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One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation–borylation, allylation and Prins cyclisation reactions

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ABSTRACT

2,3,4,5,6-Pentasubstituted tetrahydropyrans have been prepared in good yield (42–57%) with excellent *dr* (>95:5) and *er* (>95:5) using a one-pot lithiation–borylation, allylation and Prins cyclisation reaction.

Substituted tetrahydropyrans (THPs) are ubiquitous in Nature.[1] They show great diversity in structure and complexity, from the relatively simple tri-substituted THP, (−)-diospongin A[2] to the highly complex polyketide marine metabolites clavosolide A[3] and (−)-kendomycin[4] with penta-substituted THP cores (Fig. 1). One of the most efficient strategies for their construction involves the Prins cyclisation,[5] as demonstrated by numerous research groups.[5a,6] Indeed, the acid-catalysed Prins cyclisation of an in situ generated oxocarbenium ion has been extensively used for the stereoselective synthesis of diversely functionalised THPs.[7] Although allyltin[8] and allylsilyl[9] reagents have been used in this context, to the best of our knowledge, there is only a single report of allylboron reagents being used for the stereoselective synthesis of racemic THPs via a tandem allylation and Prins cyclisation.[10]

We recently reported the enantioselective synthesis of α-substituted allylic boron reagents which could be reacted with aldehydes to give homoallylic alcohols with control of all elements of stereochemistry (*syn*/*anti*; *E*/*Z*).[11] We recognised that if these products could be used in a subsequent Lewis acid-catalysed Prins cyclisation we would have the ability to form highly substituted THPs with excellent diastereoselectivity and enantioselectivity.[12]

We postulated that if the allylation products, **6** or **7** formed via an initial allylation with the first equivalent of aldehyde, could be trapped by a second aldehyde in the presence of a Lewis acid, a Prins cyclisation should ensue (**8** → **10** or **9** → **11**) to give highly substituted THPs (Fig. 2). The enantioselectivity would be set in the lithiation–borylation reaction (>98:2 *er*) and the diastereoselectivity would be set in the allylation reaction (>95:5 *dr*), and subsequent Prins cyclisation.

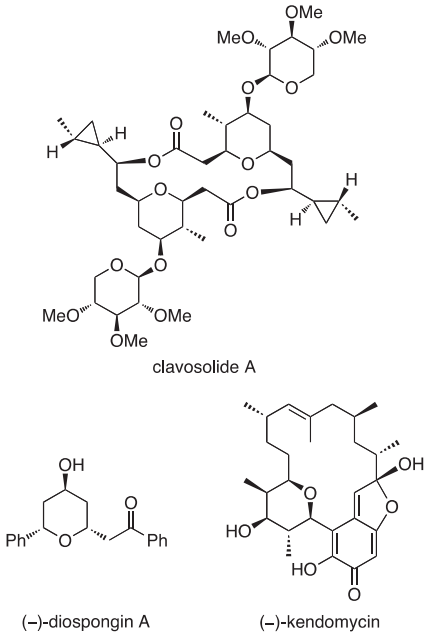

Figure 1. THP-containing natural products.

