Pergamon

Tetrahedron Letters 39 (1998) 415–418

TETRAHEDRON LETTERS

First Total Synthesis of 25(R)-Ruscogenin-1-yl β-D-xylopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranoside, an Ophiopogonis Saponin from the Tuber of *Liriope muscari* (Decne.)

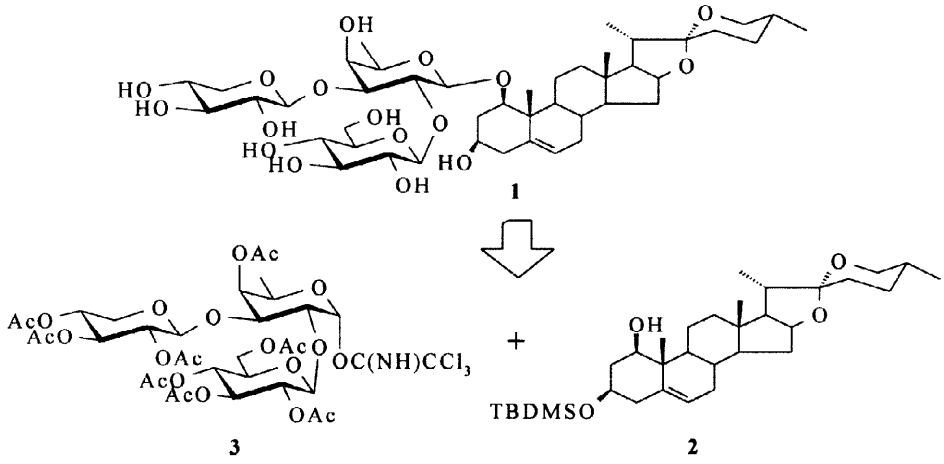
Meizheng Liu, Biao Yu,* Yongzheng Hui*

State Key Laboratory of Bio-organic and Natural Products Chemistry,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Received 4 September 1997; revised 24 September 1997; accepted 15 October 1997

Abstract: The first total synthesis of 25(R)-ruscogenin-1-yl β-D-xylopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranoside (**1**), an Ophiopogonis saponin with strong anti-inflammatory and immunopharmacological activities from the tuber of *Liriope muscari* (Decne.), is described. The glycosylaton of a highly hindered alcohol by Schmidt's "inverse procedure" is demonstrated. © 1997 Elsevier Science Ltd. All rights reserved.

A great number of saponins from a wide variety of both plant and animal species have recently been paid considerable attention due to the importance of their physiological and pharmacological activities. [1] On the other hand, few effort so far has been exerted on the total synthesis of this important group of natural products.[2] Herein, we wish to describe the first total synthesis of a steroidal trisaccharide saponin **1**, which was isolated and characterized by Yu and Shoji in 1990 from the tuber of *Liriope muscari* (Decne.),[3] an Ophiopogonis plant commonly used in Chinese herb medicines.[4] Pharmacological studies showed that **1** possessed strong anti-inflammatory and immunopharmacological activities. [5]

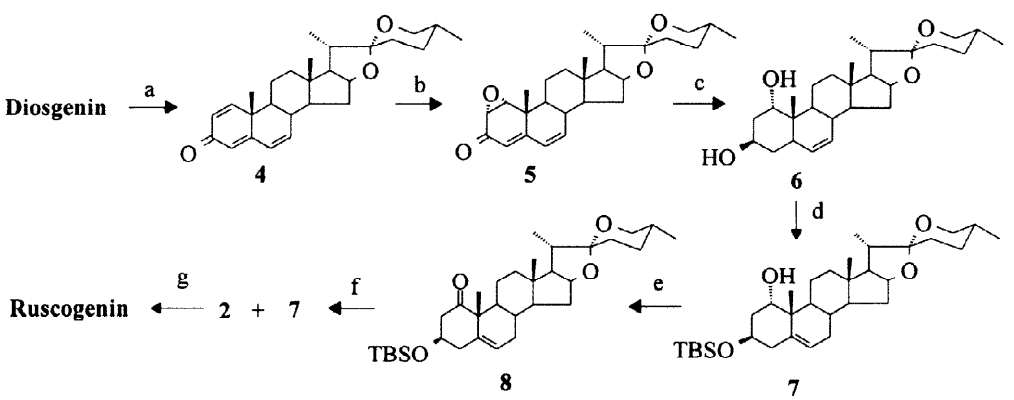


Scheme 1

A key to assembling a saponin is the construction of the glycosidic bond between the sugar moiety and

