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Aryloxyacetamides derived from resveratroloside and pinostilbenoside

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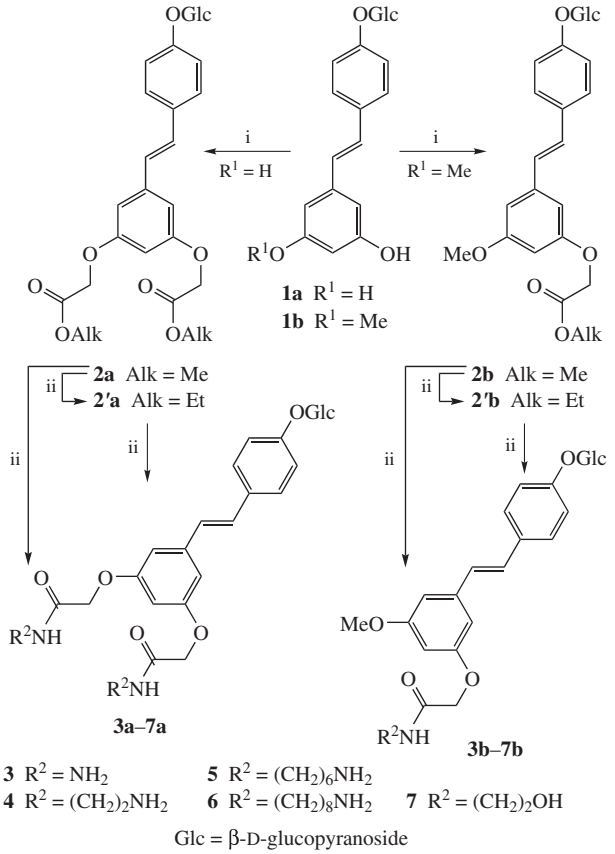
Etherification of phenolic hydroxyl groups of resveratroloside and pinostilbenoside (natural 3,4′,5-trihydroxystilbene derivatives) with methyl bromoacetate afforded compounds $ArOCH_2CO_2Me$, which on treatment with amines produce the corresponding 'stilbenyloxyacetamides' in good yields.

Stilbenes represent a family of biologically active substances, among which resveratrol (*trans*-3,4′,5-trihydroxystilbene) having antioxidant,[1] antitumor,[2] and cardioprotective properties[3] is most studied. Glycosilated stilbenes isolated from some plants[4–6] possess antioxidant,[1] antileukaemic,[7,8] antifungal[9,10] and hepatoprotective,[11,12] effects. On the other hand, amide function is a principal fragment of many bioactive compounds. For instance, betulonic acid-derived dipeptide bearing phenylalanine residue affects the early stages of the viral reproduction cycle and is highly active against the Herpes simplex virus, as well as having an immunostimulating activity greater than that of Freund's incomplete adjuvant.[13–15]

In our ongoing study of chemical and biological properties of resveratroloside **1a** and pinostilbenoside **1b**, two major stilbene glycosides of Siberian pine (*Pinus sibirica*) bark,[16,17] we report herein on the synthesis of a series of their amide-containing derivatives.

Amides are generally accessed by acylation of amines with carboxylic acids or their derivatives such as acid chlorides, anhydrides, or esters. Since compounds **1a** and **1b** contain remote glycoside moiety, it seemed necessary to protect the sugar residue prior to the amide synthesis employing anhydride or acid chloride method. We suggested, however, that a straightforward way to obtain amides from glycoside-containing substrates is the treatment of a carboxylic acid ester with corresponding amines which is not affected by free hydroxy groups. To introduce an ester function, we etherified phenolic groups of compounds **1a**,**b** with methyl bromoacetate in refluxing acetonitrile in the presence of K_2CO_3 and obtained methyl aryloxyacetate derivatives **2a** and **2b** (Scheme 1).†

The reaction of compound **2b** with $N_2H_4 \cdot H_2O$ in refluxing methanol proceeded very slowly and only trace amounts of the product were observed in 4 h. On moving to higher boiling EtOH (absolute), the reaction was complete in 3.5–4 h to bring about



Scheme 1 *Reagents and conditions*: i, $BrCH_2CO_2Me$, K_2CO_3, MeCN, reflux; ii, R^2NH_2, EtOH, reflux.

