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Synthesis of Glaucogenin D, a Structurally Unique Disecopregnane Steroid with Potential Antiviral Activity

Jinghan Gui,* Hailong Tian, and Weisheng Tian*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, China

guijh@sioc.ac.cn; wstian@sioc.ac.cn

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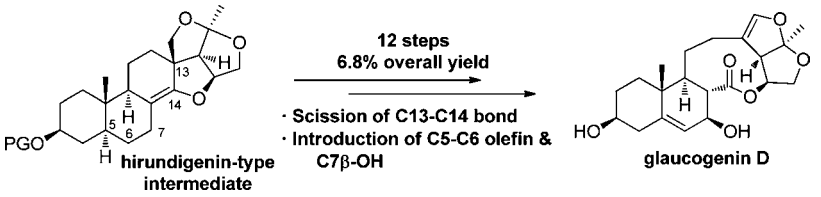
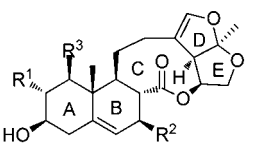
ABSTRACT



The first chemical synthesis of glaucogenin D, a 13,14:14,15-disecopregnane steroid with potential antiviral activity, has been accomplished in 12 steps from a hirundigenin-type intermediate. The present route would also be amenable to the synthesis of natural and unnatural glaucogenin derivatives for SAR studies.

Natural products and their derivatives have long been important sources for drug discovery and development.[1] A countless variety of terrestrial and marine organisms produce a rich diversity of natural products, constantly presenting new structural features that elicit chemical and biological curiosity. Glaucogenins (Figure 1, **1**–**5**) are steroids with unusual structures of 13,14:14,15-disecopregnane from the asclepiadaceae plant, typical of three Chinese herbal medicines "Bai-Qian", "Bai-Wei", and "Xu-Chang-Qing" from the 1980s.[2] Structurally, the glaucogenins possess a characteristic nine-membered lactone C ring, bis-furan *cis*-fused D/E rings, and polyhydroxylated A/B rings. The unique features of the C, D, and E rings make the glaucogenins appealing targets for synthetic chemists. Importantly, glaucogenin C (**3**) was found to display effective and selective inhibitory activity to α-virus-like positive-strand RNA viruses (IC_{50} = 17 nm),[3] although the activities of other members of this family remain to be elucidated. The intriguing chemical structures as well as the limited biological data of the glaucogenin family prompted us to initiate a synthetic project aiming to offer efficient access to all glaucogenin members and their analogues, together with evaluating their potential as novel antiviral drugs.



	R^1	R^2	R^3
glaucogenin A (**1**)	OH	H	H
glaucogenin B (**2**)	OH	OH	H
glaucogenin C (**3**)	H	H	H
glaucogenin D (**4**)	H	OH	H
glaucogenin E (**5**)	OH	H	OH

Figure 1. Structures of glaucogenin family.

Previously, we have studied the biomimetic synthesis of a key disecopregnane skeleton from hirundigenin-type intermediate **6**, which allowed us to complete the first

