Syntheses of C2'-Fluorinated Analogs of Solamin

Naoto Kojima,*a Hiromi Hayashi,b Hiroki Iwasaki,a and Masayuki Yamashitaa

a Kyoto Pharmaceutical University; 1 Misasagi-Shichono-cho, Yamashina-ku, Kyoto 607–8412, Japan; and
b Graduate School of Pharmaceutical Sciences, Osaka University; 1–6 Yamadaoka, Suita, Osaka 565–0871, Japan.

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The details of the total syntheses of C2'-fluorinated analogs of solamin, an antitumor annonaceous acetogenin, are described. Fluorine was enantioselectively introduced at the C2'-position by organocatalytic α-fluorination of the aldehyde according to a previously reported method. C2'-fluorinated solamin and its C2'-diastereomer were synthesized by the Sonogashira coupling of a tetrahydrofuran fragment and fluorne-containing γ-lactone fragments.

Key words annonaceous acetogenin; fluorinated analog; antitumor agent; convergent synthesis

Introduction

The fluorination of organic molecules is a powerful tool for the development of novel drugs and agrichemicals. In medicinal chemistry, the fluoride atom is of particular interest due to its similar size to the hydrogen atom, its high electron-withdrawing ability, the greater stability of the C–F bond compared to the C–H bond, and its influence on the lipophilicity of a molecule.1 These properties provide various benefits, such as improved metabolic stability, altered physicochemical properties, and increased binding affinity.

Annonaceous acetogenins are polyketides isolated from the Annonaceae plant that grows in tropical and sub-tropical regions. More than 500 acetogenins have been isolated to date, with the majority possessing long hydrocarbon chains bearing one to three adjacent or non-adjacent 2,5-disubstituted tetrahydrofuran (THF) moieties at their molecular centers, in addition to an α,β-unsaturated-γ-lactone ring moiety at the end of each molecule.2–6 Acetogenins are known as potent inhibitors of mitochondrial reduced nicotinamide adenine dinucleotide (NADH) ubiquinone oxidoreductase (complex I),7–9 and chemists have been attracted to acetogenins because of their unique chemical structures and broad biological activities, which include immunosuppressive, antimalarial, and antifeedant properties, in addition to cytotoxicity against human cancer cells. Although many total syntheses of natural acetogenins10 and their analogs11–18 have been reported, the preparation of their fluorinated analogs have remained unexamined until our report into the synthesis of C2'-fluorinated solamin.19–21

Solamin is a mono-THF acetogenin with a simple structure, but contains all of the components that characterize acetogenins22–24 (Fig. 1). Murisolin, a C2'-hydroxy solamin, was isolated from the same plant as solamin, namely Annona muricata. Although the two structures are identical, except for the hydroxy group at the C2' position in the latter, their growth inhibitory activities against human cancer cell lines differ significantly. More specifically, murisolin inhibits the growth of DMS114, a human lung cancer cell line, 400-times more strongly than solamin. We were therefore interested in the biological activity of C2'-fluorinated solamin 1, since the fluoride atom is known to mimic the hydrogen atom and can also potentially function in a similar manner to the hydroxy group due to its high electron density. In fact, the introduction of a fluoride atom at the C2' position was previously reported to increase growth inhibitory activity against human cancer cell lines compared to solamin, albeit to a lesser extent than the activity displayed by murisolin.19

In this context, functionalizing the C2' positions of acetogenins is an attractive research topic; however, to the best of our knowledge, only a single report has been published into C2'-chlorinated analogs, which were synthesized by the Appel reactions of natural C2'-hydroxy acetogenins.25,26 Recently, some efficient late-stage deoxy-fluorinations of secondary alcohols have also been reported26,27; however, it may be difficult to apply this method to the syntheses of C2'-fluorinated acetogenins, since natural acetogenins contain highly reactive chiral α,β-unsaturated-γ-lactone moieties that are easily epimerized.28 With this in mind, we herein report the details of the syntheses of C2'-fluorinated solamin 1 and its C2'-diastereomer.

Results and Discussion

Our approach to C2'-fluorinated analog 1 is outlined retrosynthetically in Chart 1. More specifically, analog 1 can be synthesized by the Sonogashira coupling29 of alkylene 2, prepared by our stereodivergent synthetic route,30,37 and vinyl iodide 3. The γ-lactone fragment 3 can be obtained by the α-alkylation of the known α-sulfenyl-γ-lactone 539 with iodide 4. We planned to construct the chiral center of 4 by the enantioselective α-fluorination of known aldehyde 6.39Table 1 summarizes the results obtained during the optimization of the enantioselective α-fluorination of known aldehyde 6. The enantioselective organocatalytic α-fluorination of aldehydes has previously been developed by Beeson and MacMillan40 and was used in this study. The resulting α-fluoro aldehyde was isolated as the β-fluoro alcohol 7 after reduction due to the instability of the α-fluoro aldehyde. According to the reported procedure, aldehyde 6 (E/Z = 85:15) was treated

![Fig. 1. Conceptual Route to C2'-Fluorinated Solamin 1](image)

* To whom correspondence should be addressed. e-mail: kojima@mb.kyoto-phu.ac.jp

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with 5.0 equiv. of N-fluorobenzenesulfonimide (NFSI) in the presence of 20 mol% (R)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt [(R)-8] at −10°C, followed by reduction with NaBH₄ to give 7 in 53% yield over two steps (entry 1). Both higher and lower reaction temperatures were found to produce lower yields (entries 2–3). Although the reaction with 1.0 equiv. of NFSI afforded an inseparable mixture of 7 and 5-iodopent-4-en-1-ol from unreacted 6 (entry 5), a similar yield to that of entry 1 and high enantioselectivity were achieved when 2.5 equiv. of NFSI was employed (entry 4). Using the optimized conditions, a larger scale reaction gave enantiomerically pure 7 in 50% yield (entry 6).

