

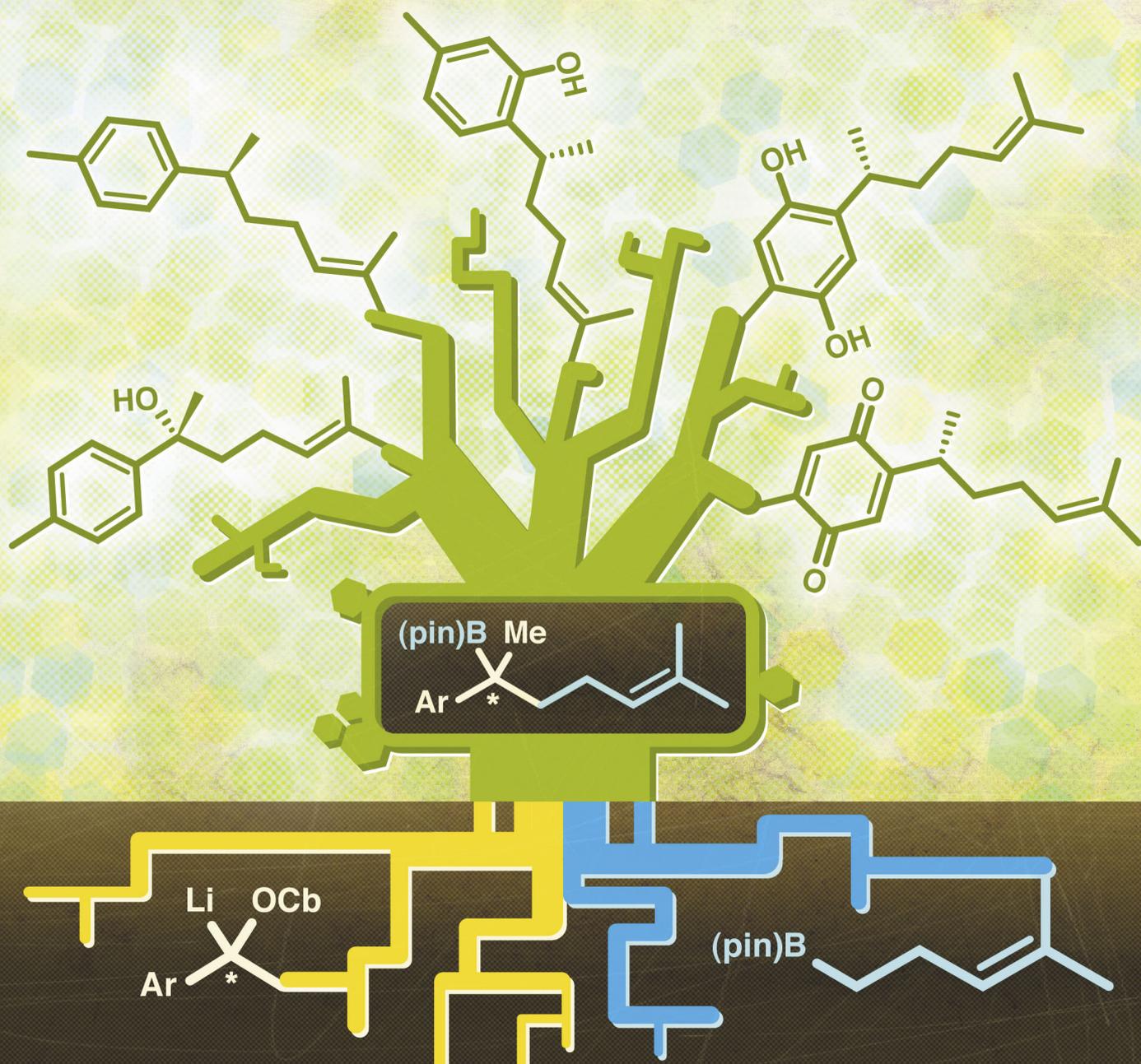
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COMMUNICATION

Application of the lithiation–borylation reaction to the rapid and enantioselective synthesis of the bisabolane family of sesquiterpenes†

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The expedient enantioselective synthesis of 5 bisabolane sesquiterpenes has been achieved using a common, one-pot lithiation–borylation reaction of secondary benzylic carbamates and either protodeboronation or oxidation to give the natural products in fewer than 5 steps, with high yield and >94 : 6 er.

