Stereocontrolled Synthesis of Carbon Chains Bearing Contiguous Methyl Groups by Iterative Boronic Ester Homologations. Application to the Total Synthesis of (+)-Faranal**

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Carbon chains bearing 1,3,5…n polymethyl groups are ubiquitous in natural products. Recently, effective solutions for a flexible, stereoc ontrolled synthesis of such arrays have been achieved by the groups of Feringa-Minnaard,[1] Breidt[2] and Negishi.[3] Carbon chains bearing adjacent methyl groups, although less common, are also frequently encountered[4] (Fig 1) but a general stereocontrolled solution to this problem has not been advanced.[5] For example, in the previous syntheses of the insect pheromone faranal 1,[5b] one or both methyl groups originate from a carboxylic ester to enable control of relative stereochemistry during C-C bond formation (both utilise resolution to effect absolute control).[6] Introducing the methyl groups in the wrong oxidation state invariably leads to an increase in the total number of steps required.

We recently reported a method to homologate carbon chains bearing boronic esters using Hoppe’s lithiated carbamates.[7,8] Through appropriate choice of the diamine ligand employed in the lithiation of the carbamate [(-)-sparteine[9] or O’Brien’s[10] (+)-sparteine surrogate] we showed that either enantiomer of either diastereomer of the homologated product could be easily obtained (Scheme 1). We now demonstrate the application of this methodology to a stereocontrolled synthesis of faranal and furthermore, highlight a new one-pot multiple homologation process.

Our retrosynthetic analysis of faranal 1 is shown in Scheme 2. We envisaged that the target compound could be obtained through a suitable two-carbon homologation of boronic ester 2. This could be obtained by two consecutive homologations of boronic ester 5 using the lithiated carbamate 3 derived from (-)-sparteine. This was expected to control both the relative and absolute stereochemistry and thus deliver the required anti isomer 2. Boronic ester 5 could be obtained from the corresponding alkyne 6.[11]

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**Figure 1.** Examples of natural products bearing adjacent methyl groups.
**Scheme 2.** Retrosynthetic analysis of faranal 1.

**Scheme 3.** Model study for the synthesis of faranal (see end, after references)

Model studies to test the multiple homologation reactions were initially conducted on geraniol (Scheme 3), which was converted directly into the allylic boronic ester 8 (93:7, E:Z) through a novel coupling process employing Bpin and the commercially available palladium catalyst 7.[12] This intermediate 8 was treated with the lithiated carbamate 3, furnishing the 1st homologated boronic ester 9 in 78% yield and 96:4 e.r. (determined by oxidation to the alcohol and analysis by Mosher’s ester). A further homologation with the same lithiated carbamate 3 gave the 2nd homologation boronic ester 10 in 52% yield, >98:2 e.r. and 94:6 d.r. (determined as above). A third homologation with vinyl lithium followed by treatment with I2 and NaOMe[13] gave an intermediate alkene 11 which was directly hydroborated and oxidised to give the alcohol 12 in 76% yield, with the same selectivity. Remarkably, it was possible to convert boronic ester 8 directly into alcohol 12 by simply carrying out all three homologations consecutively in a one-pot operation. Not only did this provide substantial savings in time but it also led to a significant increase in overall yield without detriment to the selectivity observed (60 % yield; 94:6 d.r.; 93:7, E:Z).

Key to the success of this one pot operation, we believe, is the fate of the reactive intermediates that are generated. The lithiated carbamate reacts rapidly with the boronic ester forming the intermediate ate complex 13. An excess of the lithiated carbamate is employed to ensure complete reaction with the boronic ester. Fortunately, the unreacted lithiated carbamate decomposes at a lower temperature than that required to effect the 1,2-metallate rearrangement of the ate complex.[14] Thus, as the reaction is heated, the excess lithiated carbamate is destroyed and then the homologated boronic ester is formed ensuring that with each successive addition of the lithiated carbamate single homologations occur in high yield.

**Scheme 4.** Potential reactions of lithiated carbamate.

Having established a highly effective one pot protocol for the direct conversion of the allylic boronic ester 8 into alcohol 12 we began the synthesis of (+)-faranal 1 itself (Scheme 4), although we wished to improve the E/Z selectivity of the alkenes in the final product as this had been the bane of previous syntheses.[6]

**Scheme 5.** Total synthesis of (+)-faranal 1.

Although vinyl iodide 21 had been reported previously[11,15] our current route represents a practical improvement as it avoids having to handle HMPA and acetylene. The route began with a zirconium catalysed ethyl aluminiation[16] of propyne followed by quenching with I2, to furnish the Z vinyl iodide 18. Subsequent Negishi cross-coupling with the alkyl iodide 19 gave the unsaturated acetylene 20. Desilylation[17] followed by a second zirconium catalysed carboalumination, trapping with I2 gave the vinyl iodide 21 which was lithiated and coupled with the chloromethyl boronic ester 22 furnishing 5 with complete E selectivity. Application of the one pot, triple homologation sequence then furnished alcohol 23 in 69% yield; >98:2 e.r.; 94:6 d.r.; >98:2, E.Z. During the course of this work, we discovered that Lewis acid activation of the carbamate group by MgBr2 was not required to trigger the 1,2-metallate rearrangement, simply heating to 40 °C was sufficient. This modification simplified the one pot protocol significantly and resulted in a 57% yield of alcohol 23, again without detriment to the selectivity observed. We have even found that the simple vinyl iodide 21 can be converted into the complex alcohol 23 in 40% yield in a quadruple homologation sequence without purification of any intermediates which avoids having to handle the sensitive allylic boronic ester 5. Finally, the alcohol 23 was converted into (+)-faranal 1 by PDC oxidation.[18] The synthetic material was identical in all respects to the natural product. The asymmetric, fully stereocontrolled synthesis of (+)-faranal was completed in just 6 steps from propyne, a substantial saving from previously reported synthesis (19 steps[6,10], 29 steps[6,8] and 10 steps[5]).

In conclusion, we have developed methodology for the stereocontrolled synthesis of carbon chains bearing adjacent methyl groups and applied it to a short synthesis of (+)-faranal. This methodology is akin to a molecular assembly line in which successive groups are added to a growing chain with control of a relative and absolute stereochemistry. Remarkably, these successive additions can be carried out in one pot with improved efficiency (yield and manpower!) and without detriment to selectivity. Further work is now ongoing to identify the practical limits of this multiple homologation process.
**Experimental Section**

(Experimental Details)

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4. See for examples: (+)-Faranal 1: a) F. J. Ritter, I. E. M. Brügger-  

5. a) For a recent example of the problems encountered in trying to create this motif see reference 4f; b) During the course of this work Feringa and Minnaard reported a potential solution and summarised past approaches to this problem. They also applied their methodology to a synthesis of faranal in which the contiguous methyl groups were introduced in the correct oxidation state; A. W. van Zijl, W. Synnaski, F. Lopez, A. Minnaard, B. L. Feringa, J. Org. Chem. 2008, 73, 6994-7002.


17. The acetylide 6 was found to be unstable to distillation and so was used crude.
Scheme 3. Model study for the synthesis of faranal (see end)

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Multiple homologations

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A quadruple homologation of a boronic ester converts a simple vinyl iodide into a complex precursor to faranal with very high levels of diastereo- and enantio-control. This enables the synthesis of faranal to be completed in just 6 steps and 18% overall yield from propyne.