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Natural Product Synthesis

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Stereoselective Total Synthesis of (+)-Giganin and its C10 Epimer Using Late-Stage Lithiation-Borylation Methodology**

*Catherine J. Fletcher,[a] Katherine M. P. Wheelhouse[b] and Varinder K. Aggarwal[a]**

Giganin **1a**[1] (Figure 1) is a member of the annonaceous acetogenins, a class of compounds characterized by a long aliphatic chain punctuated by oxygen functionalities and bearing a terminal methyl-substituted α,β-unsaturated γ-lactone. They exhibit a broad range of important biological activities[2] but in particular are highly active anti-cancer agents. These compounds are potent inhibitors of adenosine triphosphate (ATP) production and consequently deprive the cell of energy leading to cell death.[3] As cancer cells have a high energy demand due to rapid multiplication, this action renders the annonaceous acetogenins selective inhibitors of cancer cells. Of particular interest is that the annonaceous acetogenins show potential for the treatment of multi-drug resistant cancer cells as these have an even higher requirement for ATP than the parental wild-type.[4] Giganin in particular exhibits good cytotoxicity to human lung carcinoma, human breast carcinoma, and human colon adenocarcinoma in preliminary tests,[5] making it an especially important target for total synthesis.

Several members of the annonaceous acetogenins have previously been synthesised[6] (of particular relevance are the syntheses of annonacin,[7], pyranicin[8] and pyragonicin[8c, 9]), but giganin itself has not. This class of molecules is challenging to synthesise due to the multiple and remote stereogenic centers present along the carbon chain (which have been identified as 4*R*, 10*R*, 17*R*, 18*R* and 34*S*[10]). A common strategy towards this family of molecules has been to first add a functional group (an alkene) somewhere between the C4 and C10 hydroxyls and then to use it to aid disconnection.[6] However, this is wasteful as the functionality has to be introduced and then removed at the end. An alternative approach would be to disconnect the molecule directly at a secondary alcohol as this would not only enable C-C bond formation but also potentially control stereochemistry in the process. In this paper we report the application of our lithiation-borylation methodology to a highly convergent and stereoselective synthesis of giganin and demonstrate facile access to other stereoisomers.

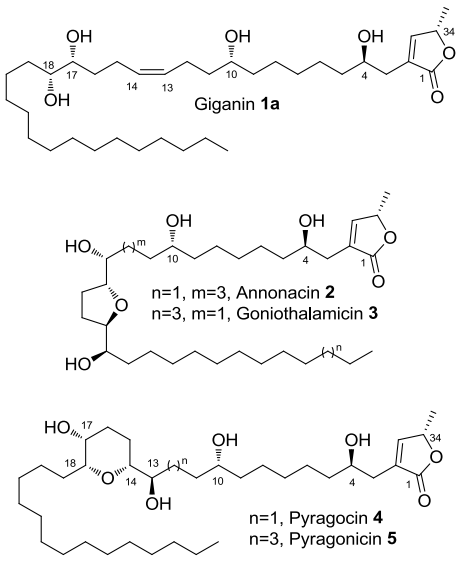
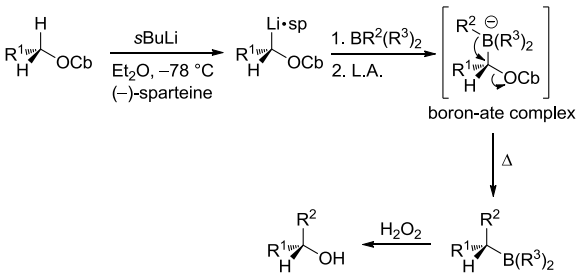


Figure 1. Annonaceous acetogenins.

Recently, we reported the synthesis of enantioenriched secondary alcohols using a lithiation-borylation reaction between an α-lithiated carbamate and a borane or boronic ester.[11] The method involved the reaction of an α-lithiated carbamate, generated by stereoselective deprotonation in the presence of (−)-sparteine,[12] with a borane or boronic ester thus forming a boron-ate complex with retention of stereochemistry. The boron-ate complex then underwent a 1,2-metallate rearrangement with migration of the R group and expulsion of the carbamate leaving group, resulting in a secondary boronic ester.[13,14] Oxidation led to secondary alcohols in very high enantiomeric ratios (Scheme 1). Exchanging the diamine ligand for (+)-sparteine surrogate[15] enables access to the opposite enantiomer of secondary alcohol from the same starting materials. The methodology is particularly good for generating secondary alcohols flanked by similar side chains, as present in giganin, which are difficult to synthesise by other methods (e.g. stereoselective reduction).