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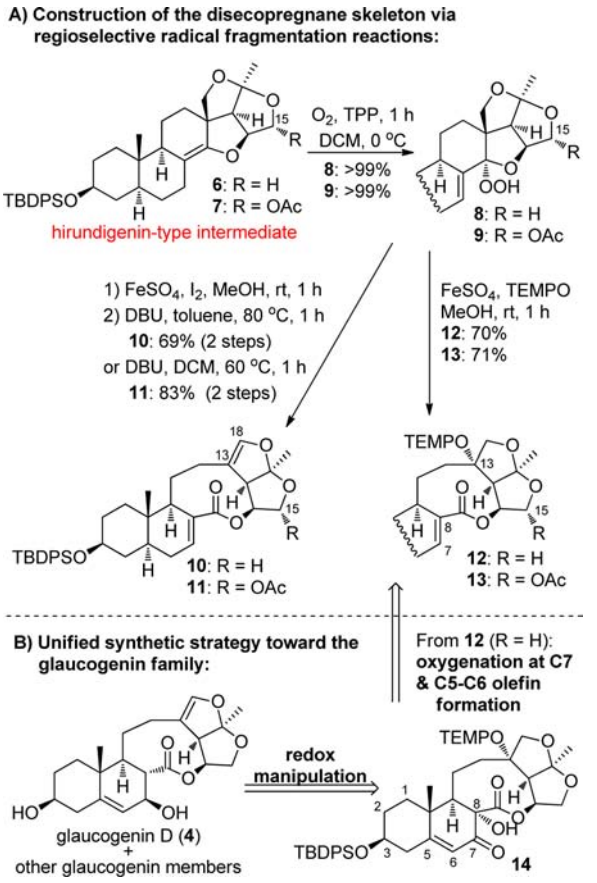
Scheme 1. (A) Construction of the Disecopregnane Skeleton from Hirundigenin-Type Intermediates via Regioselective Radical Fragmentation Reactions. (B) Unified Synthetic Strategy toward the Glaucogenin Family



synthesis of 5,6-dihydroglaucogenin C.[4] Key features of the previous synthesis were a Schenck ene reaction and subsequent iron(II)-promoted regioselective fragmentation of an α-alkoxy hydroperoxide (Scheme 1A, see **6** → **8**, **8** → **10**, and **12**). To synthesize more glaucogenin members as well as their analogues by utilizing our methodology, we continued to explore the reactivity of **7**, an analogue of **6** bearing an additional C15-acetal group. Pleasingly, Schenck ene reaction[5] of **7** also afforded the alkoxy hydroperoxide **9** as a single diastereomer in quantitative yield. Hydroperoxide **9** was found to display a similar reactivity under the optimal conditions[4] we had developed for the fragmentation reaction of **8**. Upon exposure to iron(II), **9** decomposed efficiently to give a C13-alkyl radical that can be trapped by either TEMPO or I_2 to produce, respectively, C13-TEMPO-substituted product **13** in 71% yield or C13−C18 olefin product **11** in 83% yield after iodide elimination. This successful synthesis of disecopregnane intermediate **13** would provide access to more glaucogenin analogues with a variety of possible substituents at C15, which could be easily realized via acetal chemistry.

With a powerful approach to construct the nine-membered lactone ring in hand, efforts were then directed toward the synthesis of natural glaucogenins. Through inspection of the structures of the glaucogenin family (Figure 1), one could easily observe that they differ only in the oxidation patterns at C1, C2 and C7. As such, we postulated that a unified synthetic strategy[6] with enone **14** as the key intermediate would enable access to the entire glaucogenin family (Scheme 1B): reduction or deoxygenation of enone **14** would provide glaucogenin D or C, while further introduction of hydroxyl groups at C1 or C2 via the C3-carbonyl group should afford glaucogenin A, B, or E. Herein, we report the first synthesis of glaucogenin D (**4**), which represents an entry toward the unified synthesis of the glaucogenin family.

As shown in Scheme 2, our synthesis of glaucogenin D (**4**) commenced with a diastereoselective *cis*-dihydroxylation of **12** with $KMnO_4$[7] to furnish diol **15** in 70% yield. Oxidation of the C7-hydroxyl group led to ketone **16**, which was primed for the dehydrogenation event to install the critical C5−C6 olefin. Initial attempts to effect this dehydrogenation directly with DDQ[8] or IBX[9] met with failure. Alternatively, ketone **16** reacted with LDA−TMSCl to afford the corresponding silyl enol ether **17**, which underwent bromination to produce bromide **18** in excellent yield. Unfortunately, dehydrobromination of **18** proved to be a dead end under a variety of conditions. We surmised that this failure might result from the *cis*-configuration of the C6−Br and C5−H, which does not satisfy the antiperiplanar conformation requirement of an E2 elimination. Therefore, we explored an alternative selenoxide *syn*-elimination pathway[10] by converting **17** to phenylseleno ketone **20** with PhSeCl (99% yield from **16**). Surprisingly and unexpectedly, when PhSeBr was used as the selenium reagent, bromide **18** was obtained as the sole product instead of phenylseleno ketone **20**. Contrary to literature precedent, this provides a rare example of a reaction between a silyl enol ether and PhSeBr to generate a bromide product.

