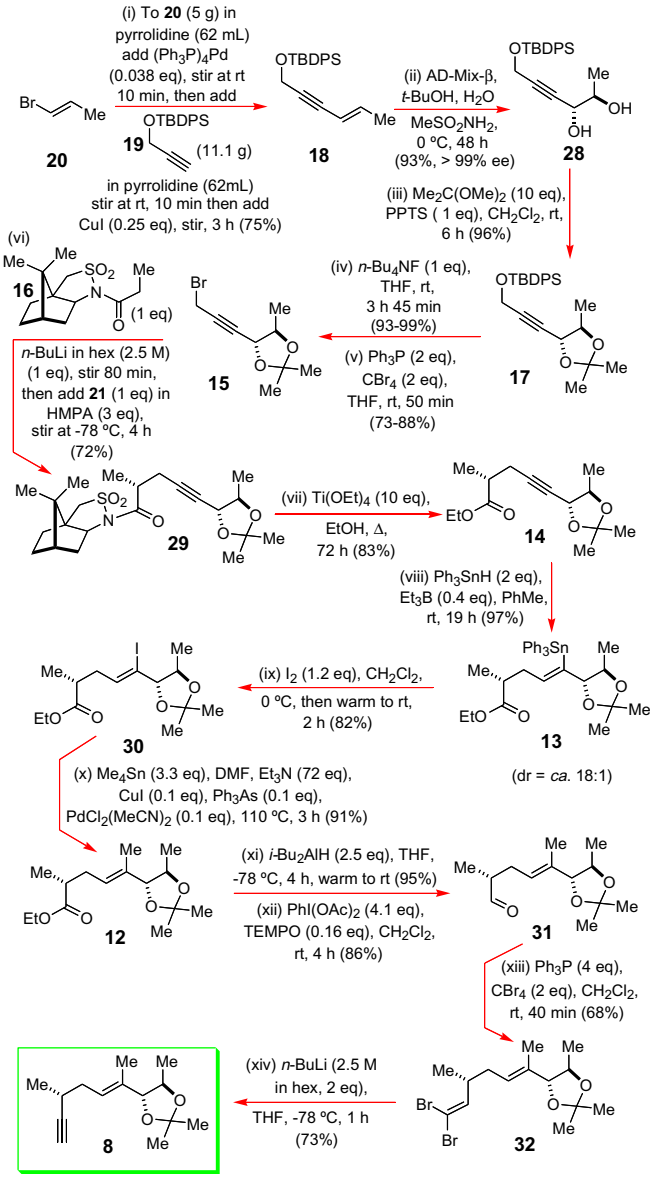
In Overman's originally published strategy to epoxide **9**,[7a] alkene **26** was epoxidised with *m*CPBA in $CH_2Cl_2$ (Scheme 4), but, rather unfortunately, this reaction lacked good stereocontrol (dr = 1:1) and it required a preparative HPLC separation to obtain **9** in pure condition. Even when this epoxidation was performed in the slightly more stereoselective solvent, hexane, this process still only delivered **9** with a 2:1 level of diastereoselectivity (61% yield) and, because of substrate solubility issues, hexane could not ultimately be used for the subsequent large scale synthesis of **9**.

Our plan for overcoming this 1:1 mixture issue would take advantage of a novel trifluoroacetamido-assisted iodo-hydroxylation reaction[11] on the alkene **11** to set the tertiary OH-stereochemistry of **10** and, most importantly, this would position a fairly easily removed N-protecting group within the product that could potentially be detached under the very mild, aqueous, basic conditions that we planned to use to form the epoxide itself. If allied with in situ N-acylation with ZCl, such a ploy would possibly allow the requisite Z-group to be successfully installed within **9** in a multi-component, one-pot, operation that, hopefully, would efficiently deliver this compound with near complete stereocontrol, and totally overcome the previous need to do preparative HPLC purification. With this as background, we will now discuss the final formal synthesis that we have devised.

An early objective in our route to alkyne **8** was the preparation of eneyne **18** and, for this, we decided to investigate the Sonogashira coupling between **20** (Aldrich) and **19** (Scheme 5). Initially, we followed a closely related literature report[12] in which propargyl alcohol was coupled to **20** and we noted, almost immediately, that this low yielding Sonogashira procedure (28%) failed to use copper iodide as an additive. When we applied similar Cu-free conditions for the Pd-catalysed cross-coupling of **19** with **20**, we too only saw a low yield of product. Fortunately, however, and after some quite painstaking experimentation on our part, which included the addition of catalytic CuI to the reaction mixture, we were eventually able to reproducibly obtain a 75% yield of **18**, using the reaction conditions specified in Scheme 5, which employed *neat* pyrrolidine as the reaction solvent, and $(Ph_3P)_4Pd$ as the co-catalyst, and which conducted the reaction for only 3 h at room temperature.

