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Stereocontrolled Methodology

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Stereocontrolled Synthesis of Adjacent Acyclic Quaternary-Tertiary Motifs and its Application to a Concise Total Synthesis of (−)-Filiformin**

*Daniel J. Blair, Catherine J. Fletcher, Katherine M. P. Wheelhouse[§] and Varinder K. Aggarwal**

***Abstract**: Lithiation-borylation methodology has been developed for the synthesis of acyclic quaternary-tertiary motifs with full control of relative and absolute stereochemistry leading to all four possible isomers of a stereodiad. A novel intramolecular Zweifel-type olefination enabled acyclic stereocontrol to be transformed into cyclic stereocontrol. These key steps have been applied to the shortest enantioselective synthesis of (−)-filiformin to date (9 steps) with full stereocontrol.*

Natural products containing quaternary stereogenic centers flanked by additional stereogenic centers, often embedded in fused or bridged ring systems are ubiquitous in nature (Figure 1). Their varied structures and complexity have stimulated a range of synthetic strategies for their synthesis.[1] A common strategy in many syntheses is to initially construct the ring(s) and then to use the ring system to control stereochemistry around its periphery. Whilst often efficient, this strategy can be limiting as it is based on substrate control. A potentially more flexible, but under-utilized strategy involves constructing an acyclic molecule with control of stereochemistry through reagent control and then to build the ring afterwards. In this way, stereocontrol can be essentially dialled in. However, whilst acyclic stereocontrol can be straightforward for many substrates, for molecules bearing quaternary-tertiary motifs this poses a considerable synthetic challenge.

Our recent methodology for acyclic stereocontrol[2] involves the reaction of primary/secondary lithiated carbamates with boronic esters and its potential strategic application in the synthesis of cyclic quaternary-tertiary motifs is illustrated in Scheme 1. In this strategy

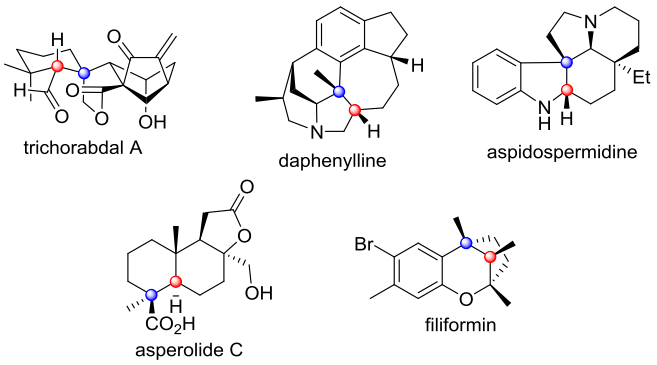
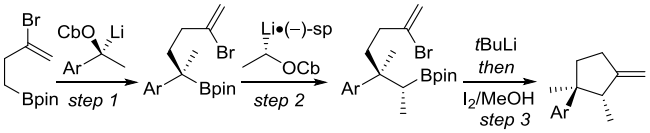


Figure 1. Natural products featuring adjacent quaternary-tertiary stereocenters.

we proposed to carry out sequential homologations with a secondary carbamate (step 1)[3] followed by a primary carbamate (step 2)[4] in order to construct quaternary-tertiary boronic esters. We then proposed to carry out an *intra*molecular Zweifel-type olefination[5] reaction (step 3) to construct the ring. Steps 2, and 3, which are key to this strategy, had not been previously reported. In this paper we describe our success in developing these reactions and applying them to a short, stereocontrolled synthesis of (−)-filiformin.



Scheme 1. Proposed route to all-carbon quaternary stereocenters with adjacent stereocenters. Cb = CON(*i*Pr)$_2$pin = pinacolato (−)-sp = (−)-sparteine.

Our initial studies began with the homologation of tertiary boronic ester *rac*-**1** with lithiated carbamate *rac*-**2** which was generated by deprotonation of ethyl carbamate with *s*BuLi at −78 °C in the presence of TMEDA (Scheme 2a). After oxidation *rac*-**3** was isolated in 53% yield and 2:1 *dr* showing that there were no appreciable matched/mismatched effects.