The bisabolane family of sesquiterpenes (Fig. 1, 1–5) exhibit a wide range of biological activity and have been used in traditional medicine.¹ Isolated from sources as diverse as marine coral and sunflowers, they feature a functionalised aromatic ring bearing a tertiary or quaternary benzylic stereocentre.² The parent sesquiterpene, α -curcumene **1** has been isolated in both enantiomeric forms.^{2c} Oxidation of α -curcumene at either the aromatic ring or benzylic carbon gives gossonorol **2**, curcuphenol **3**, curcuhydroquinone **4** and curcuquinone **5**. Although relatively simple at first glance, the benzylic stereocenter is synthetically challenging³ and various members of the bisabolane family have been targets around which the effectiveness of asymmetric methodologies have been benchmarked.⁴

The lithiation–borylation reaction has emerged as a powerful tool for the construction of complex molecular frameworks bearing secondary, tertiary and, even, quaternary stereocenters.⁵ Having recently developed a one-pot, highly stereocontrolled lithiation–borylation and protodeboronation sequence⁶ we were keen to explore the use of this transformation in enantioselective natural product synthesis. The bisabolane sesquiterpenes were identified as both suitable and challenging targets.

Key to our retrosynthetic analysis was the use of a lithiation–borylation reaction between the appropriate enantioenriched *O*-carbamates **7** and boronic ester **8** to give boronic esters **6**. These boronic esters would then give access to a series of bisabolane sesquiterpenes either directly (protodeboronation or oxidation) or with relative synthetic ease (*e.g.* demethylation, followed by oxidation) (Fig. 1). The ready availability of secondary alcohols from which carbamate **7** is derived,

increases the appeal of such a synthetic strategy as both antipodes of the enantioenriched carbamates **7** are readily accessible in high er by asymmetric reduction of the corresponding ketones **9**, using Noyori's transfer hydrogenation procedure,⁷ and subsequent carbamoylation. Although seemingly lacking in complexity, the bisabolanes pose a significant test for the lithiation–borylation reaction. The benzylic stereocenter is prone to racemisation on treatment with base or, possibly, during