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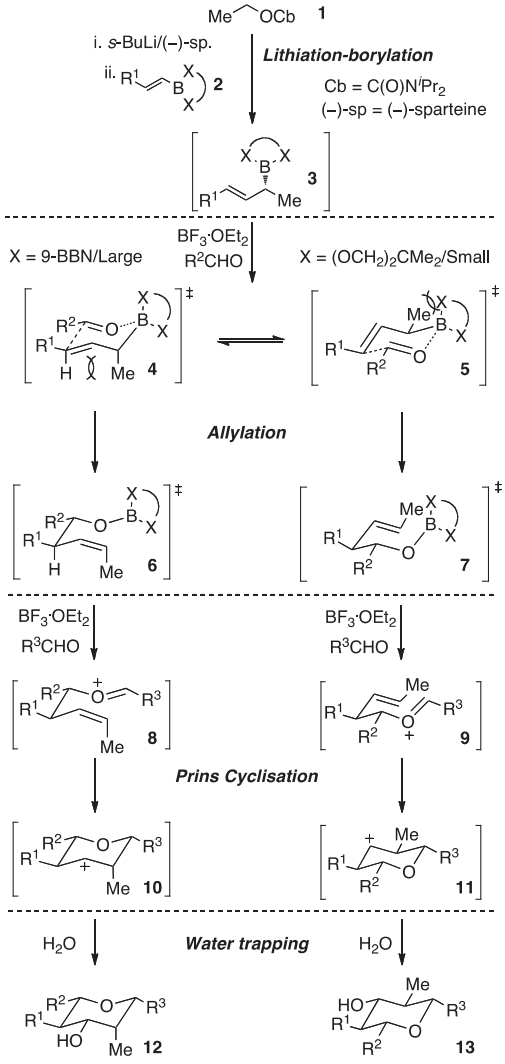


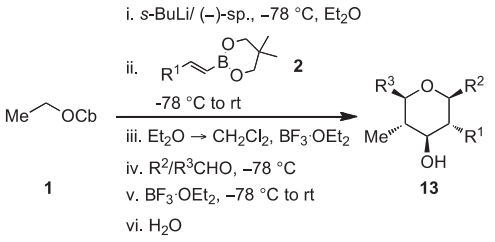
Figure 2. Proposed synthesis of highly substituted THPs via lithiation–borylation, allylation and Prins cyclisation.

Significantly, the substituents on boron could be exploited to favour one of two transition state (TS) structures **4** and **5** in the initial allylation reaction with the first aldehyde. Large substituents on boron (e.g. 9-BBN) would cause a steric clash between the Me group and the boron substituents,[13] thereby favouring the allylation product arising from TS **4**. This would give the (*Z*)-alkene which, after Prins cyclisation, would give the 3,5-*anti*-THP **12** after work-up. Use of small boron substituents [e.g. $(OCH_2)_2CMe_2$] reduces the steric clash between the Me group and the boron substituents[14] and now TS **5** with the Me group in the pseudo equatorial position would be favoured due to competing $A^{1,3}$ strain in TS **4**. This would lead to the (*E*)-alkene which, following Prins cyclisation and trapping by water, would give the all equatorial substituted THP **13**, with the 3,5-*syn* arrangement.

Furthermore, the sequential nature of our proposed THP synthesis presents the possibility for a one-pot synthesis of fully differentiated THPs via the addition of two different aldehydes. The 3- and 5-substituents arise from the carbamate **1** and boron reagent **2** and the 2- and 6-substituents from the aldehydes used in the allylation and Prins reactions, respectively.

Our studies began by targeting the all equatorial substituted THPs **13** (Table 1, entries 1–6). To favour TS **5**, neopentylglycol boronic esters were used along with a similar allylation protocol to that which we had previously used with great success.[11] Thus, deprotonation of ethyl carbamate **1** with *s*-BuLi in the presence of (−)-sparteine followed by the addition of vinyl boronic ester **2** gave an intermediate ate complex. To promote 1,2-metallate rearrangement, and thus formation of the allylboronic ester **3** [$X = (OCH_2)_2CMe_2$], a solvent exchange was carried out from Et_2O to CH_2Cl_2 and $BF_3{\cdot}OEt_2$ was added. Subsequent addition of an excess of either cyclohexylcarboxaldehyde or benzaldehyde (these were used as representative aldehydes) and further addition of $BF_3{\cdot}OEt_2$ followed by aqueous work-up gave the THPs in moderate yields but very high enantioselectivity and very high diastereoselectivity. In the one-pot process three C–C bonds, and two C–O bonds have been formed and 5 stereogenic centres have been controlled. The use of a variety of boronic esters was examined including Me- (entries 1 and 2), Bu- (entries 3 and 4) and H- (entries 5 and 6). In all cases excellent stereocontrol was observed even with the parent unsubstituted vinylboronic ester (R^1 = H, entries 5 and 6). Interestingly, no addition of fluoride was observed at the 4-position as might be expected when using BF_3 in the absence of a fluoride trap.[15,16]