With this key obstacle overridden, the stage was set for performing the Sharpless AD reaction that was required to install the C(15)- and C(16)-hydroxyls of the natural product. The latter reaction performed admirably in this capacity, delivering **28** as essentially a single enantiomer, in very high yield (93%) (see the Mosher ester analysis we did in the Supplementary data). The 1,2-diol unit of **28** was next protected as an *O*-isopropylidene acetal. The *O*-silyl group was then detached from **17** and bromination was performed with triphenylphosphine and carbon tetrabromide in THF. Although bromide **15** was somewhat unstable, it could be successfully purified in 73–88% yield by $SiO_2$ flash chromatography and it was subsequently characterised by high field NMR spectroscopy (see Supplementary data).

When *n*-BuLi was used as the base for enolisation of Oppolzer's camphorsultam-tethered[9] propionamide **16** (Scheme 5), and a solution of the bromide **15** in HMPA was added to this lithium enolate at low temperature, and the −78 °C conditions were preserved




**Scheme 5.** Our new route to Overman's advanced alkyne intermediate **8** for the total synthesis of (+)-pumiliotoxin B.

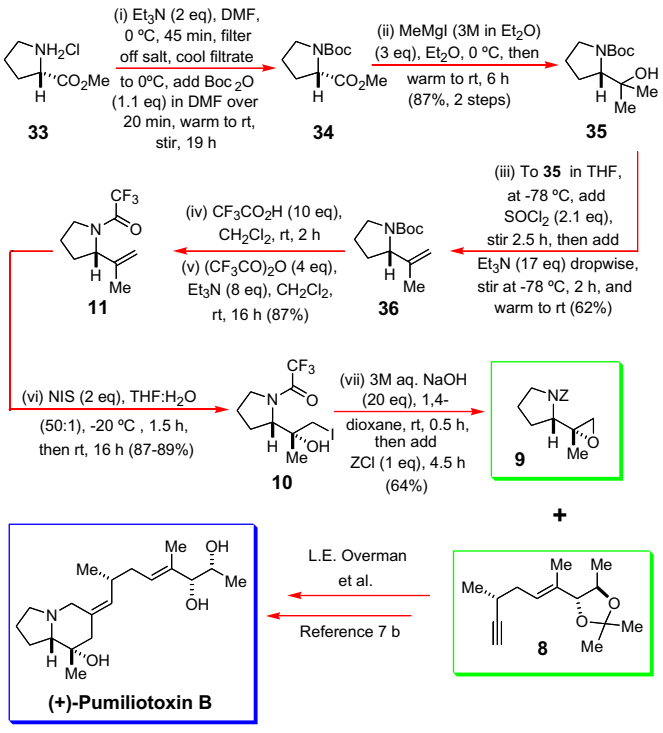
for 4 h, a highly stereocontrolled asymmetric alkylation took place, with the C(11)-Me group being introduced with total stereocontrol in a really quite respectable 72% yield. With this key C–C bond-forming step negotiated, we could now think about implementing our O-directed hydrostannation step. Although our original plan had been to detach the auxiliary from **29** and then apply the $Ph_3SnH/Et_3B$ hydrostannation on **14** we did, nevertheless, feel that it would be worthwhile examining the viability of this process on **29**, to see how well this substrate behaved but, to our great disappointment, no reaction took place at all. We can only surmise that the sulfonamido unit of the Oppolzer camphorsultam auxiliary inhibits the free radical hydrostannation process in some way.

We, therefore, proceeded with our original plan of cleaving the chiral auxiliary from **29** with $Ti(OEt)_4$ and EtOH at reflux;[13] the reaction took 3 days to reach completion but, when the end-point was finally reached, **14** was isolable in 83% yield. When we now applied the O-directed free radical hydrostannation process to **14**, over 19 h, we observed that a chromatographically inseparable 18:1 mixture of regioisomeric vinyl triphenylstannanes was

formed in which **13** predominated. Importantly, the purified 18:1 mixture enriched in **13** could be isolated in pure condition in 97% yield following $SiO_2$ flash chromatography. As expected, iodine-tin exchange and Stille cross-coupling of **30** with $Me_4Sn$ and Pd(0), both proceeded smoothly to deliver the desired trisubstituted olefin **12** in essentially pure condition in 75% yield over two steps.

