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First total synthesis of sterenins A, C and D

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Abstract

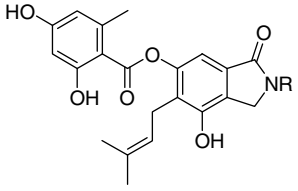
The first total synthesis of sterenins A, C and D, potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), is described. The prenyl group was regioselectively introduced by a Claisen rearrangement, whereas the construction of an isoindolinone skeleton was accomplished by the lactamization of lactones assisted by a phenolic hydroxyl group.

Keywords: 11b-HSDs; Metabolic diseases; Sterenin; Isoindolinone; Claisen rearrangement

An excess of active glucocorticoids (GC) has been shown to be associated with metabolic diseases such as diabetes, dyslipidaemia, hypertension and metabolic syndrome. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is known as one of the main regulators of the intracellular GC level by converting inactive 11-ketoglucocorticoids to active 11β-hydroxyglucocorticoids, while a related enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), catalyzes the reverse reaction.[1] Consequently, selective inhibitors of 11β-HSD1 over 11β-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 11β-HSD1 inhibitory activities.[4] Among them, sterenins A (**1a**) and C (**1c**) possess significant levels of activity and showed IC_{50} values 240 and 230 nM towards human 11β-HSD1, respectively.[4] Sterenins are not only potent competitive inhibitors of 11β-HSD1, but also show excellent selectivity over 11β-HSD2. As the limited supply of the natural products requires large scale solid-state fermentation, we carried 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.

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



Sterenin	R	IC_{50} (nM)	
		11β-HSD1	11β-HSD2
A (**1a**)	CH_2CH_2OH	240	>10,000
B (**1b**)	$CH(CO_2H)CH_2CH_2CO_2H$	6600	>10,000
C (**1c**)	H	230	>10,000
D (**1d**)	CH_2CO_2H	2600	>10,000

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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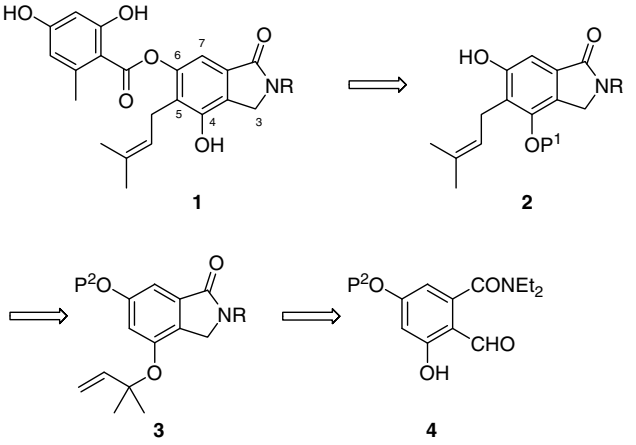
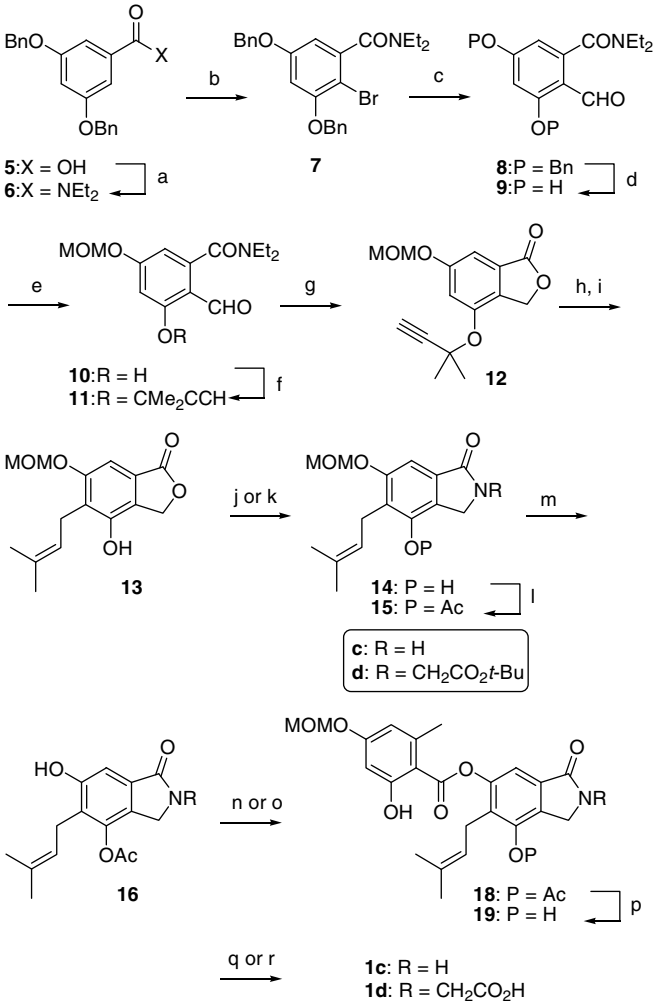


Fig. 1. Retrosynthetic analysis of sterenin (**1**).

