Assembly-Line Synthesis

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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, stereocontolled 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] (Figure 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 utilize resolution to achieve 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.

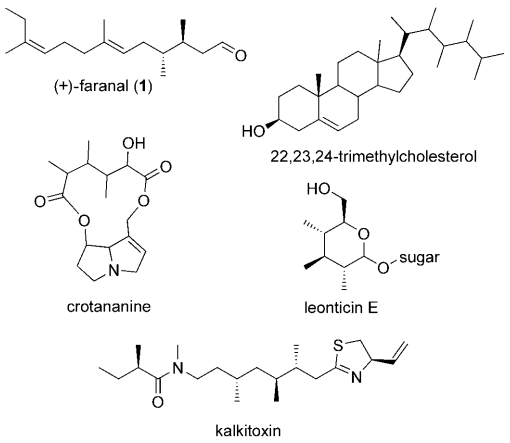
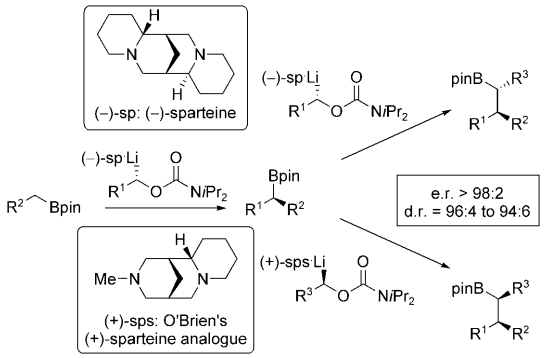
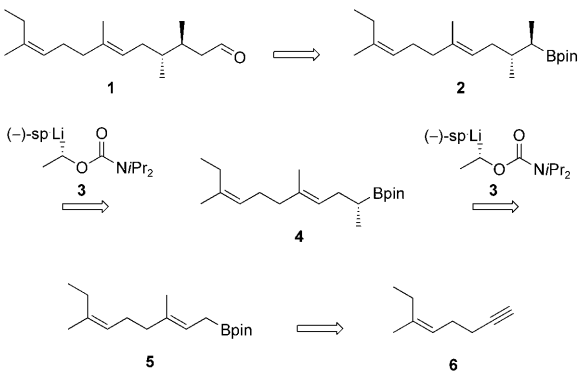


Figure 1. Examples of natural products bearing adjacent methyl groups.



Scheme 1. Access to all four isomers using iterative homologations of boronic esters. pin = pinacolate.

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 intermediate could be obtained, in turn,



Scheme 2. Retrosynthetic analysis of (+)-faranal (**1**).

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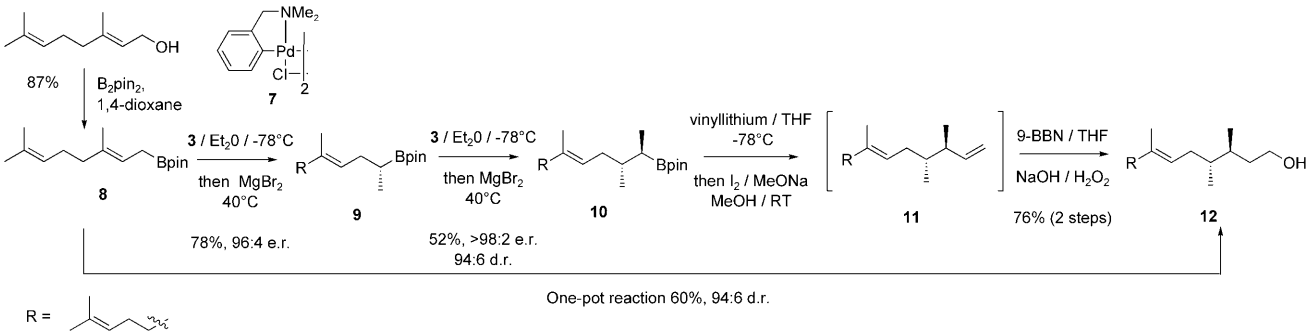


