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Total synthesis of ribisin A

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ABSTRACT

The first total synthesis of natural product ribisin A has been achieved in 11 steps from commercially available methyl α-D-glucopyranoside with 21.6% overall yield. The highly oxygenated benzofuran skeleton of this natural product was constructed, taking advantages of the inherent chirality of D-glucose, through the key reactions of Ferrier carbocyclization, Johnson iodination, Suzuki cross-coupling, and Wacker oxidative cyclization.

Phellinus ribis, a kind of fungi belonging to *Phellinus gunus* (*Hymenochaetaceae* family), has been used for treating several diseases and enhancing body immunity as a folk medicine in East Asia.[1] Recently, Fukuyama and coworker reported the isolation of four new natural products as ribisin A–D (**1**–**4**, Fig. 1) from the methanol extraction of the fruiting bodies of *P. ribis*.[2] All of these compounds have highly oxygenated benzofuran skeleton and could stimulate neurite outgrowth in NGF-mediated PC12 cells. The novel structure and the specific neural related biological activities attracted our interests in the total synthesis and SAR studies of ribisin A–D. As part of our ongoing project for drug candidate preparation using natural carbohydrates as chiral templates,[3] we report herein the first total synthesis of ribisn A from D-glucose derivative applying Ferrier carbocyclization as a key transformation in the construction of highly oxygenated core skeleton.[4]

The retrosynthetic analysis of ribisin A (**1**) is depicted in Scheme 1. The target compound **1** could be achieved from compound **5** by establishing the benzofuran core structure through Suzuki cross-coupling and furan formation. The cyclohexenone **5** in turn was envisioned to be synthesized from carbohydrate intermediate **6** utilizing Ferrier carbocyclization and the following Johnson iodination. Compound **6** could be synthesized from commercially available methyl α-D-glucopyranoside (**7**).

Synthesis of the key intermediate **6** from **7** is presented in Scheme 2. The known methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**8**) was readily obtained from the reaction of **7** with α,α-dimethoxytoluene and *p*-toluenesulfonic acid according to a literature procedure.[5] Blocking two secondary hydroxyl groups of **8** with *tert*-butyldimethylsilyl chloride (TBSCl) was conducted smoothly using 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) as base giving the desired product **9** in high yield. Reductive cleavage of the benzylidene acetal **9** was achieved under $Pd(OH)_2/C$ catalyzed hydrogenolysis obtaining compound **10**, which was subjected to the regioselective iodination on primary hydroxyl group to generate iodide derivative **11** in high yield.[6] Treatment of iodide **11** with MeI in the presence of excessive *t*-BuOK accomplished O-methylation on C4 and HI elimination between C5 and C6, forming the key intermediate hexenopyranoside **6** in one pot.

With the key intermediate **6** in hand, we then turned our attention to the Ferrier carbocyclization reaction (see Scheme 3). To get a successful rearrangement, various metal catalysts, including

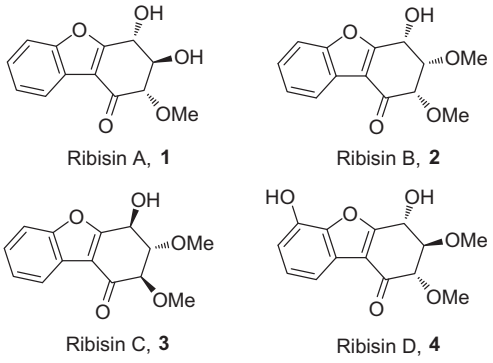

Figure 1. Structure of ribisin A–D.

