Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formal synthesis of osladin based on an activation relay process

Xiao-Fei Zhang [a], Jing-Jing Wu [b], Yong Shi [b,*], Jing-Rong Lin [a,*], Wei-Sheng Tian [b,*]

[a] Department of Chemistry, College of Life Sciences and Environment, Shanghai Normal University, 100 Guilin Road, Shanghai 200234, China
[b] The Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 20 May 2014
Revised 19 June 2014
Accepted 26 June 2014
Available online xxxx

Keywords:
Activation relay process
Intact skeleton
Osladin
E-ring opening
Steroid

ABSTRACT

An efficient five-step formal synthesis of osladin by utilizing the intact skeleton of diosgenin acetate is reported. Key features of this study include an unprecedented reductive opening of E-ring in steroidal sapogenin to give 22*S*-**5**, and an activation relay process for selective breakage of C16—O bond in furostanol to deliver 22*R*-**17**.

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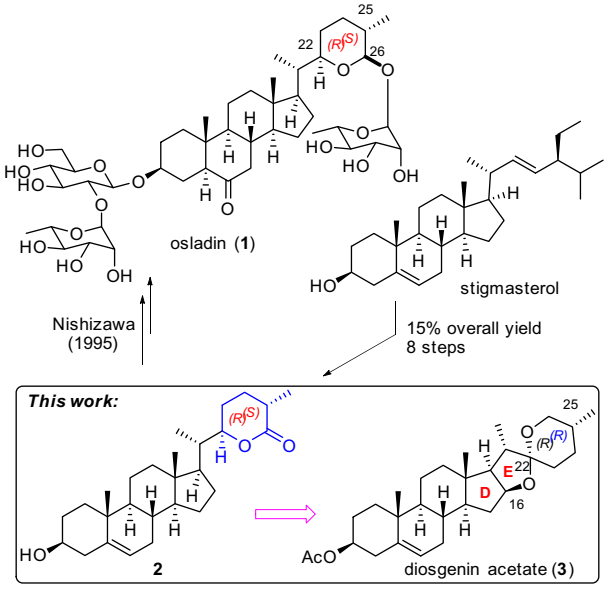
Rational selection and utilization of starting materials is not only crucial for the highly efficient synthesis of medicinal drugs, agricultural agents, and natural products with potential application value, but also meaningful for resource conservation and environmental protection. There have been many successful examples such as the syntheses of progesterone and related steroidal drugs from diosgenin, taxol and analogues from 10-deacetylbaccatin, and Qinhaosu (artemisinin) from arteannuic acid. Herein we report a five-step formal synthesis of osladin (**1**) by the utilization of the intact skeleton of diosgenin acetate (**3**).

Osladin (**1**) is a plant sweetening agent isolated by Jizba and Herout from the rhizome of the European fern *Polypodium vulgare* in 1971.[1] Its stereochemistry was eventually assigned by Nishizawa and co-workers through a single-crystal X-ray diffraction study of a natural sample and a chemical synthesis in 1990s.[2] Nishizawa's synthesis has provided elegant solutions to the selectivity issues of two glycosidation reactions, however, the preparation of the precursor of its aglucone (**2**) from stigmasterol was less efficient, therefore providing us space to explore its synthesis from diosgenin acetate which possesses the basic skeleton and all of functional groups of **2** (Scheme 1).

Diosgenin has been the steadfast starting material for the synthesis of steroidal natural products and drugs since the historic discovery of diosgenin by Marker.[3] Routinely, diosgenin was chemically degraded into 3-acetoxypregna-4,16-dien-20-one or epiandrosterone for various purposes. Using such intermediates in the synthesis of natural steroids always required to create the adequate side chains,[4] which is not attractive on the strategical level. Thereby, employing the intact skeleton of diosgenin in



Scheme 1. Two different synthetic strategies of osladin.

* Corresponding authors. Tel.: +86 21 54925178 (Y.S.), +86 21 64322511 (J.-R.L.), +86 21 54925176 (W.-S.T.).
E-mail addresses: shiong81@sioc.ac.cn (Y. Shi), jrlin@shnu.edu.cn (J.-R. Lin), wstian@sioc.ac.cn (W.-S. Tian).

http://dx.doi.org/10.1016/j.tetlet.2014.06.101
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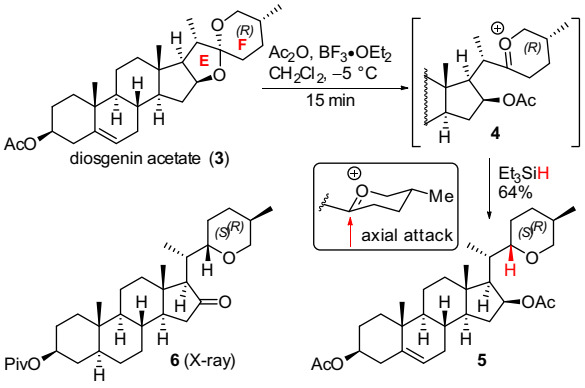
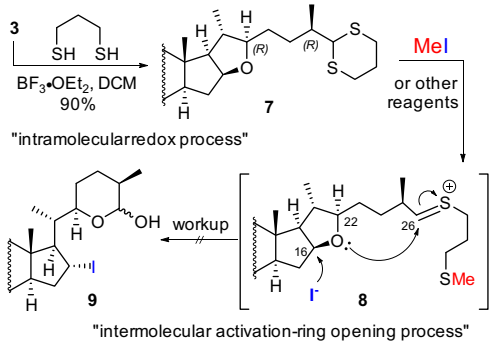


Scheme 2. E-ring opening by trapping oxonium ion **4**.



