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Approach toward the total synthesis of orevactaene. Part 1: Assembly of the contiguous trisubstituted olefin component

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Abstract

An approach to the conjugated polyene chain component of orevactaene is reported. A modular approach has been devised to link the two stereocentre-containing ends of the structure together via a trisubstituted olefin-template. Key to the success of this approach is an efficient 'one pot' lithium/halogen exchange, boron/lithium exchange, borate ester saponification, and cross-coupling sequence to provide two contiguous trisubstituted olefins with absolute stereo- and regiocontrol in excellent overall yield. These results have paved the way for a parallel synthesis approach to prepare all 16 possible stereoisomers of orevactaene so that the relative and absolute stereochemistry of this compound can be determined.

Orevactaene (**1**), recently isolated from *Epicoccum nigrum* WC47880, is a novel polyene representing a new structural class of natural products.[1] It has been shown to be an effective binding inhibitor of the HIV-1 REV protein to REV response element (RRE). This compound has yet to be synthesised which, along with its important biological implications and considerable complexity, make it an attractive target for total synthesis.

There are four discrete components of **1**: a sugar moiety, a pyrone substructure, a polyene segment, and a hydrophobic tail. Further adding to the intrigue of preparing **1** is the fact that four of the seven chiral centres in the structure (i.e. carbons 23, 25, 32, and 33) have yet to be confirmed relatively, which means that the absolute configuration is also unknown. Thus, the synthetic route must be amenable to preparing all 16 diastereomers of **1** in order to confirm all questions surrounding its stereochemistry. We have had considerable experience with the parallel synthesis of biologically active compounds[2] and the modular/template approach[2b] has proven to be an effective synthetic strategy for the simultaneous preparation of many diverse compounds. Here the target is divided into small fragments that can be varied readily and coupled together easily to a central template by one common series of transformations.[2b] By using such a strategy,

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the complexity of generating the chiral centres in **1** can be reduced by preparing them as discrete units where the control over stereocentre preparation can be maximised. These units are then coupled to the rest of the structure by templates that have been designed for stereo- and regioselective bond construction to themselves and to be substrate insensitive (i.e. generally applicable). This first paper in this series for the total synthesis of orevactaene (**1**) focuses on the preparation of a template possessing adjacent trisubstituted olefins that will ultimately link the hydrophobic tail with the pyrone substructure.

The key piece for connecting the two ends of **1** together is the contiguous trisubstituted olefin section in structure **5** (Fig. 1). This will serve as the template through which the four isomeric hydrophobic tails (i.e. C22–C27) will be connected to the rest of the structure. Trisubstituted olefins are challenging to prepare as single entities, thus preparing contiguous ones is even more interesting. Strategies that bring the olefinic carbons together during olefin formation often work with good selectivity for disubstituted targets, but rarely provide trisubstituted olefins with even reasonable stereocontrol.[3–6] The routes we have opted for to prepare the trisubstituted olefins are transition metal-catalysed hydrometallation[7] and metallometallation.[8,9] Propargyl alcohol (**10**) can be elaborated to the requisite cross-coupling partner **7** by stannylcupration.[9] In this way, the two metallic centres are significantly differentiated to undergo electrophilic capture at the cuprate site, while the tin centre is inert to such conditions. However, the stannane is a suitable partner for cross-coupling with Pd catalyst.[10] The distal chiral centre in the tail will be set by the use of (*R*)- and (*S*)-**12** while the proximal one will be set by enantioselective hydrogenation which will provide the (*R*,*R*) and (*S*,*R*) configurations from (*R*)-**12** using Ru–BINAP catalyst.[11] Conversely, the (*R*,*S*) and (*S*,*S*) configurations will be set using (*S*)-**12**. This work is underway, but is not the focus of this report, thus progress is reported herein using isobutyraldehyde (**17**) as a model system. Compound **8** will be obtained from **12** via the corresponding alkyne-ester **11**. Such