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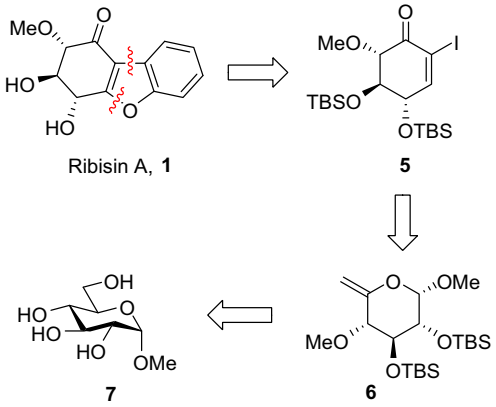
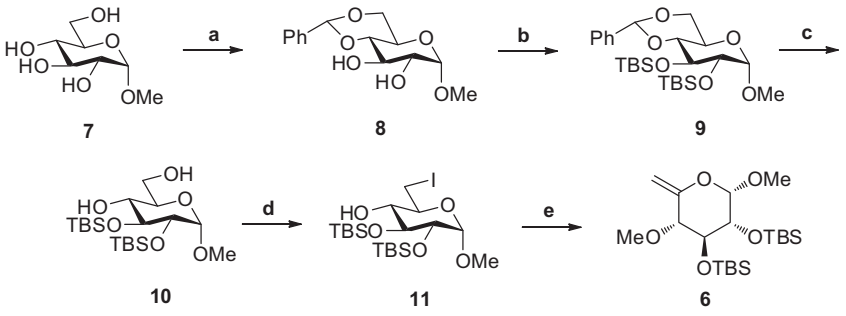
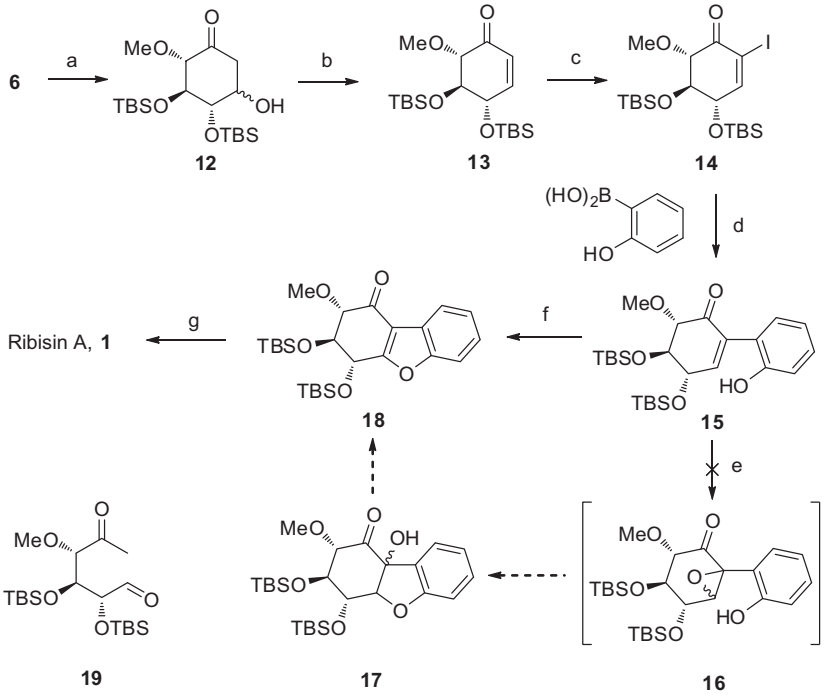


Scheme 1. Retrosynthetic analysis of ribisin A.

catalytic amounts of $Hg(OAc)_2$, $HgCl_2$, $Hg(OCOCF_3)_2$ and $PdCl_2$, were screened.[7] One of the major byproducts was isolated and postulated as an acyclic keto-aldehyde **19** based on NMR spectra analyses (^{1}H NMR, 2D COSY).[8] This reminded us of using more amount of catalyst, in the case of stereo-hindered substrate, to facilitate the fast generation of vinyl alkoxide anion intermediate in the carbocyclization. Indeed, the formation of compound **19** was almost completely prevented when the reaction was proceeded in the presence of 1.0 equiv of $Hg(OAc)_2$ in 15 min, and the desired β-hydroxyketone **12** was obtained as a mixture of stereoisomers in 68.5% yield. Treatment of mixture **12** with methanesulfonyl chloride (MsCl) and TEA at room temperature afforded α,β-unsaturated ketone **13**, which was further converted into the α-iodoenone **14** quantitatively applying Johnson's iodination protocol.[9] Suzuki cross-coupling[10] of **14** with 2-hydroxyphenyl boronic acid catalyzed by $Pd_2(PCy_3)_2$ gave benzofuran precursor **15** in a yield of 81%. Preparation of the core benzofuran structure was initially designed through epoxidation of **15** (→**16**), following a cascade epoxide-opening reaction (→**17**) and the elimination of hydroxy



Scheme 2. Reagents and conditions: (a) see Ref. 5, 80% (b) DBU, TBSCl, DCM, rt, 95%; (c) $Pd(OH)_2$/C, MeOH, rt, 98%; (d) I_2, PPh_3, imidazole, THF, 60 °C, 98%; (e) MeI, *t*-BuOK, THF, −30 °C to rt, 84%.