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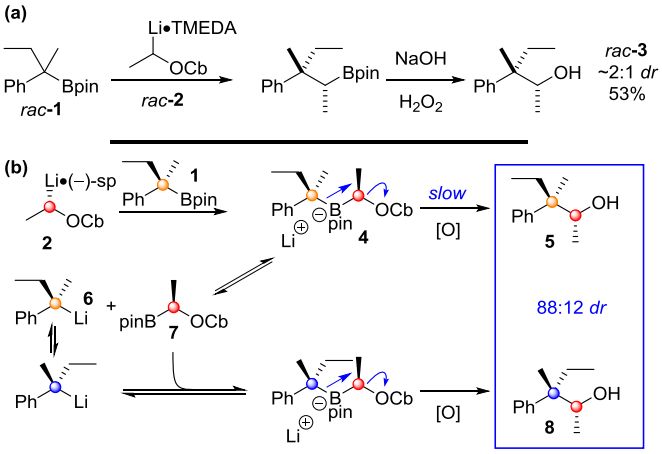
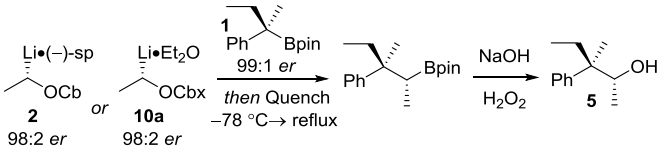


Scheme 2. (a) Racemic homologation of *rac*-**1** (b) Homologation of **1** with enantioenriched reaction partners and proposed mechanism for formation of diastereoisomers.

Table 1. Optimization of conditions for the homologation of tertiary boronic ester **1** with **2**/**10a**.



Entry	Carbamate	*Quench*	*dr*[a]	*er*[b]	Yield[c]
1	**2**		88:12 (**5**:**8**)	>99:1	nd
2[d]	**2**		88:12(**5**:**8**)	nd	nd
3	**2**	MeOH	98:2 (**5**:*ent*-**8**)	>99:1	28
4	**2**	$MgBr_2$/ MeOH	98:2(**5**:*ent*-**8**)	>99:1	22
5	**2**	AllylBr	98:2 (**5**:*ent*-**8**)	>99:1	48
6	*ent*-**2**[e]	AllylBr	1:99 (**5**:*ent*-**8**)	>99:1	32[f]
7	**10a**	AllylBr	98:2 (**5**:*ent*-**8**)	>99:1	73

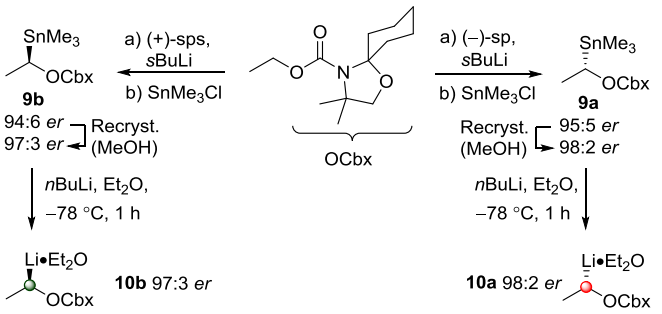
[a] Determined by GCMS [b] Determined by chiral HPLC [c] Isolated yield of **5** [d] Neopentyl glycol boronic ester used [e] (+)-sparteine surrogate used in place of (−)-sparteine [f] Isolated yield of *ent*-**8**