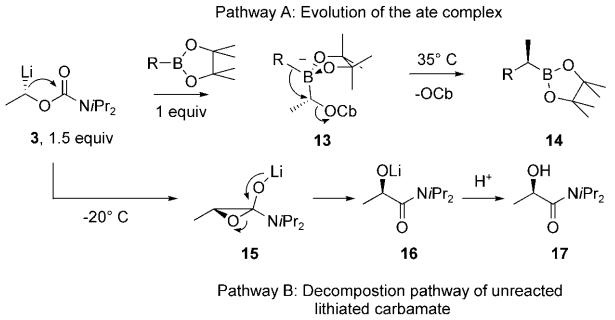
Scheme 3. Model study for the synthesis of (+)-faranal. 9-BBN = 9-borabicyclo[3.3.1]nonane.

by two consecutive homologations of boronic ester **5** using the lithiated carbamate **3** derived from (−)-sparteine. These homologations were 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]

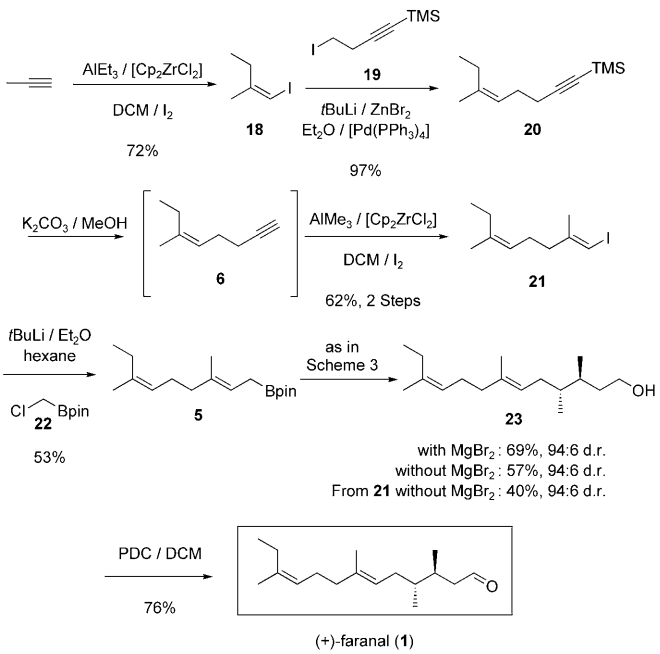
Model studies to test the multiple homologation reactions were initially conducted on geraniol (Scheme 3), which was converted directly into the allylic boronic ester **8** (93:7, *E*/*Z*) through a novel coupling process employing B_2pin_2 and the commercially available palladium catalyst **7**.[12] This intermediate **8** was treated with the lithiated carbamate **3**, furnishing the first homologated boronic ester **9** in 78% yield and 96:4 e.r. (determined by oxidation to the alcohol and analysis of the Mosher's ester). A further homologation with the same lithiated carbamate **3** gave boronic ester **10** in 52% yield, > 98:2 e.r., and 94:6 d.r. (determined as above). A third homologation with vinyllithium followed by treatment with I_2 and NaOMe[13] gave the intermediate alkene **11**, which was directly hydroborated and oxidized 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 one pot. 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** (Scheme 4). 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 mixture 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.

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, 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] 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-catalyzed ethyl alumination[16] of propyne followed by quenching with I_2, to furnish the *Z* vinyl iodide **18** (Scheme 5). Subsequent Negishi cross-coupling with the alkyl iodide **19** gave the unsaturated alkyne **20**. Desilylation[17] followed by a second zirconium-catalyzed carboalumination and trapping with I_2 gave the vinyl iodide **21**, which was lithiated and coupled with the chloromethyl boronic ester **22** to furnish **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 $MgBr_2$ 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.[6d] The synthetic material was identical in all respects to the natural product. The asymmetric, fully stereocontrolled synthesis of (+)-faranal was completed in just six steps from propyne, a substantial improvement over previously reported synthesis (19 steps[6c,d], 29 steps[6a,b] and 10 steps[5b]).



Scheme 4. Potential reactions of lithiated carbamate. Cb = *N*,*N*-diisopropylcarbamoyl.



Scheme 5. Total synthesis of (+)-faranal (**1**). TMS = trimethylsilyl, Cp = cyclopentadienyl, PDC = pyridinium dichromate, DCM = dichloromethane.

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.

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