Scheme 3. Reagents and conditions: (a) $Hg(OAc)_2$, acetone/H_2O (v/v, 4:1), rt, 68.5%; (b) MsCl, TEA, DCM, rt, 95%; (c) I_2, CCl_4/pyridine (v/v, 1:1), rt, 99%; (d) $Pd_2(PCy_3)_2$, 1 M aqueous Na_2CO_3/toluene/MeOH, 65 °C, 81%; (e) *m*CPBA, DCM, rt; (f) $PdCl_2$, CuCl, O_2, dioxane, 50 °C, 69%; (g) TBAF, THF, rt, 98%.

group under acid conditions (→**18**).[11] To our surprise, *m*CPBA or H_2O_2 promoted oxidation of **15** generated mixtures of complex and unidentified products. Palladium(II)-catalyzed Wacker reaction, a widely applied industrial process for olefin transformation and heterocycle construction through anti oxypalladation,[12] was thus investigated. As we expected, Wacker oxidative cyclization of **15** with $PdCl_2/CuCl/O_2$ was carried out smoothly at 50 °C in moisture-containing dioxane affording the desired product **18** in a yield of 69%. Global deprotection of **18** with TBAF in THF furnished the target compound ribisin A (**1**), whose spectroscopic data were identical to those of the natural product.[13]

In conclusion, we have successfully achieved the first total synthesis of ribisin A from commercially available methyl α-D-glucopyranoside in 11 steps and in 21.6% overall yield. Our synthetic procedure, employing sequential Ferrier carbocyclization, Johnson iodination, Suzuki cross coupling, and Wacker oxidative cyclization as key steps, offers a concise and efficient synthetic route toward highly oxygenated benzofuran compounds.

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Supplementary data

Supplementary data (experimental procedures, spectral characterization, and copies of ^1H and ^{13}C NMR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.052.