When we carried out the reaction with enantioenriched boronic ester **1** and enantioenriched lithiated carbamate **2** we were expecting to selectively form a single diastereomeric ate complex **4** which should then rearrange to give the single diastereomer **5**. However, when we carried out this reaction we obtained **5** in only 88:12 *dr*, albeit with perfect *er* (Table 1, entry 1). It was unclear at this point which of the two stereogenic centers was epimerizing, and so further experiments were conducted. Thus, enantioenriched lithiated carbamate **2** was reacted with racemic boronic ester *rac*-**1** and *vice versa*. Oxidation and analysis of the secondary alcohol products by chiral HPLC enabled us to map the fate of each stereogenic center individually during the homologation process (see SI). From these experiments we determined that partial racemization had occurred, not in the sensitive organolithium **2** bearing the secondary center which is undergoing significant transformations, but at the static quaternary stereogenic center derived from the boronic ester, leading to the minor diastereoisomer **8**. The mechanism for its formation is shown in Scheme 2b. Following formation of the boronate complex **4**, 1,2-metallate rearrangement will give the major isomer **5**. If this rearrangement is slow, competing fragmentation to the benzylic carbanion **6** can occur. Racemization of **6**, re-addition to boronic ester **7**, and rearrangement then leads to the minor diastereoisomer **8**. In support of this mechanism, boronic ester **7** was also isolated in high *er*.

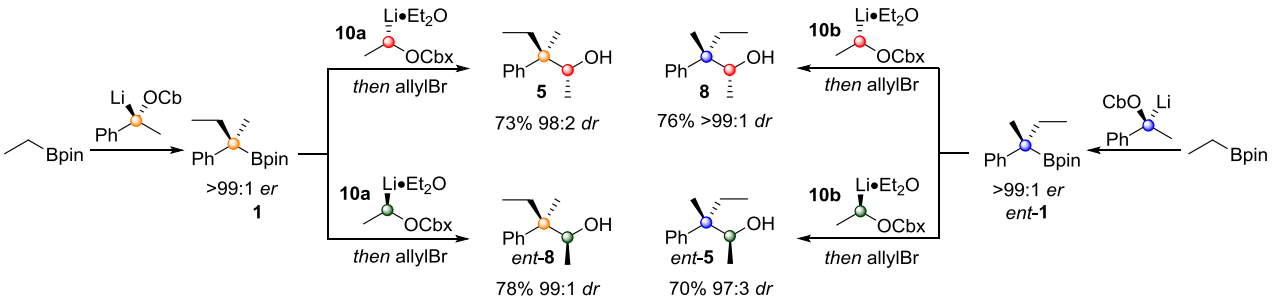
In an attempt to reduce the undesired fragmentation of ate complex **4** the less hindered neopentyl glycol boronic ester was tested, since related neopentyl boronate complexes have been shown to be less prone to reversibility than the corresponding pinacol boronates.[3a, 6] However, homologation of neopentyl-**1** gave similar results to the pinacol ester (Table 1, entry 2). As an alternative, we sought to trap the anion **6** as it was formed with an electrophile preventing its readdition to the boronic ester (Table 1, entries 2-5). Of the electrophiles tested allyl bromide proved to be highly effective leading to **5** in high *dr* and *er* (entry 5). The relative stereochemistry of **5** was determined by X-ray crystallography.[7]

However, the yield was only moderate (48%) and fell further (32%) when we attempted to synthesise the other diastereoisomer of **5** by using O'Brien's (+)-sparteine surrogate [(+)-sps][8] in place of (−)-sparteine in the lithiation step (Table 1, entry 6). We reasoned that the bulky diamine was inhibiting the addition process and therefore explored diamine-free conditions [generating the organolithium **10a** *via* tin-lithium exchange of the corresponding stannane **9a**] in order to make the carbanion less hindered.[9] This led to a considerably higher yield (73%) (Table 1, entry 7). Stannanes **9a** and **9b** were easily obtained in high *er* as shown in Scheme 3.[10]

With these optimum conditions we moved on to synthesise the remaining three stereoisomers (Scheme 4). Reaction of the opposite enantiomer of the carbamate **9b** with boronic ester **1** gave the opposite diastereomer *ent*-**8** in 99:1 *dr* and >99:1 *er*. Reaction of the opposite enantiomer of the boronic ester *ent*-**1** with the pair of lithiated carbamates **10a**/**10b** gave the remaining isomers of the series in good yield and with essentially perfect stereocontrol (Scheme 4). It is interesting to note that even in the mis-matched cases (forming **5** and *ent*-**5**) very high diastereocontrol (>97:3) was still observed.

