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

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Giganin Ia† (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‡ 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.§ 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.¶ Giganin in particular exhibits good cytotoxicity to human lung carcinoma, human breast carcinoma, and human colon adenocarcinoma in preliminary tests,** making it an especially important target for total synthesis.

Several members of the annonaceous acetogenins have previously been synthesised (of particular relevance are the syntheses of annonacin,‖, pyrancin‖ and pyragonicin‖‖), 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 4R, 10R, 17R, 18R and 34S‖‖). 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.¶¶ 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.

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.†† The method involved the reaction of an α-lithiated carbamate, generated by stereoselective deprotonation in the presence of (−)-sparteine,‡‡ 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.§§ Oxidation led to secondary alcohols in very high enantiomeric ratios (Scheme 1). Exchanging the diamine ligand for (+)-sparteine surrogate§§ 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).

| DOI: 10.1002/anie.200((will be filled in by the editorial staff)) |

**Scheme 1. Lithiation-borylation methodology for the formation of secondary alcohols.
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, 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 hindered pinacol boronic esters over hindered tert-butyl esters. The left hand fragment carbamate 6 could be prepared by a Wittig olefination of aldehyde 8 with the phosphonium ylide of 9 which itself could be derived from lactone 10. 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. Reaction of tetrade cyclo 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. which spontaneously cyclized to give lactone 10. Our modified synthesis of lactone 10 was more readily amenable to scale-up, LiAlH4 reduction followed by acetal formation gave acetamide 15 which was converted via the iodide into the phosphonium salt 9.

The aldehyde coupling partner 8 was prepared in two steps from 1,4-butanediol by firstly, selective monocarbamylation, followed by mild oxidation 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 6. End game. a) 6, 6BME, (+)-eps, sBuLi, 5 h, −78 °C; ii) 19, 1 h at −78 °C; iii) 18 h, 40 °C; iv) 2 M NaOH/H2O2 (30%) 2:1 v/v, 71%; b) 6, 6BME, (−)-sp, sBuLi, 5 h, −78 °C, ii) 19, 1 h at −78 °C, iii) 18 h, 40 °C; iv) 2 M NaOH/H2O2 (30%) 2:1 v/v, 55%; c) 3 eq. TBSCI, 3.6 eq. limidazole, CH2Cl2, rt, 24 h, 20a or 20b; d) 2 eq. LDA, then 2 eq. 11, then 1 eq. 21a or 21b; e) 1 eq. mCPBA, CH2Cl2, 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)-propyl oxide followed by cyclization with TsOH] followed by regioselective hydroboration with [Ir(OD)Cl]3, 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-phenylethyl diisopropyl 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 reaction cleanly with lithiated 1-phenylethyl diisopropyl 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 tertbutylmethyl ether at −78 °C and subsequent lithiation-borylation gave intermediate 20a in 55% yield (81% brsm) and 98:2 d.r. 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 mCPBA 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. Unsurprisingly, the two diastereomers were identical by 1H NMR but differences in the 13C NMR were discernible.

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)

Received: (will be filled in by the editorial staff)

Published online on (will be filled in by the editorial staff)

**Keywords:** giganin · total synthesis · lithiation-borylation · boronic ester · carbamate

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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.