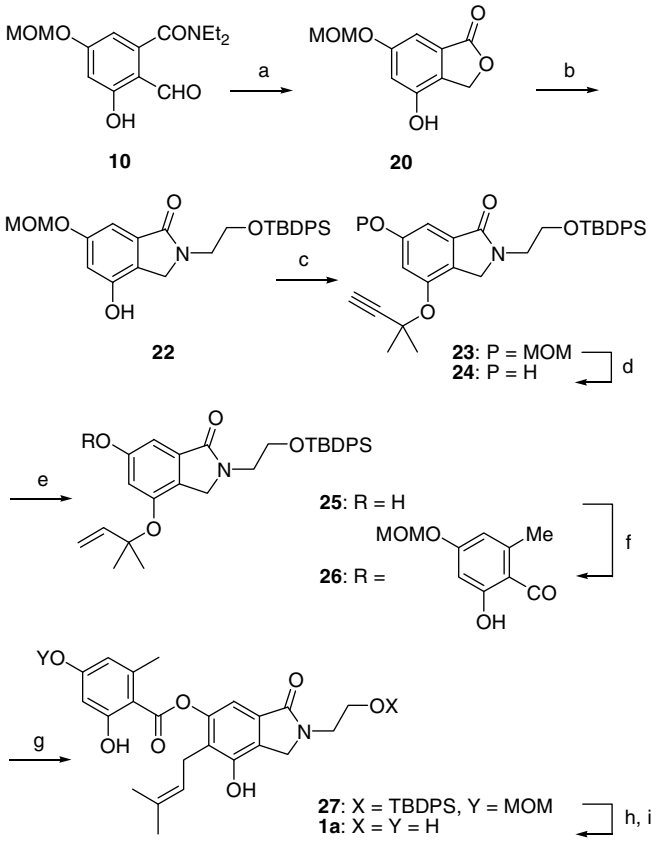
As described in Scheme 1, sterenins C and D were synthesized via lactone **13**. The synthesis was commenced with commercially available carboxylic acid **5**, which was converted to amide **6**. As the direct ortho lithiation of **6** (*sec*-BuLi, TMEDA, THF) caused decomposition,[5] halogen–metal exchange 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*-PrBu$_2$MgLi as the metalating agent[6] 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 ^{1}H 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 $CuCl_2{\cdot}2H_2O$ 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 cyclization[8] led to unsatisfactory results. Propargylic ether **11** reduced under acidic conditions with $NaBH_3CN$ 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 = CH_2CO_2*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 methide[11] 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 conditions.[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 K_2CO_3 in MeOH, as the latter method gave several



Scheme 1. Synthesis of sterenins C (**1c**) and D (**1d**). Reagents and conditions: (a) $Et_2NH{\cdot}HCl$, WSC·HCl, HOBt, Et_3N, CH_2Cl_2, 99%; (b) NBS, MeCN, 99%; (c) *i*-PrBu$_2$MgLi, THF, −78 °C then DMF, 91%; (d) H_2, Pd/C, EtOH, 99%; (e) MOMCl, K_2CO_3, 18-crown-6, acetone, 87%; (f) 3-chloro-3-methylbut-1-yne, $CuCl_2{\cdot}2H_2O$, DBU, MeCN, 94%; (g) $NaBH_3CN$, MeOH, AcOH, reflux, 82%; (h) H_2, Lindlar catalyst, quinoline, EtOAc, 96%; (i) NMP, 80 °C, 92%; (j) NH_3, MeOH, 120 °C, 63% (**14c**); (k) glycine *tert*-butyl ester, 120 °C, 88% (**14d**); (l) Ac_2O, pyridine, 93% (**15c**), 99% (**15d**); (m) CBr_4, *i*-PrOH, reflux, 98% (**16c**), 84% (**16d**); (n) 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoic acid (**17**), WSC·HCl, DMAP, CH_2Cl_2, 60% (**18c**); (o) **17**, DIPC, DMAP, CH_2Cl_2, 82% (**18d**); (p) silica gel (Chromatorex, NH), 99% (**19c**), 98% (**19d**); (q) HCl, THF, H_2O, 90% (**1c**); (r) HCl, 1,4-dioxane, 64% (**1d**).

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 (^{1}H 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 $CuCl_2{\cdot}2H_2O$ 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.



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.

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 reaction[16] 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 (^{1}H 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.

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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.

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