With alcohol 7 in hand, the Appel reaction of this compound was carried out in N,N-dimethylformamide (DMF) at 100°C to give the corresponding iodide 4 in high yield. The reaction conditions for the α-alkylation of α-sulfonyl-γ-lactone 5 with iodide 4 were optimized, the results of which are presented in Table 2. More specifically, the coupling reaction of 1.0 equiv. of 4 with 2.0 equiv. of lactone 5 was carried out with lithium diisopropylamide (LDA) in the presence of
hexamethylphosphoramide (HMPA), which are the standard reaction conditions reported for a similar substrate devoid of the fluorine atom $\beta$ to the leaving group,\textsuperscript{49} to give the desired product 9 in moderate yield (entry 1). No product was obtained in the absence of HMPA or when HMPA was used with potassium hexamethyldisilazide (KHMD) as the base (entries 2–3), while the use of t-BuOK in DMF at room temperature (r.t.)\textsuperscript{45} gave the same result as that of entry 1 (entry 4). We further investigated the reagent handling conditions, which resulted in good product yields when 4.0 equiv. of 5 was mixed with t-BuOK in DMF or dimethyl sulfoxide (DMSO) at r.t. (entries 5–6). Finally, oxidation of sulfide with potassium hexamethyldisilazide (KHMDS) as the base obtained in the absence of HMPA or when HMPA was used calorically pure 10 and 12 had been obtained, although it is unclear why there are differences in the chemical shifts in C$_6$D$_6$ since flexibility exists around the C2’ positions in both compounds.

With the $\gamma$-lactone fragments in hand, the Sonogashira coupling of the THF-ring fragment 2 with 10 gave enediyne 13 in good yield (Chart 4). Finally, the selective reduction of the enediyne moiety of 13 with a diimide,\textsuperscript{47} followed by de-protection of the TBS group under acidic conditions, gave the desired C2’-fluorinated solamin 1. The diastereomer at the C2’ position (17) was obtained in a similar manner by replacing 10 with 12 in the described Sonogashira-coupling reaction.

**Conclusion**

Convergent syntheses of C2’-fluorinated analogs of solamin were accomplished, in which a fluorine atom was success-fully introduced into the C2’ position by the enantioselective $\alpha$-fluorination of an aldehyde using the procedure developed by MacMillan. Sonogashira coupling of the THF-ring fragment and the $\gamma$-lactone fragment afforded the desired C2’-fluorinated analog. We are currently undertaking further research to establish structure–activity relationships of such attractive fluorinated analogs of the annonaceous acetogenins.

**Experimental**

Melting points are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter or a JASCO P-1020 digital polarimeter. $^1$H-NMR spectra were recorded in the specified solvent with a JEOL JNM-GX-500 spectrometer (500 MHz), a JEOL JNM-AL300 spectrometer (300 MHz), or a JEOL JNM-EX-270 spectrometer (270 MHz). $^{13}$C-NMR spectra were recorded in the specified solvent with a JEOL JNM-AL300 spectrometer (75 MHz). Chemical shifts are reported in ppm relative to the internal solvent signal [CDCl$_3$: 7.26 ppm (1H-NMR), 77.0 ppm ($^{13}$C-NMR)] or tetramethylsilane [0 ppm] as the internal standard. The following abbreviations are used: broad singlet = brs, singlet = s, doublet = d, triplet = t, quartet = q, quintet = qn, sextet = sext, septet = sep, and

**Table 3. Proton Chemical Shifts of 10 and 12**

| Position | in C$_6$D$_6$ | in CDCl$_3$ |
|----------|---------------|-------------|
| 4        | 6.20          | 7.24        |
| 5        | 4.18          | 5.07        |
| 1’       | 2.02–2.18     | 2.52–2.64   |
| 2’       | 4.26          | 4.79        |
| 3’       | 1.64–1.81     | 2.40–2.47   |
| 4’       | 6.25          | 6.56        |
| 5’       | 5.71          | 6.24        |
| 1’       | 0.78          | 1.44        |

Reagents and conditions: (a) Pd(PPh$_3$)$_2$Cl$_2$, Cu, Et$_3$N, r.t., 84% from 10; (b) 48% HF aq., CH$_3$CN/THF, r.t., 88% from 15; (c) 48% HF aq., CH$_3$CN/THF, r.t., 88% from 14, 83% from 16.

Chart 4. Syntheses of C2’-Fluorinated Solamin 1 and Its C2’-Diastereomer 17
multiplet = m. IR absorption spectra (FT = diffuse reflectance spectroscopy) were recorded with KBr powder using a Horiba FT-210 IR spectrophotometer, or as neat films on NaCl plates using a Shimadzu FTIR-8400S instrument, and only noteworthy absorptions (in cm⁻¹) are listed. Mass spectra were recorded on JEOL JMS-600H and JEOL JMS-700 mass spectrometers. Column chromatography was carried out using Kanto Chemical Silica Gel 60N (spherical, neutral, 63–210 µm), and flash column chromatography was carried out using Merck Silica Gel 60 (40–63 µm). All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N₂. All solvents were dried and distilled according to standard procedures, if necessary. All organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure with a rotary evaporator.

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Conflict of Interest The authors declare no conflicts of interest.

Supplementary Materials The online version of this article contains supplementary materials. See supplementary materials for details regarding compound preparation and characterization.

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