PII: S0040-4039(97)10536-6

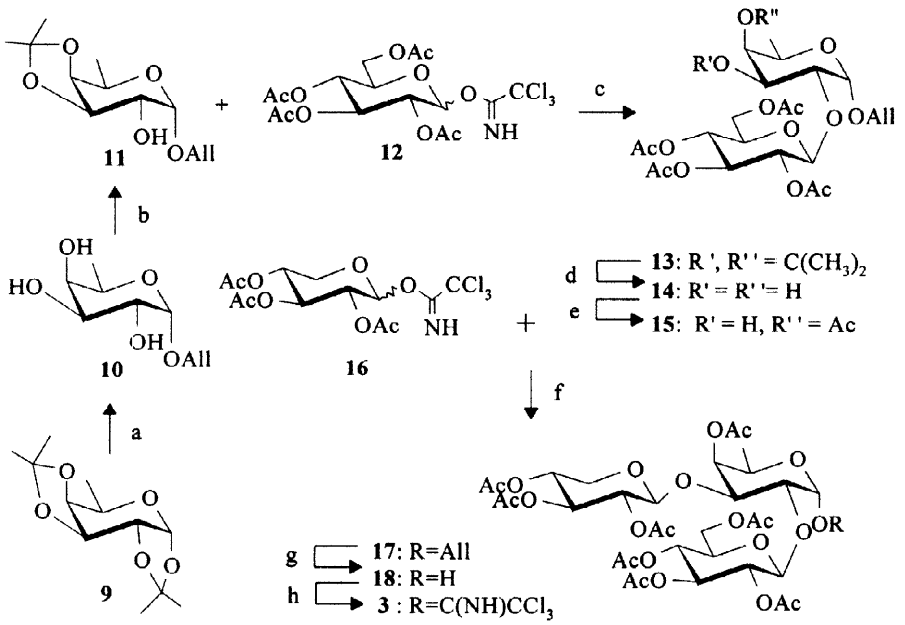
the triterpene or steroid. Therefore, **1** was retrosynthetically disconnected into steroid acceptor **2** and the trisaccharide donor **3** (Scheme 1). Acceptor **2** was synthesized by introducing a β-OH to the C-1 of diosgenin (Scheme 2). Oxidation of diosgenin by DDQ gave trienone **4**, which was further oxidized by H_2O_2 to provide the epoxide **5**. **5** was reduced with Li/NH_3 to afford the Δ^6 diol **6**, although Δ^5 diols were usually the main products under the same conditions in the previous conversion of cholestane-type steroids to vitamin D and its analogues,[6] no Δ^5 diol product was detected here. When the 3-OH of diol **6** was selectively protected by treatment with *tert*-butyldimethylsilyl chloride and imidazole in DMF, in half the amount of **6** the C6-C7 double bond was surprisingly found to be shifted to C5-C6 to furnish **7** simultaneously. Subsequent attempts to invert the 1-α-OH of **7** into β configuration by S_N2 type reactions, such as Mitsunobu reaction, all failed. It could be explained that the reaction center of **7** (C-1) was seriously hindered by the hydrogens at C-18. Therefore, we have to resort to an oxidation-reduction sequence to epimerize the 1α-OH. Thus, **7** was oxidized by PDC to give keto **8**, $NaBH_4$ reduction of **8** afforded 1β-epimer **2** mainly (**2**: 70%, **7**: 25%), taking advantage of the large bulkiness of the 3β-substituted TBDMS group.[7] Desilylation of **2** furnished the 25R-ruscogenin, which gave identical physical data with the authentic sample.



Scheme 2. Reagents and Conditions: a) DDQ, dioxane, reflux, 8h, 69%; b) H_2O_2, NaOMe , MeOH, rt, overnight, 68%; c) Li/NH_3, THF, then NH_4Cl, 53%; d) TBDMSCl, imidazol, rt, overnight, 50%; e) PDC, CH_2Cl_2, rt, 92%; f) $NaBH_4$, THF, 70%; g) 5N HCl, acetone, rt, 1h, 96%.