Table 1
Synthesis of 2,3,4,5,6-pentasubstituted THPs using neopentylglycol boronic esters[a,b]



Entry	R^1	R^2	R^3	Yield (%)	*dr*[c]	*er*[d]
1[a]	Me	Ph	Ph	54	>95:5	96:4
2[a]	Me	Cy	Cy	51	>95:5	—
3[a]	Bu	Ph	Ph	52	>95:5	98:2
4[a]	Bu	Cy	Cy	57	99:1	—
5[a]	H	Ph	Ph	45	>95:5	98:2
6[a]	H	Cy	Cy	49	>95:5	—
7[b]	Bu	Cy	Ph	50	>95:5	96:4
8[b]	Bu	Ph	Cy	48	>95:5	95:5
9[b]	Me	Cy	Ph	54[e]	>95:5	97:3
10[b]	H	Cy	Ph	44	>95:5	97:3

[a] $R^2 = R^3$ (i) *s*-BuLi (1.4 equiv), (−)-sp. (1.4 equiv), Et_2O (0.17 M), −78 °C, 5 h. (ii) Compound **2** (1.7 equiv), −78 °C to rt, 2.5 h. (iii) Et_2O to CH_2Cl_2, $BF_3{\cdot}OEt_2$ (2 equiv), rt, 0.5 h. (iv) R^2CHO (4 equiv), −78 °C, 1 h. (v) $BF_3{\cdot}OEt_2$ (2 equiv), −78 °C to rt, 18 h. (vi) H_2O, rt, 3 h.

[b] $R^2 \neq R^3$ (i) *s*-BuLi (1.4 equiv), (−)-sp. (1.4 equiv), Et_2O (0.17 M), −78 °C, 5 h. (ii) Compound **2** (1.7 equiv), −78 °C to rt, 2.5 h. (iii) Et_2O to CH_2Cl_2, $BF_3{\cdot}OEt_2$ (2 equiv), rt, 0.5 h. (iv) R^2CHO (1.5 equiv), −78 °C, 1 h. (v) R^3CHO (3 equiv), −78 °C, 1 h. (vi) $BF_3{\cdot}OEt_2$ (2 equiv), −78 °C to rt, 18 h. (vii) H_2O, rt, 3 h.

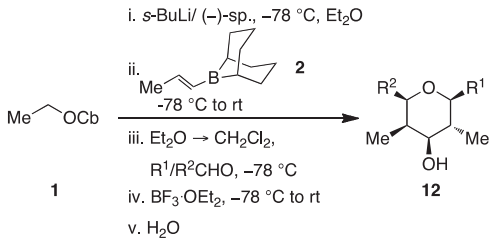
[c] Of the major product, ratio of major diastereomer: all other diastereomers.

[d] Of the major product, determined by chiral-GC. Absolute stereochemistry assigned in accordance with literature precedence.[11]

[e] Of the major product, isolated as a 2:1 mixture of 2-Ph-6-*c*-Hex- and 2,6-di-*c*-Hex-THP.

The use of different aldehydes in the sequential allylation, Prins cyclisation was also explored as this would lead to a fully differentially substituted THP, a significantly greater challenge.[5a] However, by simply adding the two aldehydes in sequence we were able to obtain the 2,6-differentially substituted THPs in good yield and excellent *dr* and *er* (Table 1, entries 7–10). In one case (Table 1, entry 9), when cyclohexylcarboxaldehyde was used as the first aldehyde (followed by benzaldehyde), we observed a significant amount of the bis-cyclohexyl substituted THP. In contrast, the use of benzaldehyde as the first aldehyde followed by cyclohexylcarboxaldehyde gave the required THP with complete control over the substitution at each THP-carbon (entry 8). Presumably, the lower selectivity of the former reaction can be explained by the decreased reactivity of benzaldehyde compared to cyclohexylcarboxaldehyde.