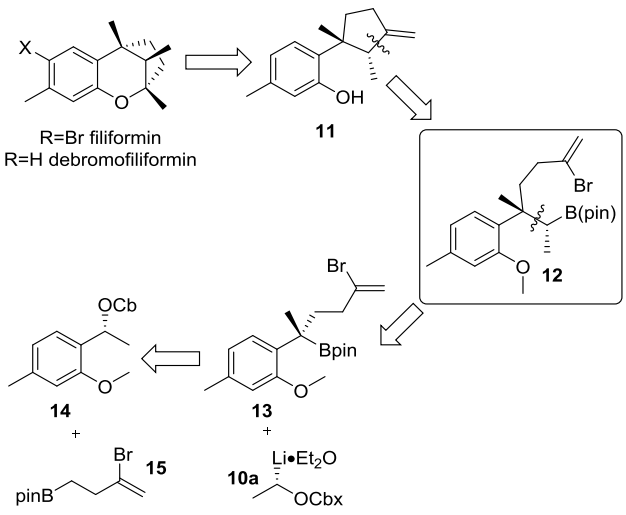


Scheme 3. Preparation of diamine-free lithiated carbamates **10a** and **10b**. (−)-sp = (−)-sparteine, (+)-sps = (+)-sparteine surrogate, OCbx =3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate.



Scheme 4. Homologation of tertiary boronic esters with lithiated carbamates under diamine-free conditions to produce adjacent quaternary-tertiary stereocenters. Reactions were performed on 1 mmol of **1**/ent-**1** using 1.5 mmol of **10a/10b.**.

We then sought to apply our methodology to a total synthesis of the sesquiterpene (−)-filiformin. Disconnecting the phenol ether of debromofiliformin leads back to 3-hydroxylaurene (**11**), which itself could potentially be obtained from an *intra*molecular Zweifel-type olefination of **12** (Scheme 5). This key intermediate could be synthesised using the above methodology through reaction of lithiated carbamate **10a** with tertiary boronic ester **13**. Boronic ester **13** could in turn be prepared by a lithiation borylation of known carbamate **14** and primary boronic ester **15**.

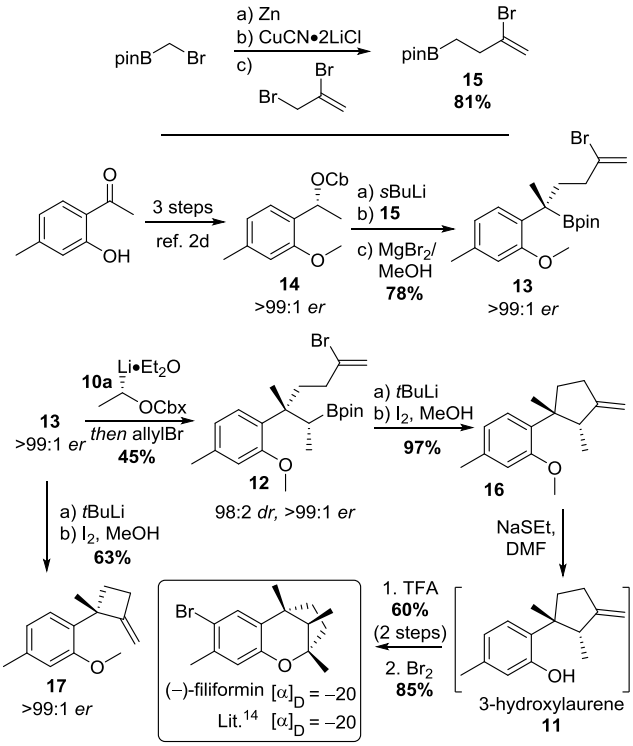


Scheme 5. Retrosynthetic analysis of (−)-filiformin.

