Natural Products

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

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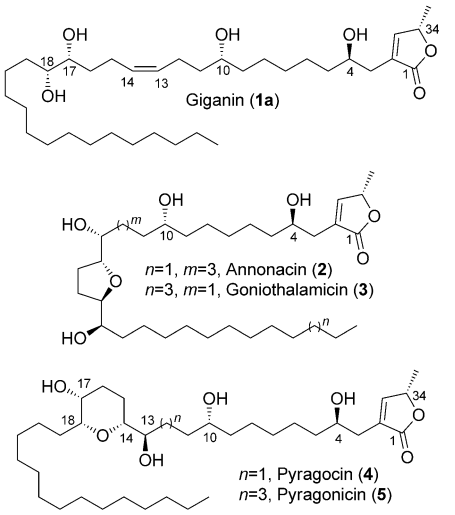
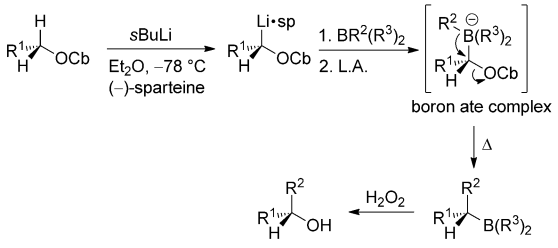
Giganin (**1a**; Scheme 1)[1] is a member of the annonaceous acetogenins, a class of compounds characterized by a long aliphatic chain punctuated by oxygen-containing functional groups and bearing a terminal methyl-substituted α,β-unsaturated γ-lactone. They exhibit a broad range of important biological activities[2] but in particular are highly active anticancer 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 owing to rapid multiplication, this action renders the annonaceous acetogenins selective inhibitors of cancer cell growth. Of particular interest is that the annonaceous acetogenins show potential for the treatment of multidrug 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] thus making it an especially important target for total synthesis.



Scheme 1. Annonaceous acetogenins.

Several members of the annonaceous acetogenins have previously been synthesized (of particular relevance are the syntheses of annonacin,[6] pyranicin,[7] and pyragonicin)[7c,8] but giganin itself has not. A common strategy towards this family of molecules has been to first add a functional group (an alkene) somewhere between the remote hydroxy groups and then to use it to aid disconnection.[6–9] However, this is wasteful as the functional group 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. Herein, 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 through a lithiation–borylation reaction.[10] The method involved the reaction of an α-lithiated carbamate, generated by stereoselective deprotonation in the presence of (−)-sparteine,[11] 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.[12,13] Oxidation led to secondary alcohols in very high enantiomeric ratios (Scheme 2). Exchanging the diamine ligand for (+)-sparteine surrogate[14] 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 synthesize by other methods (e.g. stereoselective reduction).



Scheme 2. Lithiation–borylation methodology for the formation of secondary alcohols. Cb = CON(*i*Pr)$_2$, sp = sparteine.

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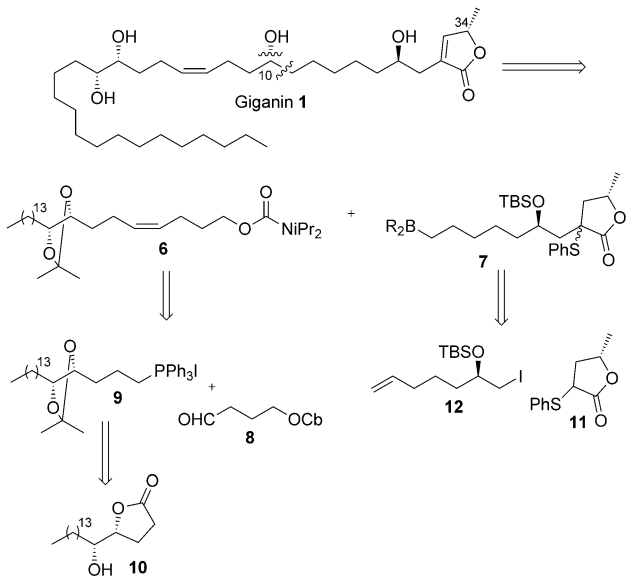
We chose the C10 hydroxy stereogenic center as a focal point for disconnection, to achieve high convergence in the synthetic route. Making this disconnection gave the left-hand fragment, carbamate **6**, and right-hand fragment, boronic ester **7** (Scheme 3). The butenolide could not be used intact as