Scheme 1. Lithiation-borylation methodology for the formation of secondary alcohols.

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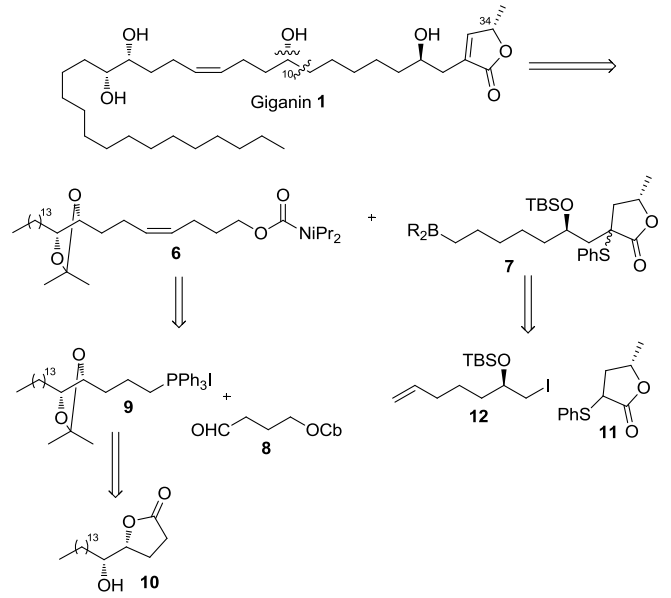
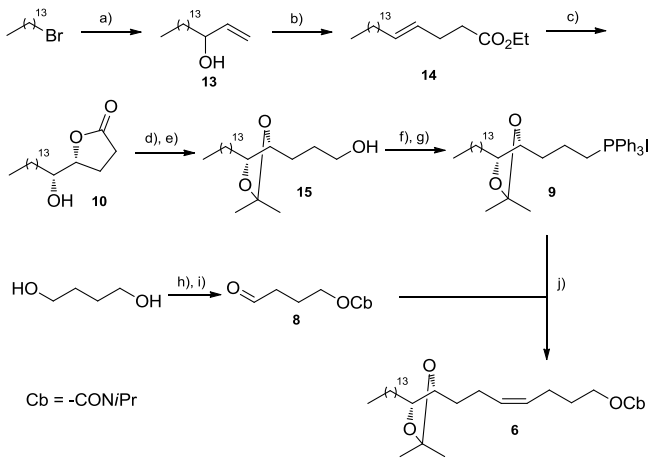
We chose the C10 hydroxyl stereogenic center as a focal point for disconnection, in order to achieve high convergence in the synthetic route. Making this disconnection lead to the left hand fragment, carbamate **6** and the right-hand fragment, boronic ester **7**. The butenolide could not be used in tact as the stereocenter at C34 was known to be very sensitive to mild base,[16] and so we planned to liberate it at the end by oxidation/elimination. We also believed that the steric bulk provided by the adjacent quaternary stereocentre in **7** might protect the lactone from nucleophilic attack as it has been shown that organolithiums can be selective for addition to hindered pinacol boronic esters over hindered *tert*-butyl esters.[17] The left hand fragment carbamate **6** could be prepared by a Wittig olefination of aldehyde **8**[18] with the phosphonium ylide of **9** which itself could be derived from lactone **10**.[19] Boronic ester **7** could be prepared by alkylation of lactone **11** with iodide **12** followed by a regioselective hydroboration of the terminal alkene.



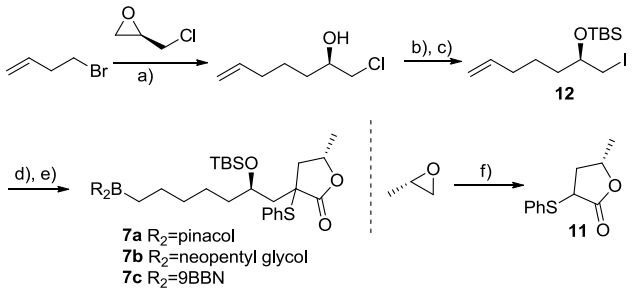
Scheme 2. Retrosynthesis of (+)-giganin.