Table 2
Synthesis of 2,3,4,5,6-pentasubstituted THPs using *B*-9-BBN boranes[a,b]



Entry	R^1	R^2	Yield (%)	*dr*[c]	*er*[d]
1[a]	Ph	Ph	48	>95:5	95:5
2[a]	Cy	Cy	45	>95:5	—
3[b]	Cy	Ph	42[e]	>95:5	97:3

[a] $R^1 = R^2$ (i) *s*-BuLi (1.4 equiv), (−)-sp. (1.4 equiv), Et_2O (0.17 M), −78 °C, 5 h. (ii) Compound **2** (1.7 equiv), −78 °C to rt, 2.5 h. (iii) Et_2O to CH_2Cl_2, R^1CHO (4 equiv), −78 °C, 1 h. (iv) $BF_3{\cdot}OEt_2$ (4 equiv), −78 °C to rt, 18 h. (v) H_2O, rt, 3 h.

[b] $R^1 \neq R^2$ (i) *s*-BuLi (1.4 equiv), (−)-sp. (1.4 equiv), Et_2O (0.17 M), −78 °C, 5 h. (ii) Compound **2** (1.7 equiv), −78 °C to rt, 2.5 h. (iii) Et_2O to CH_2Cl_2, R^1CHO (1.5 equiv), −78 °C, 1 h. (iv) R^2CHO (3 equiv), −78 °C, 1 h. (v) $BF_3{\cdot}OEt_2$ (4 equiv), −78 °C to rt, 18 h. (vi) H_2O, rt, 3 h.

[c] Of the major product, ratio of major diastereomer: all other diastereomers.

[d] Of the major product, determined by Chiral-GC. Absolute stereochemistry assigned in accordance with literature precedence.[11]

[e] Of the major product, isolated as a 1:1 mixture of 2-Ph-6-*c*-Hex- and 2,6-di-*c*-Hex-THP.

We next turned our attention to the synthesis of the diastereomeric 3,5-*anti*-THPs **12** (Table 2). To favour TS **4**, a bulky substituent at boron was required and the *B*-9-BBN group was selected. Furthermore, the increased reactivity of boranes in the lithiation–borylation reaction[17] negated the need for Lewis acids to trigger 1,2-metallate rearrangement, although a solvent exchange to CH_2Cl_2 was still needed to effect efficient Prins cyclisation.

Thus, deprotonation of ethyl carbamate **1** with *s*-BuLi in the presence of (−)-sparteine followed by addition of *B*-vinyl-9-BBN gave an intermediate ate complex which underwent rapid 1,2-metallate rearrangement at low temperatures. Solvent exchange from Et_2O to CH_2Cl_2 and the addition of an excess of either cyclohexylcarboxaldehyde or benzaldehyde, followed by further addition of $BF_3{\cdot}OEt_2$ gave the THPs in moderate yields, but with very high enantioselectivity and diastereoselectivity. Once again, excellent levels of stereocontrol were observed using both aryl- and alkyl aldehydes giving excellent *dr* (entries 1 and 2) and *er* (entry 1) and the sequential addition of two different aldehydes could be used to differentiate the 2- and 6-positions with excellent *dr* and *er* (entry 3). The use of the *B*-9-BBN reagents gave the highest levels of diastereoselectivity reported herein. Presumably the large 9-BBN group significantly shifts the TS equilibrium towards **4** in the allylation reaction and the increased reactivity of the intermediate boronic esters increases the rate of aldehyde exchange and Prins cyclisation.

In summary we have developed a one-pot synthesis of functionalised tetrahydropyrans using a sequential lithiation–borylation, allylation and Prins cyclisation reaction. The protocol has been successfully applied to the highly diastereo- and enantioselective syntheses of 2,3,4,5,6- and 2,3,4,5-substituted THPs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.091.

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