Deprotection of **20** and subsequent oxidation with ozone[11] gave the corresponding selenoxide, which underwent *syn*-elimination to afford enone **22** in 52% yield from **20**. Fortunately, we were able to obtain a single crystal structure of the deprotected phenylseleno ketone **21**,[12] which confirmed the stereochemical assignments at C6

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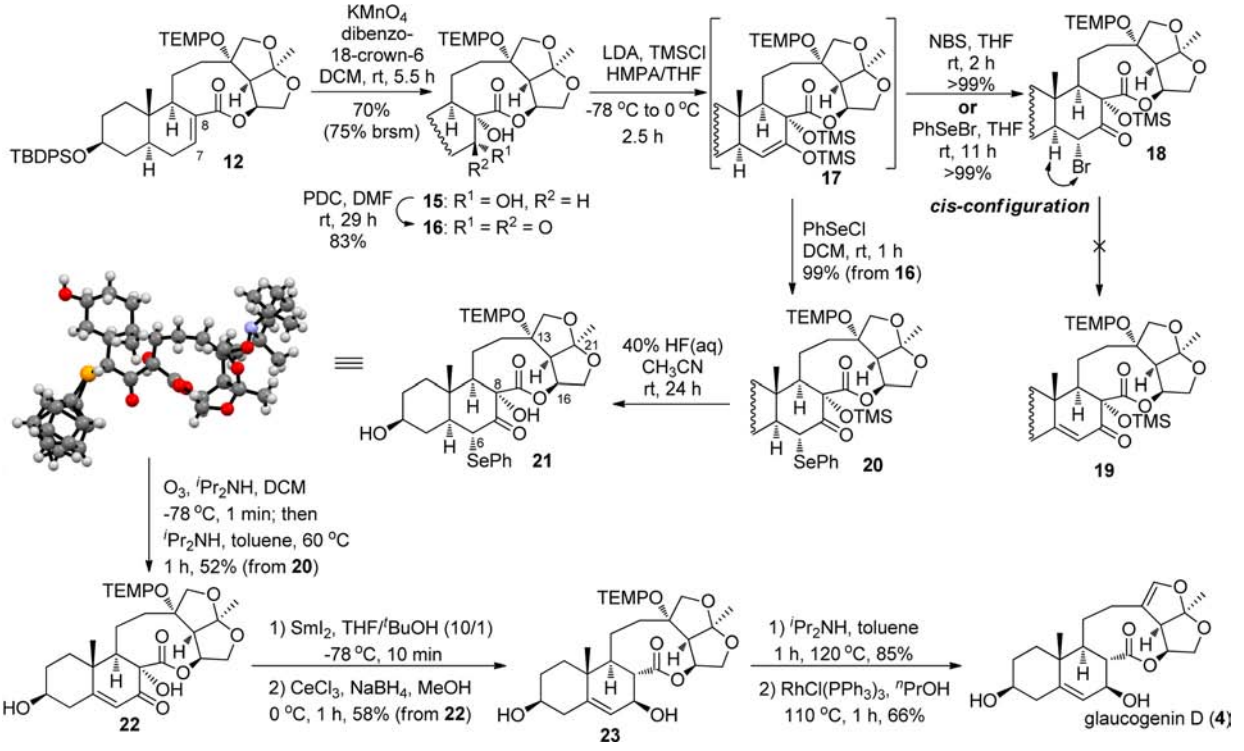
(12) CCDC-920710 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