Preparation of carbamate **6** began with the synthesis of lactone **10**.[19] Reaction of tetradecyl magnesium bromide with acrolein gave allylic alcohol **13** which was subjected to a Johnson-Claisen rearrangement to give γ,δ-unsaturated ester **14.** Subsequent Sharpless dihydroxylation gave the *syn* vicinal diol with >99:1 e.r.[20] which spontaneously cyclized to give lactone **10**. Our modified synthesis of lactone **10** was more readily amenable to scale-up.[19] $LiAlH_4$ reduction followed by acetal formation gave acetonide **15** which was converted *via* the iodide into the phosphonium salt **9**.

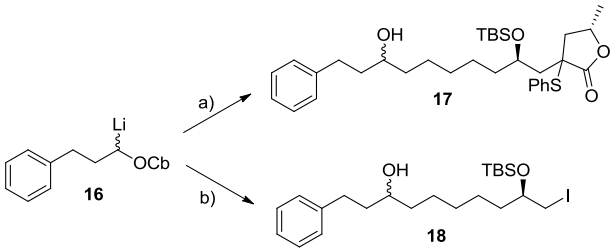
The aldehyde coupling partner **8**[18] was prepared in two steps from 1,4-butanediol by firstly, selective monocarbamoylation, followed by mild oxidation[21] of the remaining alcohol to the aldehyde. Treatment of phosphonium salt **9** with NaHMDS at −78 °C followed by aldehyde **8** and subsequent warming to room temperature led to carbamate **6** as a single diastereoisomer.



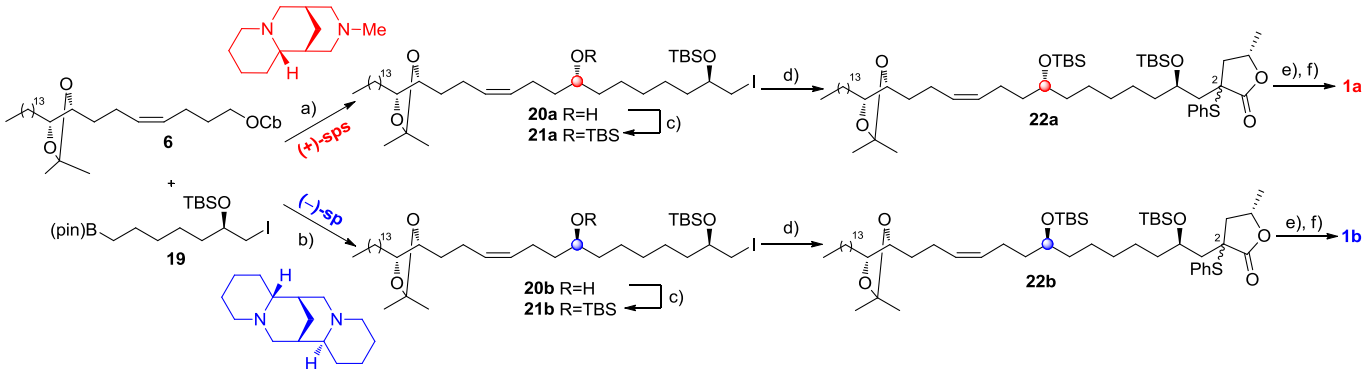
Scheme 3. Synthesis of left hand fragment carbamate **6** a)i) Mg, Et_2O, ii) acrolein, 71%; b) $CH_3C(OEt_3)$, EtCOOH, PhH, 84%; c) ADmix β, $CH_3SO_2NH_2$, *t*BuOH/H_2O, 73%; d) $LiAlH_4$, Et_2O; e) $C(CH_3)_2(OMe)_2$, TsOH, PhH 75% (over 2 steps); f) PPh_3, imidazole, I_2; g) PPh_3, MeCN, reflux 18 h, 84% (over 2 steps); h) NaH, CbCl (0.33 eq), THF; i) TCCA, TEMPO, CH_2Cl_2 82% (over 2 steps); j) **9**, THF, NaHMDS, −78 °C, *then* **8**, −78 °C to rt, 18 h, 79%.