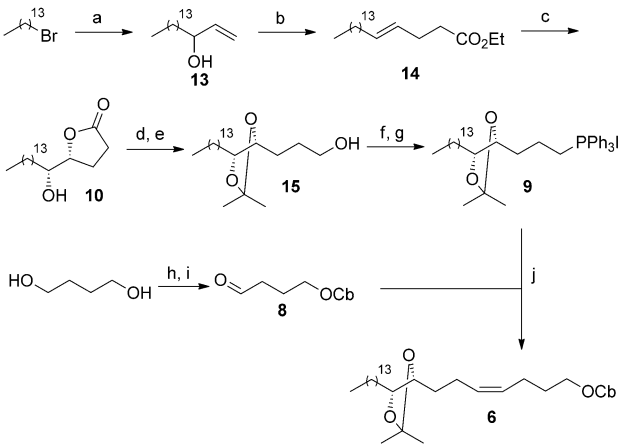


Scheme 3. Retrosynthesis of (+)-giganin. TBS = *tert*-butyldimethylsilyl.

the stereocenter at C34 was known to be very sensitive to mild base,[15] and so we planned to introduce it at the end by oxidation/elimination. We also believed that the steric bulk provided by the adjacent quaternary stereocenter 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.[16] The left-hand fragment carbamate **6** could be prepared by a Wittig olefination of aldehyde **8**[17] with the phosphonium ylide of **9**, which itself could be derived from lactone **10**.[8c] Boronic ester **7** could be prepared by alkylation of lactone **11** with iodide **12** followed by a regioselective hydroboration of the terminal alkene.

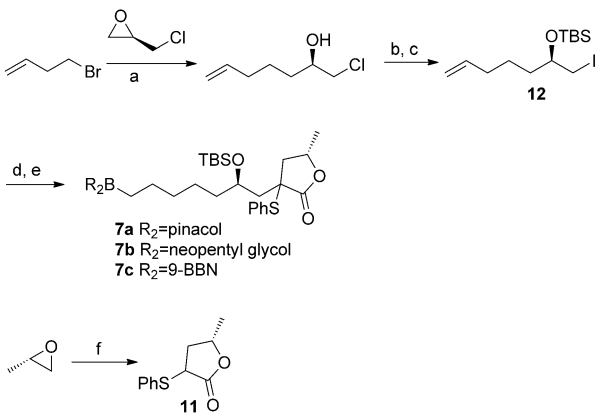
Preparation of carbamate **6** began with the synthesis of lactone **10** (Scheme 4).[8c] Reaction of tetradecyl magnesium bromide with acrolein gave allylic alcohol **13**, which was subjected to a Johnson–Claisen rearrangement to give γ,δ-unsaturated ester **14.** Subsequent Sharpless dihydroxylation[18] gave the *syn* vicinal diol with greater than 99:1 e.r.;[19] this diol spontaneously cyclized to give lactone **10**. Our modified synthesis of lactone **10**[8c] was more readily amenable to scale-up. $LiAlH_4$ reduction with subsequent acetal formation gave acetonide **15**, which was converted via the iodide into the phosphonium salt **9**.

The aldehyde coupling partner **8**[17] was prepared in two steps from 1,4-butanediol by selective monocarbamoylation[17] and subsequent mild oxidation[20] 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 4. Synthesis of left-hand fragment, carbamate **6.** a) i) Mg, Et_2O, ii) acrolein, 71%; b) $CH_3C(OEt_3)$, EtCOOH, PhH, 84%; c) AD-mix-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, 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%. HMDS = 1,1,1,3,3,3-hexamethyldisilazanide, TCCA = trichloroisocyanuric acid, TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl, Ts = *p*-toluenesulfonyl.

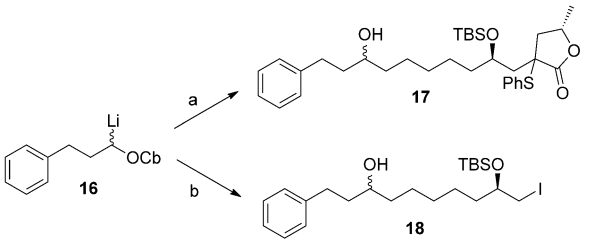
The right hand fragment, boronic ester **7a**, was synthesized as outlined in Scheme 5. Reaction of but-3-enyl magnesium bromide with (*R*)-epichlorohydrin, and a subsequent Finkelstein reaction and TBS protection led to alkene **12**. Alkylation of alkene **12** with lactone **11** (synthesized by treatment of the dianion of (phenylthio)acetic acid with (*S*)-propylene oxide and then cyclization with TsOH)[21] and a subsequent regioselective hydroboration[22] with [{Ir-



Scheme 5. Syntheses 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) **11**, 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 = 9-BBN: 9-BBN, 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). 9-BBN = 9-borabicyclo[3.3.1]nonane, cod = cycloocta-1,5-diene, dppb = 1,4-bis(diphenylphosphanyl)butane, dppe = 1,4-bis(diphenylphosphanyl)ethane, LDA = lithium diisopropylamide, pin = pinacol.

