

First total synthesis of sterenins A, C and D

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Abstract

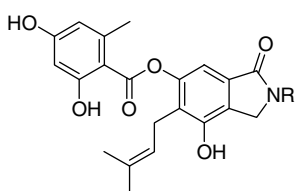
The first total synthesis of sterenins A, C and D, potent inhibitors of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), is described. The prenyl group was regioselectively introduced by a Claisen rearrangement, whereas the construction of an isoindolinone skeleton was accomplished by the lactamization of lactones assisted by a phenolic hydroxyl group.
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An excess of active glucocorticoids (GC) has been shown to be associated with metabolic diseases such as diabetes, dyslipidaemia, hypertension and metabolic syndrome. 11 β -Hydroxysteroid dehydrogenase type 1 (11 β -HSD1) is known as one of the main regulators of the intracellular GC level by converting inactive 11-ketoglucocorticoids to active 11 β -hydroxyglucocorticoids, while a related enzyme, 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), catalyzes the reverse reaction.¹ Consequently, selective inhibitors of 11 β -HSD1 over 11 β -HSD2 have gained considerable attention as therapeutics for metabolic diseases, especially diabetes and metabolic syndrome, with the increasing social concern over obesity.^{2,3}

Sterenins (**1a–d**, Table 1) were isolated from a solid-state culture of *Stereum* sp. SANK 21205 by our colleagues as the first natural products possessing potent 11 β -HSD1 inhibitory activities.⁴ Among them, sterenins A (**1a**) and C (**1c**) possess significant levels of activity and showed IC₅₀ values 240 and 230 nM towards human 11 β -HSD1, respectively.⁴ Sterenins are not only potent competitive inhibitors of 11 β -HSD1, but also show excellent selectivity over 11 β -HSD2. As the limited supply of the natural products requires large scale solid-state fermentation, we carried

Table 1
Inhibitory activities of sterenins (**1**) A–D towards human 11 β -HSDs



Sterenin	R	IC ₅₀ (nM)	
		11 β -HSD1	11 β -HSD2
A (1a)	CH ₂ CH ₂ OH	240	>10,000
B (1b)	CH(CO ₂ H)CH ₂ CH ₂ CO ₂ H	6600	>10,000
C (1c)	H	230	>10,000
D (1d)	CH ₂ CO ₂ H	2600	>10,000

out total synthesis for the purpose of further biological evaluation. Herein, we wish to describe the first total synthesis of sterenins A, C and D.

The retrosynthetic analysis of sterenin (**1**) is outlined in Figure 1. Disconnection of the ester bond in **1** gives isoindolinone **2**. The prenyl group of isoindolinone **2** could be introduced by a Claisen rearrangement. Therefore, aryl ether **3** was targeted as the inevitable precursor for placing the prenyl group at position 5 of the isoindolinone skeleton with certainty. Aldehyde **4** was thought to be a feasible compound at the earlier stage of this strategy.