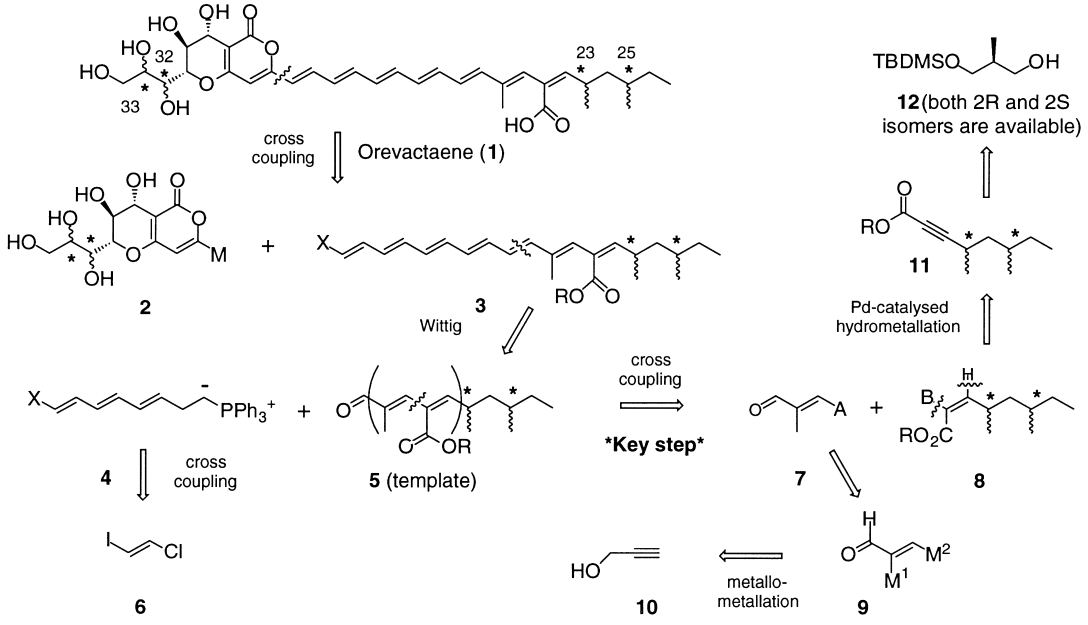
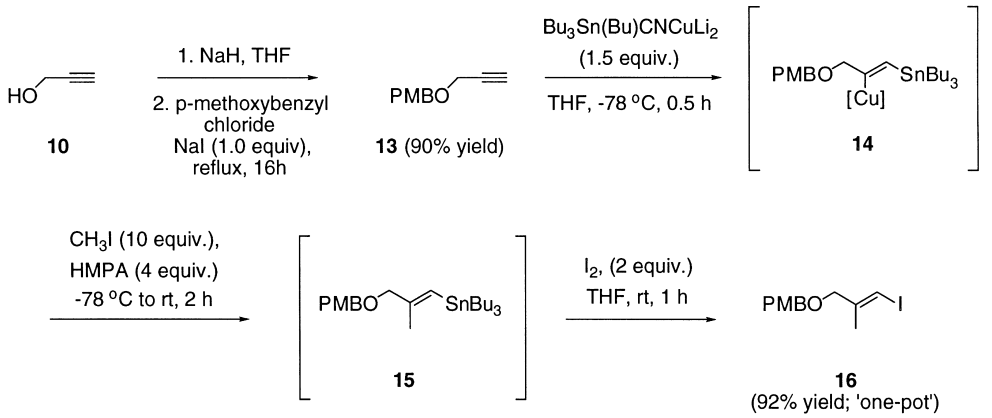


Figure 1. Retrosynthetic analysis of orevactaene (**1**)

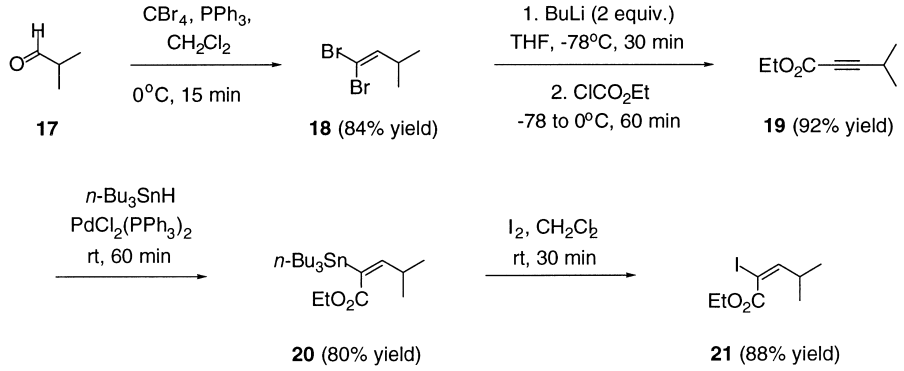
electron deficient alkynes are known to undergo regioselective Pd-catalysed hydrostannylation to place the metal where necessary for the critical cross-coupling step.[7]

The choice of protecting group for the alcohol of **10** proved to be more important than initially anticipated (Scheme 1). Silyl protecting groups were found to be less stable to some of the subsequent transformations than paramethoxybenzyl (PMB).[12] Further, PMB offers the advantage of providing the desired aldehyde in **5** directly during DDQ oxidative deprotection. Stannylcupration of **13** provided bimetallic intermediate **14** which was captured electrophilically in situ with methyl iodide yielding **15**. It was discovered subsequently that **15** was completely unreactive during the attempted Stille coupling with fragment **21**. Tin reagents have a significant steric requirement for the metal–metal exchange with the Pd(II) oxidative insertion intermediate derived from compounds such as **21**.[13] We could overcome this problem by using a metal such as zinc or boron.[13,14] Thus, we opted to capture intermediate **15** with I_2 directly in this one-pot sequence providing **16** from **13** (92% yield for the sequence), the iodide of which can be activated later by lithium/halogen exchange.



