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Synthesis of bergenin-related natural products by way of an intramolecular *C*-glycosylation reaction

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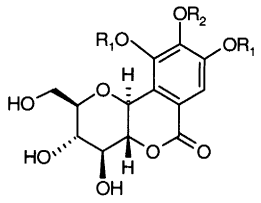
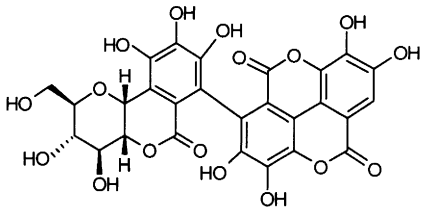
Abstract

The peracetate of tri-*O*-methylnorbergenin **16** as well as the *cis*-fused epimer of **16**, which constitutes the core *C*-aryl glycosidic fragment of castacrenin B, were prepared by way of the IDCP-mediated intramolecular *C*-arylation of a pentenyl β-D-glucopyranoside carrying, at O-2, a 3,4,5-trimethoxybenzyl substituent.

Bergenin **1**[1] and its derivatives norbergenin **2**[2] and tri-*O*-methylnorbergenin **3**[3] are gallotannin-related natural products having the unusual structure of internal *C*-aryl glycosides (Fig. 1).[4] Bergenin and its congeners occur widely in a number of plants and have been found as ingredients in plant extracts used in Indian folk medicine to treat veneral diseases.[3] Recently, the *cis*-fused epimer of norbergenin was found to occur as a fragment of an ellagitannin metabolite, namely castacrenin B, isolated from the Japanese chestnut tree.[5] The structures of bergenin and of castacrenin B are inviting targets for a synthesis by way of an intramolecular *C*-glycosylation procedure. However, attempts to prepare bergenin by such a strategy have failed so far.[6]



1 Bergenin: R_1 = H, R_2 = Me
2 Norbergenin: R_1 = R_2 = H
3 Tri-*O*-methylnorbergenin: R_1 = R_2 = Me



4 Castacrenin B

Fig. 1.

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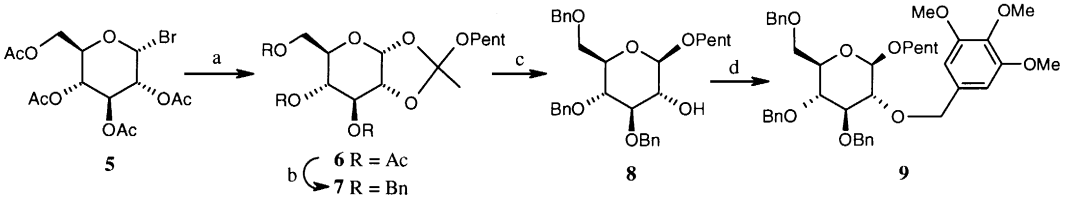
Bergenin itself has been obtained in very low yield by the reaction of acetobromoglucose with methyl 4-*O*-methyl gallate,[1] and its dimethyl ether **3** by a multistep synthesis by way of a *C*-glucopyranosyl benzene derivative.[7] In preliminary studies,[8] we have established that the internal *C*-glycosylation of gluco- and mannopyranose derivatives carrying, at O-2, a 3,4,5-trimethoxybenzoyl substituent could not be achieved, in spite of promising results in the furanose series.[9] As a consequence, we examined a synthetic approach to these natural products by way of a two-step strategy, namely internal *C*-arylation of 2-*O*-benzylated pyranosides, followed by oxidation of the benzylic position to form the lactone function.

While the intramolecular alkylation of the benzyl group took place readily in sugars carrying, at O-2, a 3-methoxybenzyl or a 3,5-dimethoxybenzyl substituent,[8,9] the conditions of the reaction ($SnCl_4$, $BF_3 \cdot Et_2O$, etc.) were not compatible with a 3,4,5-trimethoxybenzyl group as they promoted rapid de-*O*-benzylation of the substrate. A solution was found to this problem by using, as the anomeric activator, a pentenyl glycoside,[10] a function that can be activated selectively using a soft Lewis acid. We report herein the first synthesis of tri-*O*-methylnorbergenin and of the core *C*-glycosidic structure of castacrenin B by way of an internal *C*-glycosylation reaction.

The required precursor, partially protected pentenyl β-D-glucopyranoside **8**, was prepared in 59% overall yield from tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** by the orthoester procedure[11,12] (Scheme 1): *O*-pentenyl orthoester **6** was obtained from **5** under Lemieux–Morgan conditions,[11] the acetyl groups of **6** were replaced by benzyl groups, and the orthoester **7** was rearranged into the corresponding pentenyl β-glycoside **8** by treatment with trimethylsilyl triflate[13] followed by de-*O*-acetylation at O-2. Benzylation of **8** with highly reactive 3,4,5-trimethoxybenzyl chloride (from 3,4,5-trimethoxybenzyl alcohol and $SOCl_2$) provided substrate **9** (80%).