Boronic ester **15** was prepared from bromomethyl boronic acid pinacol ester and 2,3-dibromo-1-propene to give **15** in 81% yield using a procedure described by Knochel.[11] Carbamate **14** was prepared in three steps starting from 2'-hydroxy-4'-methyl acetophenone as previously described.[2d] The lithiation-borylation of carbamate **14** with boronic ester **15** proceeded smoothly to give tertiary boronic ester **13** in 78% yield with complete enantioselectivity.

Tertiary boronic ester **13** is especially hindered due to the *ortho* methoxy group and the long alkyl chain so formation of the boronate complex was expected to be even more challenging than in the model system. Nevertheless, under our optimized conditions using lithiated carbamate **10a** we were able to obtain **12** in 45% yield, 98:2 *dr*, and perfect *er*.[12] Using the conditions shown in Table 1, entry 5, no product was obtained, highlighting the advantages of the diamine-free conditions with especially hindered substrates.

We then sought to perform the *intra*molecular Zweifel-type olefination of boronic ester **12**. Addition of *t*BuLi to a solution of **12** in THF at −78 °C followed by addition of I_2 in MeOH gave cyclopentene **16** in 97% yield and 100% es (Scheme 6). The exceptionally high yield in this reaction prompted us to explore the more challenging *intra*molecular Zweifel-type olefination of boronic ester **13** as this would lead to a highly strained exomethylene cyclobutane. We were pleased to find that application of the same conditions to **13** gave **17** in 63% yield, again with complete selectivity (Scheme 6).



Scheme 6. Total synthesis of (−)-filiformin.

Deprotection of the methyl ether using NaSEt[13] gave 3-hydroxylaurene **11** and subsequent addition of catalytic amounts of

TFA[14] led to clean cyclization to give debromofiliformin as a single diastereoisomer in 60% yield over 2 steps. Finally, bromination completed the synthesis of (−)-filiformin in a total of just 9 steps, 98:2 *dr* and >99:1 *er*. The analytical data was identical to that of the natural (−)-filiformin in all respects.[14]

In conclusion we have developed lithiation-borylation methodology for the construction of highly challenging quaternary-tertiary motifs in acyclic systems with full control of relative and absolute stereochemistry. Key to success was the use of diamine-free lithiated carbamates to promote the addition step and allyl bromide to quench any benzylic carbanions formed during the 1,2-metallate rearrangement. A unique *intra*molecular Zweifel-type olefination enabled acyclic stereocontrol to be transformed into cyclic stereocontrol. These key steps were applied to the shortest enantioselective synthesis of (−)-filiformin (9 steps), the previous being 19 steps.[15]

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Keywords: lithiation-borylation • total synthesis • filiformin • quaternary stereocenter • boronic ester

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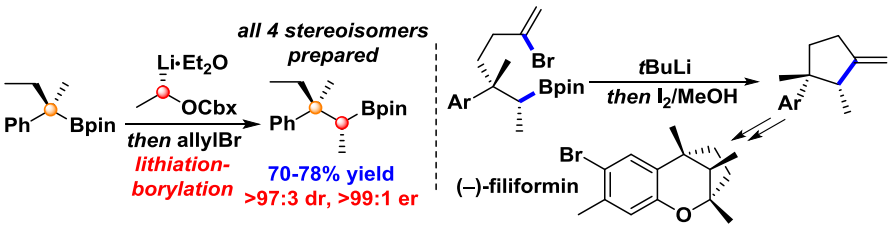

Lithiation-borylation methodology has been developed for the synthesis of acyclic quaternary-tertiary motifs with full control of relative and absolute stereochemistry leading to all four possible isomers of a stereodiad. A novel intramolecular Zweifel-type olefination enabled acyclic stereocontrol to be transformed into cyclic stereocontrol. These key steps have been applied to the shortest enantioselective synthesis of (−)-filiformin to date (9 steps) with full stereocontrol.