Scheme 4. Synthesis of boronic esters **7** and lactone **11**. a) i) Mg, Et_2O, ii) (*R*)-epichlorohydrin, CuI 87%; b) NaI, acetone 89%; c) TBSCl, imidazole, CH_2Cl_2, rt, 40 h, 94%; d) 2 eq. **11**, 2 eq. LDA, 0 °C, 30 min, *then* **12**, rt, 60 h, 73%; e) R_2=pinacol: $[Ir(COD)Cl]_2$, dppe, (pin)BH CH_2Cl_2, 79%; R_2=neopentyl glycol: $[Ir(COD)Cl]_2$, dppb, CH_2Cl_2 (cat)BH; neopentyl glycol, 59%; R_2=9BBN: 9BBN, THF, rt, 2 h, (After oxidation at rt for 2 h with $NaOAc/H_2O_2$) 98%; f) i) LDA, $PhSCH_2COOH$, ii) TsOH, PhH 84% (over 2 steps).



Scheme 5. Model systems. a) **7a**, **b** or **c**, 0.5 h, −78 °C, warm to rt; iii) $NaOAc/H_2O_2$; b) **19**, 0.5 h, −78 °C, warm to rt; iii) $NaOH/H_2O_2$.



Scheme 6. End game. a)i) **6**, *t*BME, (+)-sps, *s*BuLi, 5 h, −78 °C, ii) **19**, 1 h at −78 °C, iii) 18 h, 40 °C, iv) 2 M $NaOH/H_2O_2$ (30%) 2:1 v/v, 71%; b) **6**, *t*BME, (−)-sp, *s*BuLi, 5 h, −78 °C, ii) **19**, 1 h at −78 °C, iii) 18 h, 40 °C, iv) 2 M $NaOH/H_2O_2$ (30%) 2:1 v/v, 55%; c) 3 eq. TBSCl, 3.6 eq. Iimidazole, CH_2Cl_2, rt, 24 h, **20a** or **20b**; d) 2 eq. LDA, then 2 eq. **11**, then 1 eq. **21a** or **21b**; e) 1 eq. *m*CPBA, CH_2Cl_2, 0 °C, 15 min; f) 5% AcCl in MeOH.

The right hand fragment, boronic ester **7a**, was synthesised as outlined in Scheme 4. Reaction of but-3-enyl magnesium bromide with (*R*)-epichlorohydrin, followed by a Finkelstein reaction and TBS protection led to alkene **12**. Alkylation of alkene **12** with lactone **11** [synthesised by reaction of the dianion of (phenylthio)acetic acid with (*S*)-propylene oxide followed by cyclization with TsOH[22]] followed by regioselective hydroboration[23] with $[Ir(COD)Cl]_2$, dppe and pinacol borane gave the pinacol boronic ester **7a**.

With all of the fragments in hand, our attention turned to the lithiation-borylation key step, but model studies were conducted first. Initially, boronic ester **7a** was reacted with 1-lithio-1-phenylethyldiisopropyl carbamate **16** but this only gave 25% yield of the desired product **17**. Evidently, attack of the lithiated carbamate at the lactone carbonyl competed with reaction at the boronic ester. To try to enhance the chemoselectivity, alternative boron derivatives were also tested including the less hindered neopentyl glycol ester **7b** and the more electrophilic 9-BBN derivative but no significant improvements resulted (Scheme 6). We therefore sought to simplify the boronic ester fragment by removing the lactone moiety. Boronic ester **19** was prepared by an analogous regioselective hydroboration of iodoalkene **12** with pinacol borane. Pleasingly, this reacted cleanly with lithiated 1-phenylethyldiisopropyl carbamate to give the desired product **18** in 73% yield. The excellent chemoselectivity for addition of the lithiated carbamate to the boronic ester over the iodide of **19** is also noteworthy.