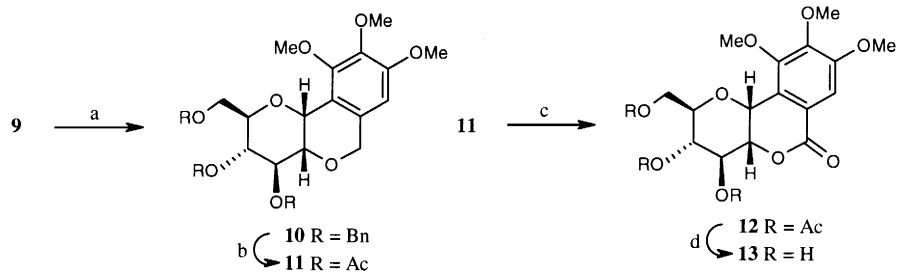
Scheme 1. Reagents and conditions. (a) 4-Penten-1-ol (3 equiv.), nBu$_4$NBr, collidine; 83%. (b) KOH, BnBr, THF, Δ; 84%. (c) (i) TMSOTf (cat.), CH_2Cl_2, 0°C, 2 h; (ii) MeONa, MeOH; 84%. (d) $ArCH_2Cl$, NaH, DMF; 80%

The treatment of **9** with iodonium dicollidine perchlorate (IDCP)[14] promoted the desired internal C-arylation reaction in excellent yield and without premature cleavage of the benzyl group at O-2 (Scheme 2). The resulting product was exclusively the kinetically favored,[15] *cis*-fused tricyclic system **10** ('α-linked'). It is also noteworthy that iodination of the activated aromatic ring did not compete with the internal alkylation.[16] Selective removal of the benzyl groups of **10** was realized by brief catalytic hydrogenation and the resulting product was acetylated to afford **11**. The benzylic position of **11** could then be oxidized using catalytic ruthenium tetroxide[17] to give compound **12** (39% yield), a protected form of the core *C*-aryl glycoside of castacrenin B.

The NMR data of **12**[18] were found to be in excellent agreement with those reported for the corresponding derivative of castacrenin B.[5] Deacetylation of **12** gave the tri-*O*-methyl analog, compound **13**.[19]

It is of interest to note that the $^3J_{H,H}$ coupling constants in the pyranose ring of both **11** and **12** are all small ($J_{1,2}$=3Hz, other $^3J_{H,H}$=3.8–5 Hz) which indicate that the conformation with an inverted chair ($^1C_4$-type, see **I** in Fig. 2) is much more favorable for these compounds than the alternate $^4C_1$ chair form in which the *C*-aryl substituent would be axial.

The synthesis of bergenin and congeners required an epimerization at the newly created benzylic position (C-1). This inversion of configuration was deemed possible on the basis of the expected greater



Scheme 2. Reagents and conditions. (a) IDCP (2 equiv.), CH_2Cl_2, 3 h, rt; 83%. (b) (i) H_2, Pd/C, MeOH; (ii) Ac_2O, pyridine; 98%. (c) $RuCl_3$ (cat.), $NaIO_4$, CCl_4/MeCN/H_2O, 18 h; 39%. (d) MeONa, MeOH; quant.

stability of the *trans*-fused (β-linked) bicyclic system (**II**) with respect to the *cis*-fused (α-linked) structure (**I**, Fig. 2) and of the likely sensitivity of the endocyclic benzylic C_1–O_5 bond to Lewis acids.

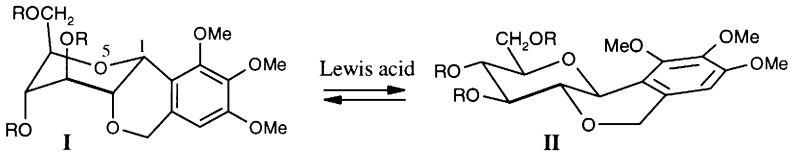
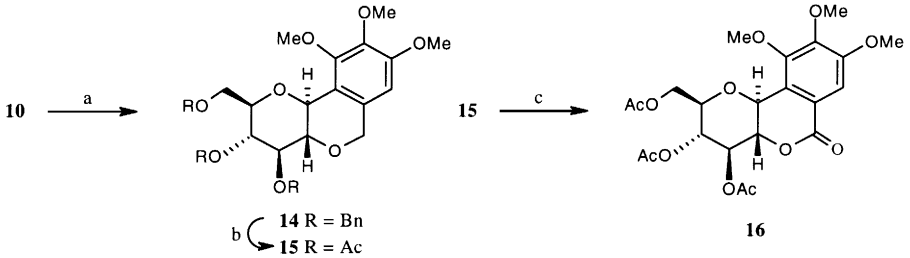


Fig. 2.