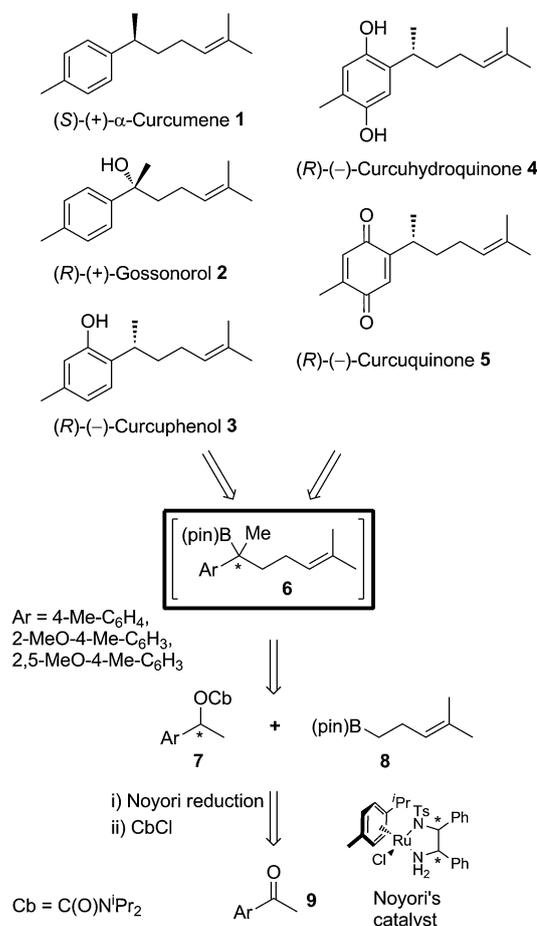


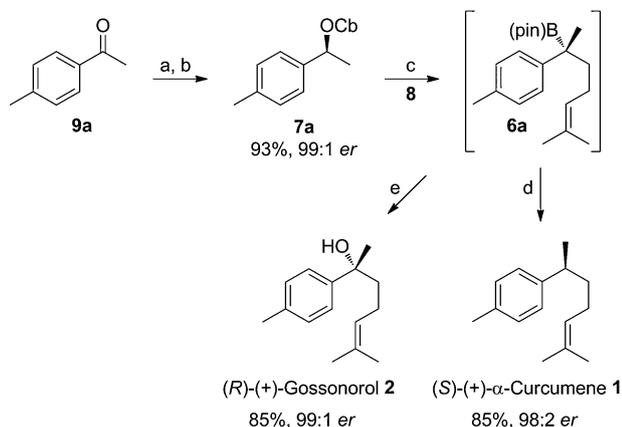
Fig. 1 Retrosynthetic analysis of the bisabolane sesquiterpenes using a common lithiation–borylation strategy.

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protodeboronation or oxidation of the boronic esters **6**, and the functionalised aromatic ring could prevent both chemoselective lithiation and, when bearing electron-donating groups, could participate in the expulsion of the carbamate group.

In order to test the viability of our retrosynthetic analysis we initially applied the lithiation–borylation and protodeboronation sequence to the enantioselective syntheses of (*S*)-(+)- α -curcumene **1** and (*R*)-(+)-gossonorol **2**, by oxidation, from a single enantioenriched carbamate **7a** (Scheme 1). Here a common boronic ester **6a** would give both natural products by either protodeboronation or oxidation, respectively. Thus, Noyori reduction of **9a** followed by carbamoylation gave carbamate **7a**^{6a} which was treated with *s*-BuLi and reacted with boronic ester **8**. Subsequent addition of MgBr₂–MeOH and warming triggered 1,2-metallate rearrangement, leading to boronic ester **6a** which was not isolated. This boronic ester was either treated with TBAF·3H₂O to give the protodeboronated product (*S*)-(+)- α -curcumene **1**, or oxidised with basic H₂O₂ to give (*R*)-(+)-gossonorol **2**. In both cases the natural products were isolated in 85% yield and excellent er, showing near-perfect retention of er from the carbamate **7a**. Our three-step syntheses of α -curcumene **1** and gossonorol **2** are, to the best of our knowledge, the shortest highly enantioselective syntheses of these natural products.

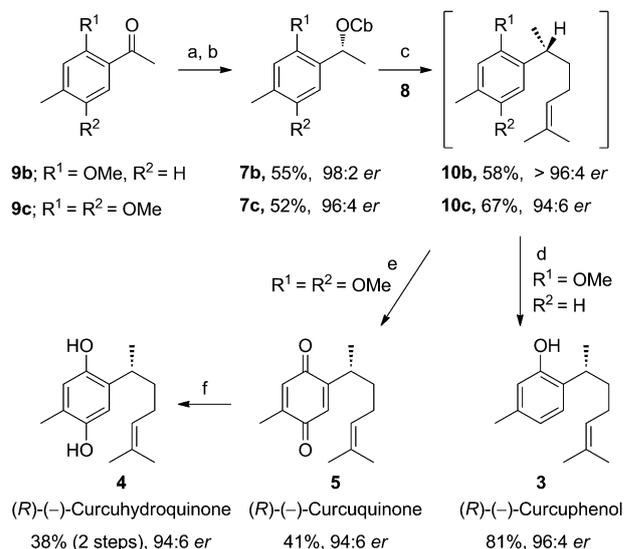


Scheme 1 Enantioselective synthesis of (*S*)-(+)- α -curcumene **1** and (*R*)-(+)-gossonorol **2**. (a) Noyori's (*R,R*)-catalyst, NEt₃, HCO₂H. (b) CbCl, NaH, THF, reflux. (c) (i) *s*-BuLi, –78 °C, Et₂O, (ii) **8**, MgBr₂ (2 M in MeOH), –78 °C to reflux. (d) TBAF·3H₂O. (e) H₂O₂, NaOH, H₂O.