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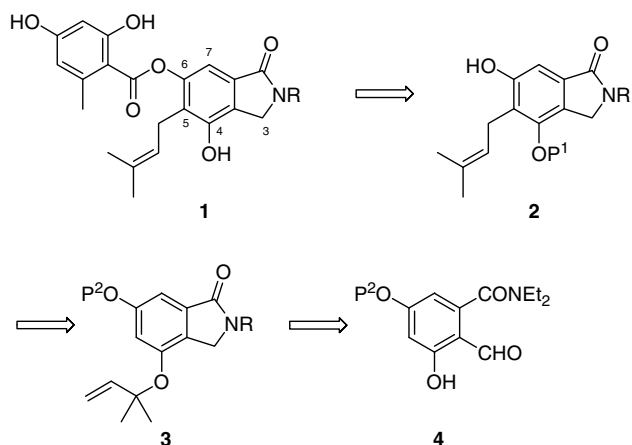
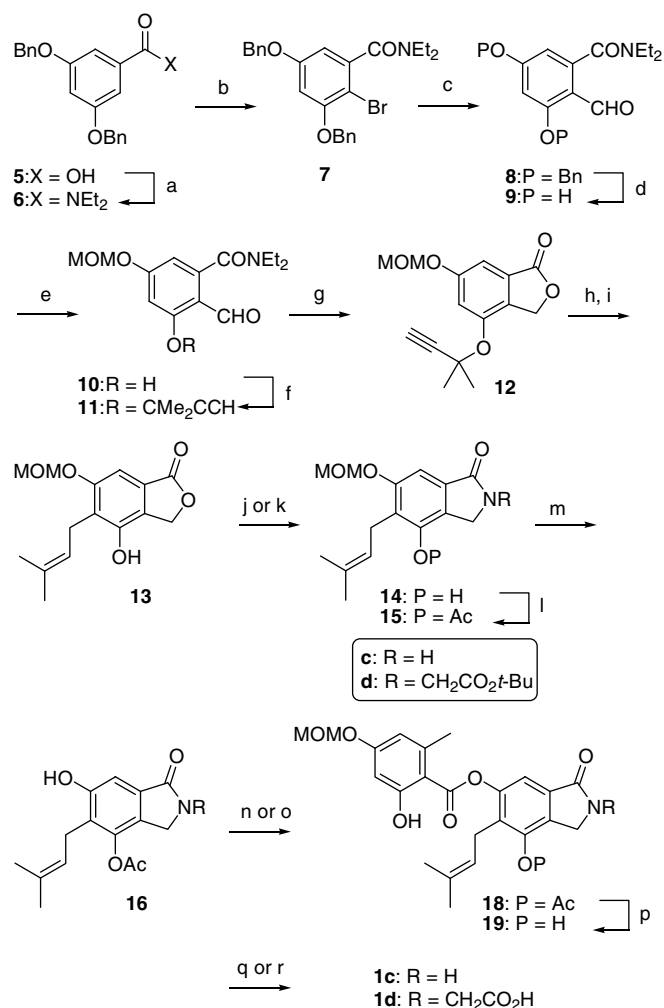


Fig. 1. Retrosynthetic analysis of sterenin (1).

As described in Scheme 1, sterenins C and D were synthesized via lactone **13**. The synthesis was commenced with commercially available carboxylic acid **5**, which was converted to amide **6**. As the direct ortho lithiation of **6** (*sec*-BuLi, TMEDA, THF) caused decomposition,⁵ halogen–metal exchange reactions were examined. After bromination of **6**, treatment of bromide **7** with *n*-BuLi in THF followed by the addition of *N,N*-dimethylformamide (DMF) provided aldehyde **8** in 46% yield. The yield was improved to 66% when the solvent was changed to 1,2-dimethoxyethane (DME). The use of *i*-PrBu₂MgLi as the metalating agent⁶ gave an excellent result, and aldehyde **8** was obtained in 91% yield. After cleavage of the benzyl groups by catalytic hydrogenation, selective protection of the 5-hydroxy group with a MOM group afforded ether **10**. The structure of **10** was confirmed by ¹H NMR with the observation of a peak at 11.90 ppm, which indicated the existence of a hydrogen-bonded phenolic hydroxy group. Propargylation of **10** using 3-chloro-3-methylbut-1-yne in the presence of DBU and a catalytic amount of CuCl₂·2H₂O afforded propargylic ether **11** in 94% yield.⁷ Transformation of propargylic ether **11** into 5-prenylisoindolinone **14** was achieved via lactone **13**, as reductive amination of aldehyde **10** or **11** with ammonia followed by thermal cyclization⁸ led to unsatisfactory results. Propargylic ether **11** reduced under acidic conditions with NaBH₃CN followed by cyclization resulted in the formation of lactone **12** in good yield. Reduction of the acetylenic moiety of **12** followed by a Claisen rearrangement in *N*-methylpyrrolidone (NMP) provided **13** in excellent yield.⁹ Isoindolinone formation was then achieved in the presence of glycine *tert*-butyl ester under thermal conditions (neat, 120 °C) to generate isoindolinone **14d** (R = CH₂CO₂*tert*-Bu), while isoindolinone **14c** (R = H) was prepared by treating lactone **13** with ammonia in MeOH at 120 °C in a sealed tube.¹⁰ It is assumed that the isoindolinone formation proceeds via an *o*-quinone methide¹¹ by the fact that the reaction does not occur with compound **12** under the same reaction conditions and the general transformation from lactone to isoindolinone requires harsher condi-