Scheme 3. A redox economic ring-opening process.

natural product synthesis has also been practiced, but only a few examples were reported.[5]

Recently, Sandoval-Ramírez and co-workers reported a mild and efficient procedure to open both rings of the spiroketal moiety in diosgenin, and proposed the formation of oxonium ion **4** as a key intermediate (Scheme 2).[6] We reasoned that trapping **4** with a reducing agent might provide the desired ring-opening product, and that the chiral center at C20 would operate as a handle for stereochemical control on C22 in the reduction. Indeed, diosgenin acetate **3** was treated with acetic anhydride and boron trifluoride etherate in CH_2Cl_2 at −5 °C for 15 min, and quenched with Et_3SiH to afford compound **5** as a single isomer in moderate yield, along with a small amount of F-ring opening product (**10**, 10–20% yield). A single crystal X-ray diffraction analysis of derivative **6** (Fig. 1, see Supplementary data for its preparation) helped us to affirm the configuration of C22 in **5** to be the unwanted *S* (Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.[7]).

Inversing the C22 stereochemistry of **5** required redundant functional-group manipulations. Direct formation of 22*R* and elimination of the oxidation/reduction reagents would be more

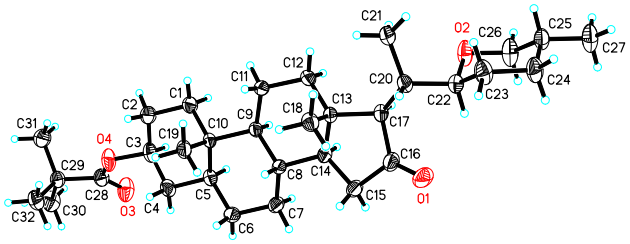


Figure 1. Ortep structure of compound **6**.

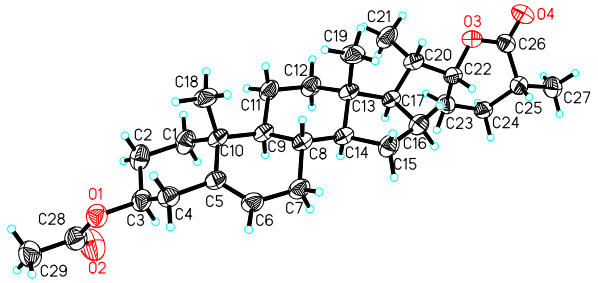


Figure 2. Ortep structure of compound **18**.

promising. Therefore, an approach taking advantage of intramolecular processes was investigated. As depicted in Scheme 3, via an internal redox process, 22*R* furostan derivative **7** were obtained by treating **3** with boron trifluoride etherate/propane-1,3-dithiol at room temperature in high yield.[8] We proposed that the thionium ion **8** formed by reacting with an alkylating agent such as MeI might be attacked by the oxygen atom of E-ring, hence enabling the nucleophilic cleavage of C16—O bond by attacking with iodide ion to give **9**. Unfortunately, we investigated several alkylating and oxidating reagents, and failed to find out a suitable one for this interesting transformation.

But we still were intrigued by the notion that internal activation would stand the best chance to selectively break C16—O ether bond over C22—O bond, and shifted our attention from thionium ion to acylium ion. Therefore 26-acid **11** was prepared from **3** with high yield in two steps: (1) reductive cleavage of F-ring with $Et_3SiH/BF_3{\cdot}OEt_2$ at 0 °C;[9] (2) Jones oxidation[10] of the resulting furostanol **10**.

In 1974, Suárez and co-workers reported an E-ring opening procedure of furostan sapogenins, that is refluxing **12** in acetic anhydride in the presence of TsOH for 30 min gave products **13** and **14** (Scheme 4).[11] We assumed that both **13** and **14** were generated from intermediate **15** through a Wagner–Meerwein rearrangement and a β-elimination of C16-carbocation, and envisaged that the presence of a nucleophile in the reaction system would give the 16-substituted product (preferably a halogen atom) that is of use for forthcoming steps.[12]

We then moved forward to find a proper combination of activator and nucleophile. Iodide ion is an excellent nucleophile and the

Table 1
Internal activation method for ring-opening

Entry	Conditions	Results
1	$SOCl_2$, DCM, rt, 8 h; $BF_3{\cdot}OEt_2$ (3 equiv), LiI (5 equiv), 2 h	35% **17**, 55% **11**
2	$SOCl_2$, DCM, $BF_3{\cdot}OEt_2$ (3 equiv), LiI or NaI (5 equiv), 0 °C to rt, 8 h	41% **17**, 50% **11**
3	Ac_2O (3 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), NaI (5 equiv), DCM, 0 °C, 24 h	No reaction
4	Ac_2O (8 equiv), $BF_3{\cdot}OEt_2$ (12 equiv), NaI (6 equiv), DCM, 0 °C, 24 h	70% **16**, 5% **17**
5	Ac_2O (8 equiv), $BF_3{\cdot}OEt_2$ (12 equiv), NaI (6 equiv), Bu_4NI (1 equiv), DCM, 0 °C, 7 h	64% **16**, 17% **17**
6	Ac_2O (8 equiv), $BF_3{\cdot}OEt_2$ (12 equiv), Bu_4NI (6 equiv), DCM, 0 °C, 7 h	92% **17**
7	**10**, Ac_2O, $BF_3{\cdot}OEt_2$, Bu_4NI, DCM, 0 °C, 7 h; rt, 12 h	Complex

Please cite this article in press as: Zhang, X.-F.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.06.101

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