Having established a successful lithiation-borylation reaction in our model system we moved to the real system. However, the attempted coupling of boronic ester **19** with the required carbamate **6**, initially gave only low yields (~25%) and significant quantities of starting materials were recovered. Upon close examination, it was found that the reaction mixture had formed a gel at low temperature, presumably due to the unusual physical properties of the long alkyl chain of the carbamate. Fortunately, the carbamate was sufficiently soluble in *tert*butylmethyl ether at −78 °C and subsequent lithiation-borylation gave intermediate **20a** in 55% yield (81% brsm[24]) and 98:2 d.r.[25] By using the diamine (−)-sparteine in place of (+)-sparteine surrogate, intermediate **20b** with the opposite configuration at the C10 carbon was obtained in 71% yield (94% brsm) and 98:2 d.r. Alcohol **20a** had the required stereochemistry to complete the synthesis of (+)-giganin **1a**. The alcohol at C10 in both diastereomers of **20** was protected as the TBS ether followed by alkylation with lactone **11** to give **22a** and **22b** each as a ~5:1 inconsequential mixture of epimers at the C2 position and in 66% and 68% yields respectively. Selective oxidation of the sulfide to the sulfoxide was achieved by treatment with 1 equivalent of *m*CPBA and elimination of the sulfoxide to give the butenolide occurred spontaneously during solvent removal *in vacuo* to give **23a** and **23b** in 89% and 85% respectively. Finally, deprotection with AcCl in MeOH led to natural (+)-giganin **1a** and (+)-C10-*epi*-giganin **1b** in 99% and 93% yields respectively. The synthetic material of (+)-giganin **1a** was identical to the natural product in all respects.[1] Unsurprisingly, the two diastereomers were identical by ^1H NMR but differences in the ^{13}C NMR were discernible.[26]

In summary, we have completed the first synthesis of (+)-giganin **1a** in 13 steps (longest linear sequence) and 7% overall yield using the lithiation-borylation reaction. Not only does the methodology lead to a convergent synthesis in good overall yield, but it also provides complete control over the stereochemistry at the C10 secondary alcohol, illustrated by the synthesis of both (+)-giganin **1a** and (+)-C10-*epi*-giganin **1b** with equal ease. The stitching together of large complex fragments as part of the end game also demonstrates the power of lithiation-borylation methodology as a practical tool for synthesis.

Experimental Section

((Experimental Details))

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[25] The diastereomeric ratio was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative.

[26] Although other examples of annonaceous acetogenins with remote stereocenters show that epimers can have identical NMR, the comparison of ^{13}C NMRs of (+)-giganin and (+)-C10-*epi*-giganin show significant differences in a number of the carbons (see SI). This enabled us to confirm that the samples were essentially single diastereoisomers. For other examples of the challenges of distinguishing between diastereoisomers with remote stereogenic centers see: Curran, D. P., Zhang, Q. S., Lu, H. J., Gudipati, V., *J. Am. Chem.Soc.* **2006**, *128*, 9943–9956.

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Natural Product Synthesis

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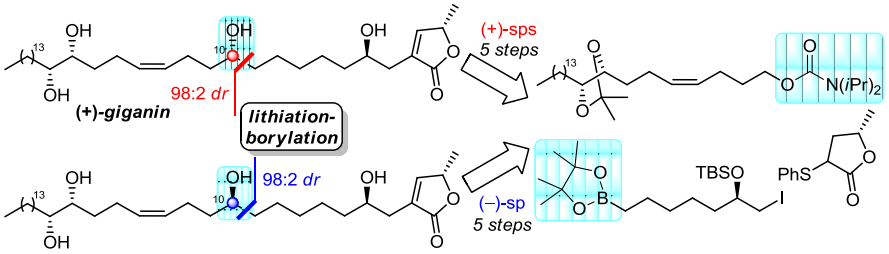
Stereoselective Total Synthesis of (+)-Giganin and its C10 Epimer Using Late-Stage Lithiation-Borylation Methodology



The first total synthesis of (+)-giganin and its unnatural diastereoisomer (+)-C10-*epi*-giganin has been completed in a total of 13 linear steps, and 7% and 8% overall yield respectively. Lithiation-borylation methodology has been successfully applied in the key step, coupling together advanced intermediates with very high diastereoselectivity, demonstrating its power as a tool for total synthesis.