(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** (Scheme 6).



Scheme 6. 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) $NaOH/H_2O_2$.

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. 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 (ca. 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 owing to the unusual physical properties of the long alkyl chain of the carbamate. Fortunately, the carbamate was sufficiently soluble in *tert*-butyl methyl ether at −78 °C and subsequent lithiation–borylation gave intermediate **20a** in 55% yield (81% brsm[23]) and 98:2 d.r (Scheme 7).[24] 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 for the synthesis of (+)-giganin **1a**. The alcohol at C10 in both diastereomers of **20** was protected as the TBS ether and subsequent alkylation with lactone **11** gave **22a** and **22b**, each as an approximately 5:1 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 of **22a** and **22b** with 1 equivalent of *m*CPBA, and elimination of the sulfoxide occurred spontaneously during solvent removal in vacuo to give the corresponding butenolides **23a** and **23b**, in 89% and 85% yield, 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 ^{1}H NMR spectra of the two diastereomers were identical but differences in the ^{13}C NMR spectra were discernible.[25]

In summary, we have completed the first synthesis of (+)-giganin **1a** in 13 steps (longest linear sequence) and 7% overall yield by 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, as 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.

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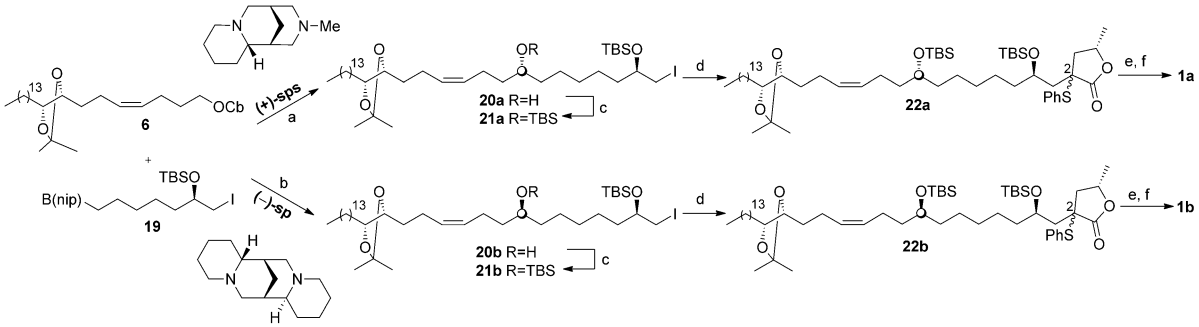

Scheme 7. End game. a) i) **6**, *t*BME, (+)-sps, *s*BuLi, 5 h, −78 °C, ii) **19**, 1 h at −78 °C, iii) 18 h, 40 °C, iv) 2 M $NaOH/H_2O_2$ (30%) 2:1 v/v, 71%; b) i) **6**, *t*BME, (−)-sp, *s*BuLi, 5 h, −78 °C, ii) **19**, 1 h at −78 °C, iii) 18 h, 40 °C, iv) 2 M $NaOH/H_2O_2$ (30%) 2:1 v/v, 55%; c) TBSCl, imidazole, CH_2Cl_2, RT, 24 h, **20a** or **20b**; d) LDA, then **11**, then **21a** or **21b**; e) *m*CPBA, CH_2Cl_2, 0 °C, 15 min; f) 5% AcCl in MeOH. *t*BME = *tert*-butyl methyl ether, *m*CPBA = *meta*-chloroperoxybenzoic acid, (+)-sps = (+)-sparteine surrogate.

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[23] We believe the moderate yield in the key step is due to incomplete lithiation, a result of the poor solubility of carbamate **6** even in *tert*-butyl methyl ether.

[24] The diastereomeric ratio was determined by chiral HPLC analysis, on a chiral stationary phase, of the *p*-nitrobenzoate derivative.

[25] Although other examples of annonaceous acetogenins with remote stereocenters show that epimers can have identical NMR spectra, the comparison of ^{13}C NMR spectra of (+)-giganin and (+)-C10-*epi*-giganin show significant differences in a number of the signals (see the Supporting Information). 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: D. P. Curran, Q. S. Zhang, H. J. Lu, V. Gudipati, *J. Am. Chem. Soc.* **2006**, *128*, 9943 – 9956.