The treatment of **10** with an oxophilic Lewis acid promoted indeed the desired epimerization, albeit in a yield not exceeding 50%. The best results were obtained using $BF_3 \cdot Et_2O$. The resulting product, **14** (Scheme 3), was deprotected by hydrogenolysis and reacetylated to give **15**, and the remaining primary benzylic position oxidized under the same conditions as **11** to give lactone **16** (68%). The ^1H and ^{13}C NMR data of this product **16**[20] were found to match those reported for the triacetate of tri-*O*-methylnorbergenine.[3,7]



Scheme 3. Reagents and conditions. (a) $BF_3 \cdot Et_2O$ (cat.), CH_2Cl_2, 2 h, 0°C to rt; 48%. (b) (i) H_2, Pd/C, MeOH; (ii) Ac_2O, pyridine; 95%. (c) $RuCl_3$ (cat.), $NaIO_4$, CCl_4/MeCN/H_2O, 18 h; 68%

In conclusion, we have achieved the first synthesis of tri-*O*-methylnorbergenin triacetate, as well as of the core *C*-aryl glycoside of castacrenin B by way of an intramolecular *C*-glycosylation. This work demonstrates that pentenyl glycosides constitute very convenient substrates for the internal alkylation/glycosylation of highly Lewis-acid sensitive benzyl groups.

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16. Partial iodination of the ring occurred in the course of the internal *C*-arylation of the 2-*O*-(3,5-dimethoxybenzyl) derivative of **8** using IDCP.
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18. M.p.: 141–142°C; $[\alpha]_D$ +20.8 (*c*=1.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.08 (s, 6H), 2.12 (s, 3H) (3OAc), 3.89, 3.91, 3.93 (3s, 9H, 3OMe), 4.12 (m, 1H, $J_{4,5}$=3.8 Hz, H-5), 4.32 (dd, 1H, $J_{5,6a}$=4.7, $J_{6a,6b}$=12.0 Hz, H-6a), 4.45 (br t, 1H, J=3.3 Hz, H-2), 4.53 (dd, 1H, $J_{5,6b}$=7.2Hz, H-6b), 4.94 (t, 1H, J=4.1 Hz, H-4 or 3), 5.19 (d, 1H, $J_{1,2}$=3.0 Hz, H-1), 5.31 (t, 1H, J=4 Hz, H-3 or 4), 7.45 (s, 1H, H_{Ar}); ^{13}C NMR (62.9 MHz): δ 20.75 (3C), 56.28, 60.84 (C-6), 61.02, 61.91, 65.85, 68.09, 73.11, 73.54, 108.81 (ArCH), 119.97, 122.89, 147.46, 150.76, 154.8, 162.5, 168.75, 169.9, 170.53.
19. ^{13}C NMR (62.9 MHz, CD_3OD): δ 57.2, 61.43, 61.98, 62.54, 63.12, 69.58, 73.51, 80.87, 81.62, 109.94, 121.82, 126.07, 149.41, 152.93, 156.49, 166.01.
20. $[\alpha]_D$ –8.7±0.8 (*c*=1.3, $CHCl_3$) {lit.[7] $[\alpha]_D$ –8 (*c*=1, $CHCl_3$)}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.05, 2.08, 2.09 (3s, 3×3H, 3OAc), 3.84, 3.89, 3.93 (3s, 3×3H, 3OMe), ~3.85 (occluded m, 1H, H-5), 4.24–4.35 (m, 2H, H-6a,6b), 4.28 (t, 1H, J=10 Hz, H-2), 4.81 (d, 1H, $J_{1,2}$=10.3 Hz, H-1), 5.10 (t, 1H, J=9.6 Hz, H-4 or 3), 5.50 (t, 1H, J=9.4 Hz, H-3 or 4), 7.43 (s, 1H, H_{ar}); ^{13}C NMR (62.9 MHz): δ 20.63, 20.74, 20.82, 56.28, 61.08, 61.71, 62.46, 68.87, 72.31, 72.50, 77.20, 109.92, 118.8, 124.95, 148.92, 151.3, 154.05, 163.0, 169.75, 170.16, 170.59; one carbon hidden by the $^{13}CDCl_3$ signal.