Scheme 1. Synthesis of sterenins C (**1c**) and D (**1d**). Reagents and conditions: (a) Et₃NH·HCl, WSC·HCl, HOBT, Et₃N, CH₂Cl₂, 99%; (b) NBS, MeCN, 99%; (c) *i*-PrBu₂MgLi, THF, −78 °C then DMF, 91%; (d) H₂, Pd/C, EtOH, 99%; (e) MOMCl, K₂CO₃, 18-crown-6, acetone, 87%; (f) 3-chloro-3-methylbut-1-yne, CuCl₂·2H₂O, DBU, MeCN, 94%; (g) NaBH₃CN, MeOH, AcOH, reflux, 82%; (h) H₂, Lindlar catalyst, quinoline, EtOAc, 96%; (i) NMP, 80 °C, 92%; (j) NH₃, MeOH, 120 °C, 63% (**14c**); (k) glycine *tert*-butyl ester, 120 °C, 88% (**14d**); (l) Ac₂O, pyridine, 93% (**15c**); (m) CBr₄, *i*-PrOH, reflux, 98% (**16c**), 84% (**16d**); (n) 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoic acid (**17**), WSC·HCl, DMAP, CH₂Cl₂, 60% (**18c**); (o) **17**, DIPIC, DMAP, CH₂Cl₂, 82% (**18d**); (p) silica gel (Chromatorex, NH), 99% (**19c**), 98% (**19d**); (q) HCl, THF, H₂O, 90% (**1c**); (r) HCl, 1,4-dioxane, 64% (**1d**).

tions.¹⁰ After protecting the phenolic hydroxy group as an acetate, the MOM group was removed under mild conditions to provide compounds **16c** and **16d**.¹² As products **16c** and **16d** were prone to cyclize to give benzopyran byproducts in the presence of acid,¹³ the yield of **16** decreased when the reaction was run for a prolonged time. The following condensation of **16** with carboxylic acid **17**¹⁴ provided **18**. The removal of the acetyl group was achieved by passing through a pad of basic silica gel (Chromatorex, NH, Fuji Silysia Ltd) to give **19** in quantitative yield. This deprotection method was superior to the method using K₂CO₃ in MeOH, as the latter method gave several

byproducts. Finally, removal of all the protecting groups of **19c** and **19d** under acidic conditions afforded sterenins C (**1c**) and D (**1d**), which were identical in all respects to natural sterenins (^1H and ^{13}C NMR, IR, HRMS).⁴ Unlike compounds **16c** and **16d**, compounds **19c** and **19d** did not easily cyclize to give benzopyrans under these acidic conditions in spite of possessing a phenolic hydroxy group.

As described above, sterenins C and D were successfully synthesized in 16% and 20% overall yields, respectively. This route required several protection–deprotection sequences. Sterenin A (**1a**), one of the most potent compounds, was synthesized by a more direct approach, which involved a Claisen rearrangement of densely functionalized compound **26** as depicted in Scheme 2. The synthesis commenced with aldehyde **10** described in Scheme 1. After conversion of aldehyde **10** to lactone **20** in excellent yield, lactam formation using amine **21**¹⁵ provided isoindolinone **22** in 90% yield. The introduction of the propargyl group led to propargylic ether **23** in 78% yield using K_2CO_3 as a base, whereas the combination of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and DBU gave **23** in 56% yield.⁷ After deprotection of the MOM group,¹² reduction of the acetylenic moiety of

phenol **24** in the presence of Lindlar catalyst generated the corresponding olefin **25**. Esterification of **25** with benzoic acid **17**¹⁴ afforded ester **26** in 82% yield.