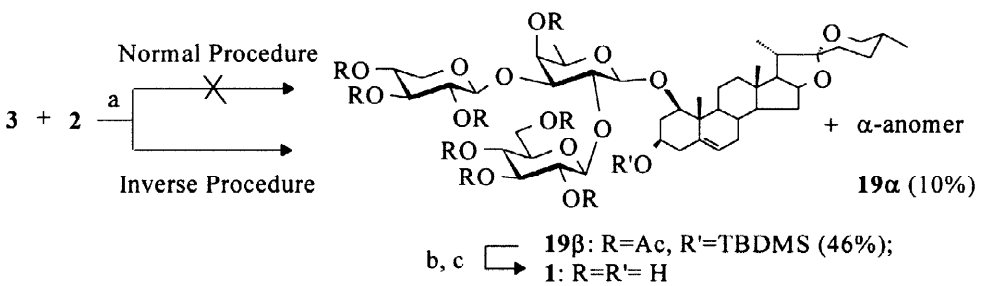
In the synthetic course of the trisaccharide donor **3**, Schmidt glycosylation [8] was repeatedly used (Scheme 3). D-Fucopyranoside **9** [9] was treated with 3% HCl/AllOH to give allyl α-D-fucopyranoside (**10**), which was isopropylidenated to provide acceptor **11** with 2-OH free. β Glucosylation of **11** with glucose imidate **12**[10] led to the desired disaccharide **13**. Removal of the isopropylidene group of **13** afforded **14** with 3,4-OH free, which was selectively acetylated at 4-OH to afford 3-OH free **15**.[11] **15** was easily xylosylated with **16**[12] to give the desired trisaccharide **17** in high yield. The stereochemistries of the three glycosidic linkages of **17** were determined to be 1α, 1'β, and 1"β based on ^1H NMR spectrum (doublets at δ 4.98 ($J_{1,2}$=3.2), 4.59 ($J_{1',2'}$=7.8), and 4.64 ($J_{1'',2''}$=6.3), respectively). Deallyllation of **17**,[13] followed by addition with Cl_3CCN,

afforded the trisaccharide donor **3**, which was determined to be the expected α imidate by its ^{1}H NMR (doublet at 6.23 for H-1, J=3.5).



Scheme 3. *Reagents and Conditions*: a) 3% HCl, AllOH, 80 °C, 92.5%; b) TsOH (0.1 equiv), $(CH_3)_2C(OCH_3)_2$, rt, 83%; c) BF_3OEt_2 (0.7 equiv), CH_2Cl_2, 4ÅMS, -20°C, 73.1%; d) 50% HOAc, 60°C, 1h, 92.5 % ; e) $CH_3C(OCH_2CH_3)_3$, TsOH (0.1 equiv), rt, 20min; then 20% HOAc, rt, overnight, 87.3%; f) BF_3OEt_2 (0.7 equiv), CH_2Cl_2, 4ÅMS, -20 °C, 90%; g) $PdCl_2$, NaOAc, 50% HOAc, 60 °C, 87%; h) Cl_3CCN, DBU, CH_2Cl_2 , 49.2%.

With donor **3** and acceptor **2** at hand, we sought to effect the final glycosylation to construct the target saponin (Scheme 4). However, all attempts to glycosylate the steroid acceptor **2** with imidate donor **3** failed to



Scheme 4. Reagents and Conditions: a) TMSOTf (0.2 equiv), -5~0 °C, CH_2Cl_2, 4ÅMS, ~2 h. b) TMSOTf (2.0 equiv), CH_2Cl_2, -78 °C, 5min; c) CH_3ONa, CH_3OH, rt, 3-4h, 85%.

provide the corresponding glycoside under the normal procedure for glycosylation with imidates.[14] It is reasonable regarding the steric hindrance of 1-OH in acceptor **2**. Fortunately, under Schmidt's "Inverse procedure"[15] whereby acceptor **2** was activated firstly by a catalytic amount of TMSOTf before adding donor **3**,

the desired glycosylation product **19** was obtained (β:α 4.6:1, separated by silica gel column chromatography). It is worthy noting that Schmidt's "inverse procedure", which was developed to improve the glycosylation efficiency by preventing the decomposition of the highly reactive donors, was demonstrated here to be an efficient method for the glycosylation of highly hindered alcohols.[16] Desilylation of **19**β with TMSOTf,[17] followed by deacetylation, then purification by silica gel column chromatography, furnished the final saponin **1**. The physical data of **1** was in well agreement with those reported.[18]

In conclusion, the first total synthesis of the title saponin **1** was achieved, this synthesis provided an entry to the synthesis of other members of Ophiopogonis saponins, especially to the glycosylation of hindered aglycones by using Schimdt's "inverse procedure" of glycosyl imidate donors.