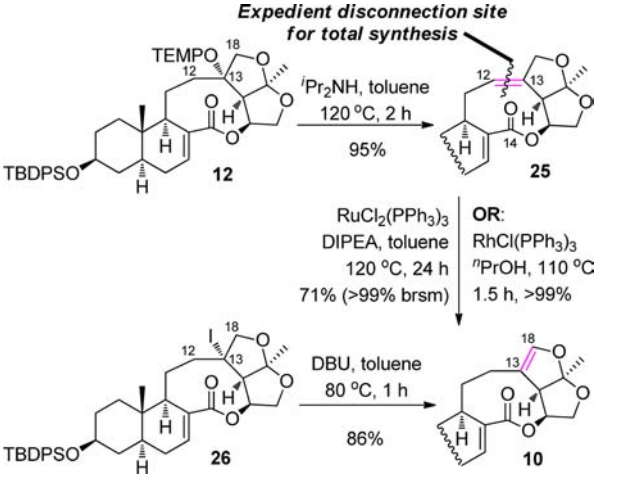
Scheme 2. Synthesis of Glaucogenin D (**4**)



and C8, as well as C13, C16 and C21 from our early synthetic route. Dehydroxylation of **22** at C8 with SmI_2[13] and Luche reduction of the resulting conjugated enol furnished C7β-OH product **23** as the major product in 58% yield.

What remained in the synthesis of glaucogenin D (**4**) was the removal of the TEMPO group in **23** to reveal the C13−C18 olefin, which unluckily proved to be a nontrivial task. Employing **12** as the model substrate (Scheme 3), we were frustrated to find that TEMPO remained intact when using conventional methods[14] for the heterolytic cleavage of the N−O bond, presumably due to the severe steric hindrance around the N−O bond in **12** (four methyl groups around N and a tetrasubstituted C13 atom attached to O). We then drew inspiration from the thermal decomposition of alkoxyamines in the field of living radical polymerization where the TEMPO group could be removed to afford an olefin directly through homolytic cleavage of the C−O bond rather than the N−O bond.[15] Surprisingly, under thermal conditions, **12** decomposed in a highly regioselective manner to give C12−C13 olefin **25** in 95% yield, which is complementary to the regioselectivity observed in the thermal elimination of iodide **26** affording C13−C18 olefin **10**. Luckily, olefin **25** could be

Scheme 3. Complementary Olefin Formation from Two Distinct C13-Substituted Disecopregane Intermediates



isomerized to enol ether **10** using $RuCl_2(PPh_3)_3$ in toluene (71% yield),[16] or using the more robust Wilkinson's catalyst in ^{n}PrOH (>99% yield).[17] The unexpected formation of the C12−C13 olefin in the TEMPO thermal decomposition deserves further comment: (1) it provides a facile approach to the synthesis of glaucogenin analogues

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(14) Conditions screened: Zn−HOAc, $Mo(CO)_6$, 10% Pd/C, SmI_2, etc.

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bearing a C12−C13 olefin, and (2) for future total synthesis endeavors, a strategic disconnection could be reasonably made via cleavage of the central nine-membered lactone at the C14 ester bond or the C12−C13 olefin.

Finally, a two-step sequence as shown in Scheme 2, including removal of the TEMPO group in **23** and isomerization, delivered synthetic glaucogenin D (**4**), whose ^{1}H and ^{13}C NMR spectra were in good agreement with that of natural glaucogenin D (**4**).[2i]

In conclusion, we have completed the first chemical synthesis of glaucogenin D (**4**) in 12 steps and 6.8% overall yield starting from hirundigenin-type intermediate **6**. Salient features of the current synthesis include (1) establishment of the requisite C5−C6 olefin via a thermal *syn*-elimination reaction of a phenyl selenoxide; (2) discovery of thermal conditions to remove the TEMPO group to give a complementary C12−C13 olefin that can be either isomerized to a C13−C18 olefin or deconstructed for future total synthesis endeavors; (3) the possibility of structural diversification toward glaucogenin analogues, including but not limited to C15-acetal, C12−C13 olefin, and various oxidation states of the B ring, which are of significant importance to the pharmaceutical research of disecopregnane steroids. Additionally, we anticipate that allylic deoxygenation of glaucogenin D (**4**) would provide glaucogenin C (**3**), and further oxidation of the A-ring might realize the synthesis of other glaucogenin members, which is currently being pursued in our laboratory.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.