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13. *Spectroscopic data for selected compounds:* Compound **11**: $[\alpha]_D^{22}$ +193.4 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 4.68 (d, J = 3.2 Hz, 1H), 3.80 (t, J = 8.8 Hz, 1H), 3.59–3.55 (m, 2H), 3.52–3.47 (m, 1H), 3.43 (s, 3H), 3.29 (dd, J = 10.4, 7.6 Hz, 1H), 3.21 (t, J = 8.8 Hz, 1H), 0.91 (d, J = 1.6 Hz, 18 H), 0.12 (s, 6H), 0.09 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 100.0, 75.1, 74.5, 73.6, 70.4, 55.3, 26.1, 26.0, 18.3, 18.1, 7.1, −3.4, −3.6, −4.3, −4.5 ppm. HRMS (ESI) calcd for $C_{19}H_{41}IO_5Si_2Na$ [$(M+Na)^+$] 555.1429, found 555.1438. Compound **6**: $[\alpha]_D^{22}$ +78.0 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 4.69–4.67 (m, 3H), 3.77 (t, J = 8.8 Hz, 1H), 3.66 (dd, J = 8.8, 3.6 Hz, 1H), 3.48 (s, 1H), 3.40–3.37 (m, 4H), 0.92–0.91 (m, 18H), 0.12–0.09 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.9, 101.1, 95.9, 82.7, 74.1, 73.8, 59.9, 55.3, 26.1, 26.0, 18.3, 18.1, −3.6, −3.7, −4.3, −4.6 ppm. HRMS (ESI) calcd for $C_{20}H_{42}O_5Si_2Na$ [$(M+Na)^+$] 441.2462, found 441.2475. Compound **13**: $[\alpha]_D^{22}$ +217.6 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 6.71 (dd, J = 10.4, 1.6 Hz, 1H), 5.98 (dd, J = 10.4, 3.6 Hz, 1H), 4.40 (dt, J = 6.0, 2.0 Hz, 1H), 3.80 (dd, J = 10.4, 8.0 Hz, 1H), 3.60 (s, 1H), 3.50 (d, J = 10.4 Hz, 1H), 0.93–0.91 (m, 18H), 0.16–0.08 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.2, 151.5, 127.2, 86.5, 78.3, 73.9, 60.7, 26.1, 26.0, 18.2, 18.1, −3.6, −3.9, −4.2, −4.7 ppm. HRMS (ESI) calcd for $C_{19}H_{38}O_4Si_2Na$ [$(M+Na)^+$] 409.2201, found 409.2200. Compound **14**: $[\alpha]_D^{22}$ +93.2 (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 2.4 Hz, 1H), 4.37 (dd, J = 7.6, 2.4 Hz, 1H), 3.82 (dd, J = 10.4, 7.6 Hz, 1H), 3.59–3.56 (m, 4H), 0.93 (s, 9H), 0.90 (s, 9H), 0.16 (d, J = 4.4 Hz, 6H), 0.08 (d, J = 5.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.2, 159.1, 101.4, 84.6, 77.7, 75.4, 60.4, 26.0, 18.1, 18.0, −3.7, −4.0, −4.3, −4.7 ppm. HRMS (ESI) calcd for $C_{19}H_{37}IO_4Si_2Na$ [$(M+Na)^+$] 535.1167, found 535.1180. Compound **15**: $[\alpha]_D^{22}$ −118.2(*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.31–7.26 (m, 2H), 7.03–6.91 (m, 3H), 6.78 (d, J = 2.0 Hz, 1H), 4.57 (dd, J = 7.2, 2.0 Hz, 1H), 4.00–3.95 (m, 1H), 3.74 (d, J = 10.4 Hz, 1H), 3.60 (s, 3H), 0.943–0.929 (m, 18H), 0.19 (d, J = 4.0 Hz, 6H), 0.14 (d, J = 8.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.2, 154.1, 152.5, 137.5, 130.6, 130.3, 123.3, 120.9, 118.7, 86.8, 78.4, 74.1, 60.3, 26.0, 25.9, 18.1, 18.0, −3.7, −4.0, −4.2, −4.6 ppm. HRMS (ESI) calcd for $C_{25}H_{42}O_5Si_2Na$ [$(M+Na)^+$] 501.2463, found 501.2472. Compound **18**: $[\alpha]_D^{22}$ −7.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.14–8.10 (m, 1H), 7.57–7.53 (m, 1H), 7.44–7.37 (m, 2H), 4.97 (d, J = 5.2 Hz, 1H), 4.25 (dd, J = 7.2, 5.6 Hz, 1H), 3.76 (d, J = 7.2 Hz, 1H), 3.68 (s, 3H), 1.03 (s, 9H), 0.94 (s, 9H), 0.31 (d, J = 13.2 Hz, 6H), 0.18 (d, J = 5.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.0, 166.8, 155.4, 125.7, 124.6, 123.2, 122.3, 114.6, 111.3, 85.6, 70.0, 60.2, 25.9, 25.8, 18.3, 18.0, −4.0, −4.1, −4.4, −4.5 ppm. HRMS (ESI) calcd for $C_{25}H_{40}O_5Si_2Na$ [$(M+Na)^+$] 499.2306, found 499.2320. Ribisin A (**1**): $[\alpha]_D^{22}$ −23.3 (*c* 1, MeOH). ^1H NMR (400 MHz, methonal-d_4) δ = 7.98 (dd, J = 7.5, 1.2 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.41 (dt, J = 7.5, 1,4 Hz, 1H), 7.37 (dt, J = 7.5, 1.2 Hz, 1H), 4.98 (d, J = 7.6 Hz, 1H), 4.03 (d, J = 10.0 Hz, 1H), 3.98 (dd, J = 10.0, 7.2 Hz, 1H), 3.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, methonal-d_4) δ = 193.1, 169.3, 157.4, 127.1, 125.9, 124.3, 122.8, 116.1, 112.7, 87.1, 78.8, 70.3, 60.8 ppm. HRMS (ESI) calcd for $C_{13}H_{12}O_5Na$ [$(M+Na)^+$] 271.0577, found 271.0564.