Then, the Claisen rearrangement of **26** was examined. Although it is known that polar solvents accelerate the rearrangement,¹⁶ the use of polar aprotic solvents like acetonitrile or 1,4-dioxane did not provide rearranged product **27** at all, whereas the reaction in NMP afforded a trace amount of **27**.⁹ To our delight, using *i*-PrOH as a solvent gave **27** in 45% yield. In this reaction, the isolated byproduct was isopropyl benzoate **28**.¹⁷ Attempts to prevent this competitive alcoholysis were all unsuccessful. The use of more hindered *t*-BuOH led **27** in 38% yield. This reaction under microwave irradiation in *i*-PrOH gave isopropyl benzoate **28** in quantitative yield, while the addition of water to accelerate the reaction¹⁶ led to the hydrolysis of **26**.

Finally, the removal of the protecting groups furnished sterenin A (**1a**). Synthetic sterenin A was identical in all respects with the physical and spectroscopic data (^1H and ^{13}C NMR, IR, HRMS) as well as the biological activity determined for the natural product.⁴

In summary, the first total synthesis of sterenins A, C and D has been achieved. The prenyl group was efficiently introduced by a Claisen rearrangement. The construction of the isoindolinone skeleton was accomplished by the formylation of benzamide derivative using an ate complex, followed by lactonization and thermal lactamization assisted by a phenolic hydroxy group. We have synthesized 80 mg of sterenin A as the first batch, which will be used for further in vivo biological evaluation. This total synthesis also enables us to evaluate the potential of these isoindolinone-type compounds as lead compounds for the drug discovery of metabolic diseases, which will be reported elsewhere.

Acknowledgement

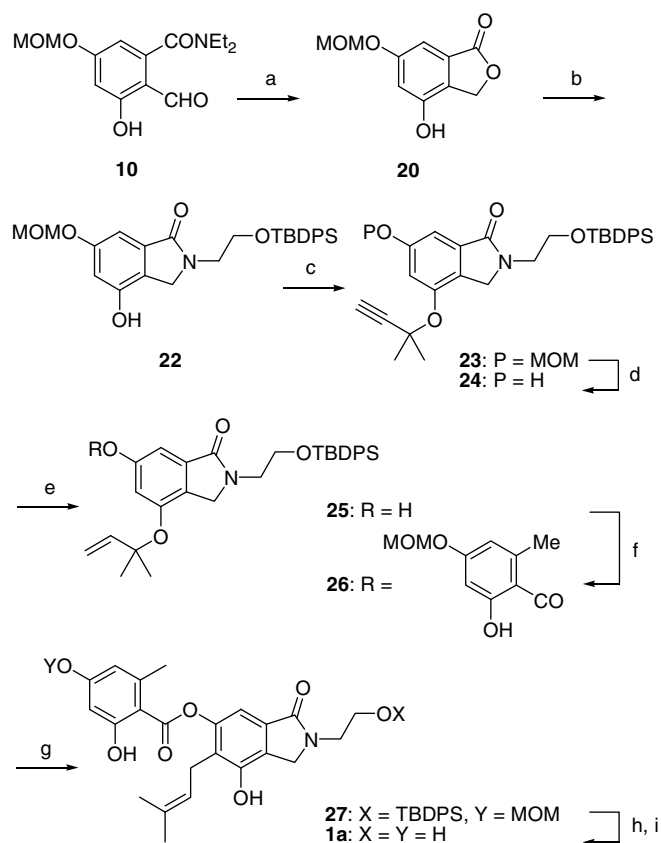
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.01.031](https://doi.org/10.1016/j.tetlet.2008.01.031).

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Scheme 2. Synthesis of sterenin A (**1a**). Reagents and conditions: (a) NaBH_3CN , THF, AcOH, 98%; (b) 2-[[*tert*-butyl(diphenyl)silyl]oxy]-ethanamine (**21**), 120 °C, 90%; (c) 3-chloro-3-methylbut-1-yne, CuI, KI, K_2CO_3 , acetone, reflux, 78%; (d) CBr_4 , *i*-PrOH, reflux, 97%; (e) H_2 , Lindlar catalyst, EtOH, 50 °C, 99%; (f) **17**, DIPC, DMAP, CH_2Cl_2 , 82%; (g) *i*-PrOH, reflux, 45%; (h) TBAF, THF; (i) HCl, MeOH, H_2O , reflux, 65% over two steps.

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