Acknowledgments: We thank the State Science and Technology Committee of China for financial support. We are grateful to Prof. Hou-Ming Wu for 600 MHz NMR support and Prof. Qiang Xu for providing the authentic sample of 25R-ruscogenin.

References and Notes:

1. a) Hostettmann, K.; Marston, A. *Saponins;* Cambridge University Press, **1995**. b) Rouhi, A. M. *C & EN*, **1995**, Sept. 11, 28.
2. a) Yamada, H.; Nishizawa, M. *J. Org. Chem.* **1995**, 60, 386. b) Randolph, J. T.; Danishefsky, S. T. *J. Am. Chem. Soc.* **1995**, 117, 5693.
3. Yu, B.-Y.; Hirai, Y.; ShoJi, J.; Xu, G.-J. *Chem. Pharm. Bull.* **1990**, 38, 1931.
4. *Species Systematization and Quality Evaluation of Commonly used Chinese Traditional Drugs*: Xu, G. J.; Xu, L. S. Eds.; Fujian Science and Technology Press, **1994**; p 56.
5. Xu, Q.; Wang, R; Yu, B. *J. China Pharm. Univ.* **1993**, 24, 98.
6. (a) Gamoh, K.; Hirayama, M.; Ikekawa, N. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 449. (b) Von Fürst, A.; Labler, L.; Meier, W. *Helv. Chim. Acta,* **1981**, 64, 1870.
7. Noam, M.; Tamir, I.; Breuer, E.; Mechoulam, R. *Tetrahedron,* **1981**, 37, 597.
8. (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, 50, 21. (b) Schmidt, R. R. *Angew. Chem. In. Ed. Engl.* **1986**, 25, 212.
9. Lerner, M. L. *Carbohydr. Res.* **1993**, 241, 291.
10. Schmidt, R. R.; Michel, J. *Angew. Chem. In. Ed. Engl.* **1980**, 19, 731.
11. Zhou, W.; Jennings, H. J. *J. Carbohydr. Chem.* **1996**, 15, 279.
12. Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, 195, 199.
13. Ogawa, T.; Nakabayashi, C. *Carbohydr. Res.* **1981**, 93, C1.
14. For the normal procedure for glycosylation with imidates: a catalyst (BF_3OEt_2 or TMSOTf) was added to the mixture of donor and acceptor, or an acceptor was added to the mixture of donor and catalyst.[8]
15. Schmidt, R. R.; Toepfer, A. *Tetrahedron. Lett.* **1991**, 32, 3353.
16. For glycosylation of hindered alcohols see: Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, 111, 6881, and the refs cited therein.
17. Nelson, T. D.; Crouch, R. D. *Synthesis,* **1996**, 1031.
18. **1**: $[\alpha]^{20}_D$ - 87.3 (*c* 0.11, pyridine, lit.[3] -90.3, c 0.63). ^{1}H NMR (Py-d_5, 600 MHz): 5.85 (1H, d, J= 7.0), 5.78 (1H, br), 5.47 (1H, d, J= 7.8), 5.20 (1H, d, 1H, J= 6.9), 4.93 (1H, dd, 1H, J= 10.5), 4.86 (1H, dd, 1H, J= 3.0), 4.65-4.62 (3H, m), 4.58 (1H, dd), 4.54 (1H, dd, J= 11.2, 5.3), 4.40-4.37 (2H, m), 4.31 -4.27 (4H, m), 4.17 (1H, t, J= 8.6), 4.15 (1H, m), 4.06 (1H, dd, J= 11.8, 4.1), 3.90 (1H, dd, J= 10.9), 3.88 (1H, m), 3.71 (1H, m), 3.65 (1H, t, J= 10.6), 1.64 (3H, d, J= 6.5), 1.47 (3H, s), 1.25 (3H, d, J= 6.5), 1.12 (3H, s), 0.85 (1H, d, J= 5.8). HREIMS (*m/z*): 871.4674, (MH^+, 871.4691) for $C_{44}H_{70}O_{17}Si$.