Ester **12** was now reduced to the primary alcohol with DIBAL-H, and this product oxidized to aldehyde **31** with catalytic TEMPO and excess iodobenzene diacetate, using the excellent procedure of Piancatelli.[14] Significantly, all of the other oxidants that were examined in this reaction also caused an extensive, and highly problematical, epimerization of the C(11)-methyl stereocentre α- to the aldehydo group, and quite considerable oxidant screening was required before we eventually identified these optimal oxidation conditions. Following $SiO_2$ flash chromatography, aldehyde **31** was isolated in pure condition in 86% yield and it was used directly for the subsequent Corey–Fuchs dibromolefination[15] step without delay. The latter reaction was first applied on **31** by Kibayashi[8d] in his total synthesis of *allo*-pumiliotoxin 339A. Dibromoalkene **32** also featured in Overman's pathway to (+)-pumiliotoxin B and, in this context, **32** had previously been converted into alkyne **8** by low temperature treatment with two equivalents of *n*-BuLi in THF;[7b] both sets of chemistry were successfully repeated by us.

Although we did indeed attempt the direct alkynylation of aldehyde **31** with the Ohira–Bestmann reagent,[16] the fairly basic conditions under which this method operates proved totally incompatible with preservation of the C(11)-Me stereochemistry in **31**. Whilst the reaction was itself chemically successful at delivering the alkynylated product **8** in high yield, it also led to a significant amount of terminal alkyne diastereomer at C(11), which proved inseparable by $SiO_2$ flash chromatography. Thus, this particular direct method for converting **31** into **8** was simply not viable, making the lengthier two-step Corey–Fuchs alkynylation pathway to **8** almost mandatory.[17]




**Scheme 6.** The final stages of our new formal total synthesis of (+)-pumiliotoxin B.

Concurrent with our development of this new pathway to alkyne **8**, we also addressed the synthesis of epoxide **9** (Scheme 6). Our new route repeated some of the excellent chemistry of Stevenson[18] for the acquisition of alkene **36**. The latter had its Boc-group replaced by an *N*-trifluoroacetamido-group in order to permit the anchimerically-assisted stereoselective iodo-hydroxylation reaction on **11**; a reaction which proceeded in 87–89% yield and delivered **10** as the major component of a 11.7:1 mixture.[11] Treatment of the latter with excess 3 M aqueous NaOH in dioxane thereafter simultaneously formed the terminal epoxide and cleaved the *N*-trifluoroacetamido substituent to allow an in situ N-acylation with benzyl chloroformate to obtain **9**. Although this new route to **9** is 3 steps longer than the previous Overman route it does, nonetheless, proceed with high stereocontrol and, it does now finally overcome the previous requirement to use preparative HPLC to continue the synthesis.

To summarise, we have completed a new and greatly improved formal asymmetric total synthesis of (+)-pumiliotoxin B that intersects with Overman's elegant 1996 synthesis[7b] of this natural product. Significantly our new route to his advanced intermediates **8** and **9** is 2 steps shorter than his second-generation path to this target, and its major advantage resides in the fact that it is highly stereocontrolled and it now removes the need to do preparative HPLC to advance forward. By completing this new formal route, we have demonstrated here, for the first time ever that our new O-directed free radical hydrostannation process can be beneficially and powerfully used to position an ornate trisubstituted olefin within a complex natural product. Further applications of the O-directed free radical hydrostannation process in the total synthesis of other complex natural products will be reported in due course.

## Acknowledgements

We thank Novartis Pharma AG, the ACS and Queen's University Belfast for financial support. We thank Dr. Paul Stevenson (QUB) for helpful advice on the preparation of **36**.

## Supplementary data

Supplementary data (copies of the 400 and 500 MHz $^1H$ and 125 MHz $^{13}C$ NMR spectra are supplied for all the new and previously unreported intermediates described in this route) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.141.

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17. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108. We also examined the reaction of crude aldehyde **31** with the Shioiri reagent derived from *n*-BuLi/$TMSCHN_2$ in THF at −78 °C. Whilst the reaction worked in 70% yield, a mixture of alkyne C(11)-Me epimers was obtained. Since this aldehyde was derived by TFAA/$Me_2SO$/$Et_3N$ Swern-type oxidation, we now have good reason to suspect that the latter process may have epimerized the C(11)-centre before the alkynylation was effected. Our future full account will look into this step again.
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