Scheme 1.

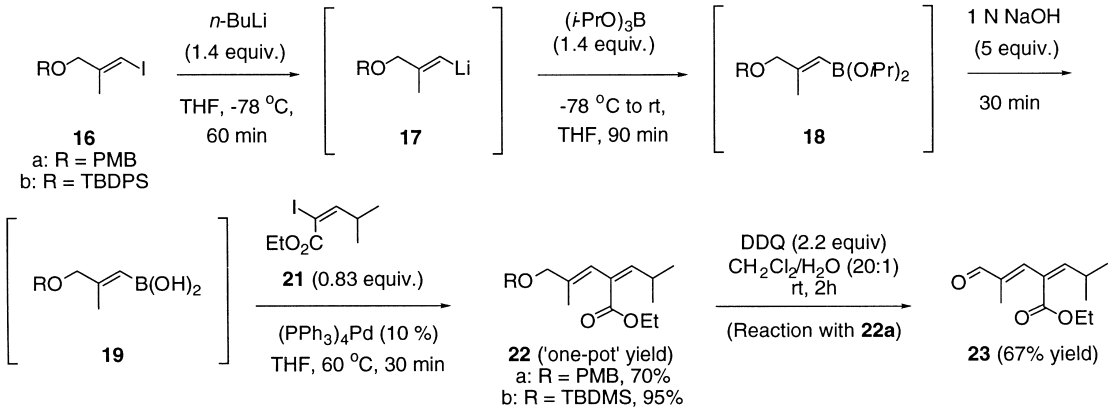
Elaboration of **17** to **19** using a variation of the Corey–Fuchs reaction proceeded smoothly (Scheme 2).[15] Pd-catalysed hydrostannylation provided **20** in a fully selective fashion which was subsequently iodinated to provide **21**. Also of note, and further confirming the steric considera-



Scheme 2.

tions for stannanes, **20** was found to be completely unreactive when we tried to couple it to **16**. Thus, while the tin moieties were critical for obtaining the correct regio- and stereochemistry of both trisubstituted olefin partners, the tin moieties could not be used to assemble them together.

With compounds **16** and **21** efficiently prepared and in hand, attention shifted to the critical cross coupling that would join the hydrophobic tail to the template and ultimately to the pyrone subunit. Boronic acids are known to be less sterically demanding than the corresponding stannane, thus our first attempt at coupling **16** and **21** was via the boron derivative.[14] Compound **16** does not contain any organolithium-sensitive groups, so we chose to install the metal on it. Treatment of **16** with *n*-butyllithium provided intermediate **17** that was quenched with triisopropylborate giving rise to borate ester **18** (Scheme 3). It was found that the ester was not very reactive toward the coupling reaction, thus it was hydrolysed to the corresponding acid (**19**) and compound **21** was added directly to the pot followed by catalyst. The 'one pot' lithium/halogen exchange, boron/lithium exchange, saponification, and cross-coupling sequence provided the desired product as one single isomer. The *t*-butyldiphenylsilyl-protected (TBDPS) alcohol provided the final product in 95% yield overall, thus we are confident that the yield with the PMB-protected product can be improved. The DDQ oxidative deprotection of the PMB group provided aldehyde **23** directly which is necessary to connect the template to the pyrone which we plan to do employing a Wittig strategy. Similar Wittig reactions have proceeded stereoselectivity with analogous poly disubstituted olefin systems.[16]



Scheme 3.

In summary, a route has been designed for the efficient construction of the tail portion of orevactaene, a recently isolated but yet to be synthesised natural product with demonstrated anti-HIV activity. This general strategy will allow for the construction of four diastereomeric tails that will be joined to the pyrone substructure of the molecule via a common Wittig reaction through a common trisubstituted olefin template. The route to the template is direct involving one three-step and one four-step 'one-pot' preparation of the necessary precursors. Preparation of the four isomeric dimethyl-containing fragments (i.e. C22–C27) is underway and progress will be reported in due course.

Acknowledgements

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