With our synthetic strategy validated, we turned our attention to the three phenolic sesquiterpenes (*R*)-(-)-curcuphenol **3**, (*R*)-(-)-curcuhydroquinone **4** and (*R*)-(-)-curcuquinone **5** (Scheme 2). These substrates posed additional synthetic challenges as the aryl-methoxy groups could be expected to direct *ortho*-lithiation on the aromatic ring or, following α -oxy-lithiation, give a lithium-carbenoid by expulsion of the carbamate group. All three syntheses began with asymmetric transfer-hydrogenation of ketones **9b** and **9c** using Noyori's (*S,S*)-catalyst⁷ to give, after carbamoylation, the carbamates **7b** and **7c** in 98 : 2 er and 96 : 4 er, respectively. Although reduction of dimethoxy-substituted ketone **9c** proved to be slow, good yield (92% brsm) and excellent er (96 : 4) was nevertheless achieved with increased catalyst loading and longer reaction time.

Lithiation–borylation reaction of carbamates **7b** and **7c** with boronic ester **8** gave, after MgBr₂–MeOH promoted 1,2-metallate rearrangement, boronic esters **6b** and **6c**, which were treated directly with TBAF·3H₂O to give the *O*-methyl protected natural products **10b** and **10c**. In the case of the dimethoxy substituted carbamate **7c** no loss of carbamate er was observed and only a 2% erosion in er was observed in the case of the mono-methoxy substituted analogue **7b**. The synthesis of (*R*)-(-)-curcuphenol **3** was completed by demethylation of **10b** to give (*R*)-(-)-curcuphenol **3** in just 4 steps from the commercially available ketone, 11% overall yield and excellent er (96 : 4).

Although the preparation of protodeboronation product **10c** represented formal syntheses of both (*R*)-(-)-curcuhydroquinone **4** and (*R*)-(-)-curcuquinone **5**, we chose to complete the syntheses. Thus CAN-mediated oxidation of the dimethoxy-protected natural product **10c** gave (*R*)-(-)-curcuhydroquinone **5** in 4 steps and moderate yield, but excellent er (94 : 6). Reduction of the quinone **5** with ethanolic NaBH₄ gave (*R*)-(-)-curcuhydroquinone **4** in 5 linear steps and excellent er (94 : 6).



Scheme 2 Enantioselective synthesis of (*R*)-(-)-curcuphenol **3**, (*R*)-(-)-curcuhydroquinone **4** and (*R*)-(-)-curcuquinone **5**. (a) Noyori's (*S,S*)-catalyst, NEt₃, HCO₂H. (b) CbCl, NaH, THF, reflux. (c) (i) *s*-BuLi, –78 °C, Et₂O. (ii) **8**, MgBr₂ (2 M in MeOH), –78 °C to reflux. (iii) TBAF·3H₂O. (d) EtSH, NaH, DMF, 120 °C (e) CAN, H₂O, MeCN, rt. (f) NaBH₄, EtOH, rt.

In summary, we have completed the expedient enantioselective synthesis of 5 sesquiterpenes in excellent er using a common lithiation–borylation strategy. In the case of (*S*)-(+)- α -curcumene and (*R*)-(+)-gossonorol the syntheses were completed in single one-pot, two-step reactions giving the products in 85% yield in both cases, from the known carbamate **7a**. The syntheses of (*R*)-(-)-curcuphenol, (*R*)-(-)-curcuquinone and (*R*)-(-)-curcuhydroquinone demonstrated the successful application of the lithiation–borylation protodeboronation sequence to more functionalised targets. Once again, these sesquiterpenes were prepared in very high er in fewer than 5 linear steps.

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