Natural Products

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

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Giganin (1a; Scheme 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 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. 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. Giganin, in particular, exhibits good cytotoxicity to human lung carcinoma, human breast carcinoma, and human colon adenocarcinoma in preliminary tests, thus making it an especially important target for total synthesis.

Several members of the annonaceous acetogenins have previously been synthesized (of particular relevance are the syntheses of annonacin, pyranicin, and pyragonicin 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. 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. 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 2). 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 synthesize by other methods (e.g. stereoselective reduction).

Scheme 1. Annonaceous acetogenins.

Scheme 2. Lithiation–borylation methodology for the formation of secondary alcohols. $\text{Cb} = \text{CON}(\text{iPr})_2$, $\text{sp} = \text{sparteine}.$

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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 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.

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.

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-

\[\text{Scheme 3.} \text{ Retrosynthesis of (}\psi\text{-}giganin. TBS = tert-butylimethylsilyl.}\n\]

\[\text{Scheme 4.} \text{ Synthesis of left-hand fragment, carbamate 6. a) i) Mg, EtO, i) acrolein, 71%; b) CH₃C(OEt)₃, EtCOOH, PhH, 84%; c) AD-
\text{mix-}\psi, \text{CH₃SO₂NH, tBuOH/H₂O, 73%; d) LiAlH₄, EtO, e) C(CH₃)₂(OMe)₂, TsOH, PhH, 75% (over 2 steps); f) PPh₃, imidazole, i; g) PPh₃,
\text{MeCN, reflux, 18 h, 84% (over 2 steps); h) NaH, CbCl, THF; i) TCCA, TEMPO, CH₂Cl₂, 82% (over 2 steps); j) 9, THF, NaHMDS, −78°C, then 8, −78°C to RT, 18 h, 79%; HMDS = 1,1,1,3,3,3-hexamethyldisilazanide, TCCA = trichloroisocyanuric acid, TEMPO = 2,2,6,6-tetramethylpiperidine-N-oxyl, Ts = p-toluenesulfonfyl.}\n\]

\[\text{Scheme 5.} \text{ Syntheses of boronic esters 7 and lactone 11. a) i) Mg, EtO, i) (R)-epichlorohydrin, CuI, 87%; b) NaI, acetone 89%; c) TBSCl,
imidazole, CH₂Cl₂, RT, 40 h, 94%; d) 11, LDA, O°C, 30 min, then 12, RT, 60 h, 73%; e) R₂ = pinacol: [{Ir(cod)Cl₂}], dppe, (pin)BH CH₂Cl₂, 79%; R₂ = neopentyl glycol: [{Ir(cod)Cl₂}], dppb, CH₂Cl₂ (cat)BH, neopentyl glycol, 59%; R₂ = 9-BBN: 9-BBN, THF, RT, 2 h, (after oxidation at RT for 2 h with NaOAc/H₂O₂) 98%; f) j) LDA, PhSCH₂COOH, i) TsO, PhH, 84% (over 2 steps). 9-BBN = 9-borabicyclo[3.3.1]nonane, cod = cycloocta-1,5-diene, dppb = 1,4-bis(di-phenylphosphanyl)butane, dppe = 1,4-bis(di phenylphosphanyl)ethane, LDA = lithium disopropylamide, pin = pinacol.}\n\]
(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-phenylethlydisopropyl carbamate 16 but this only gave 25% yield of the desired product 17 (Scheme 6).

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-lithio-1-phenylethlydiisopropyl 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 alklylation 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 mCPBA, 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 1H NMR spectra of the two diastereomers were identical but differences in the 13C 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.

Keywords: borylation · carbamate · giganin · lithiation · total synthesis

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


[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 annocuous acetogenins with remote stereocenters show that epimers can have identical NMR spectra, the comparison of 13C 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.