† Melting points were measured on a Mettler Toledo FP 900 apparatus and are uncorrected. NMR spectra were recorded on the Bruker AV-300 and AV-400 spectrometers in DMSO-d_6, $CDCl_3$ and CD_3OD. HPLC analyses were carried out on a MiLiChrom A-02 instrument (Econova Ltd., Novosibirsk). HPLC/MS analysis was performed in an Agilent chromatograph with a micrOTOF-Q hybrid quadrupole time-of-flight mass spectrometer (Bruker) using electrospray ionization at atmospheric pressure (API-ES) in positive ion and negative ion modes in the range *m/z* 100–1500. High-resolution mass spectra were recorded on a Thermo Scientific DFS instrument. Glycosides **1a**,**b** were isolated from Siberian pine bark (*Pinus sibirica*) according to the technique developed earlier.[17]

Synthesis of compounds **2a**,**b**. A mixture of compound **1a** or **1b** with 4 or 2 equiv. of $BrCH_2CO_2Me$, respectively, and 5 equiv. of K_2CO_3 in MeCN was refluxed for 6–8 h. After the starting material was consumed (TLC), the mixture was cooled to room temperature and filtered. The solvent was evaporated from the filtrate under reduced pressure and the residue was chromatographed on SiO_2.

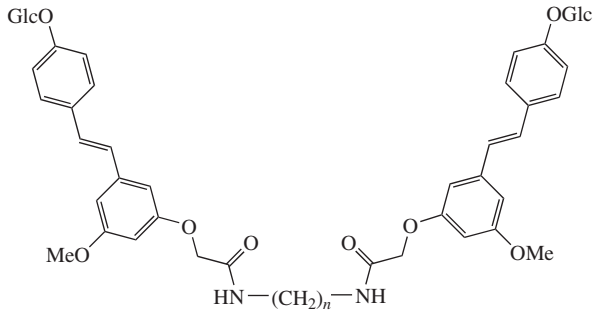
Synthesis of compounds **3**–**7** *(general procedure)*. A mixture of ester **2a** or **2b** with 4 equiv. of corresponding amino compound in absolute EtOH was refluxed until full conversion of starting compound was achieved. The solvent was removed *in vacuo* and the residue was washed with Et_2O or $CHCl_3$ to remove the excess of amine. Then the product was purified by chromatography on SiO_2 or reversed phase sorbent.

For characteristics of compounds **2**–**12**, see Online Supplementary Materials.

hydrazide **3b**. To finish such a transformation of ester **2a**, it was necessary to boil it with 24 equiv. of $N_2H_4 \cdot H_2O$ within 28 h. Similar reaction of esters **2a** and **2b** with 4–6 equiv. of alkanediamines of various chain length or monoethanolamine ended in 2–6 h, and the corresponding amides **4**–**7** (see Scheme 1) were obtained in good yields.

Note that during running the reactions between esters **2a**,**b** and some amines in EtOH, formation of relative ethyl esters **2′a** and **2′b** was detected. Apparently, they were formed upon transesterification with excess ethanol catalyzed by basic amines. However, further processing finally led to the target amides **4**–**7**, since both methyl and ethyl esters should give the same products on reaction with amines.

Taking into account the presence of two amino groups in alkanediamines used, we attempted to synthesize the corresponding diamides. When ethylenediamine was reacted with 2 equiv. of ester **2b**, the reaction mixture upon 50 h refluxing contained the product of transesterification **2′b** together with amide **4b** and starting compound **2b**. Further boiling for more 20 h reduced the amount of ethyl ester **2′b** and of amide **4b**, and formation of a new product was observed (HPLC). After chromatographic purification, it was established to be the expected diamide **8**.

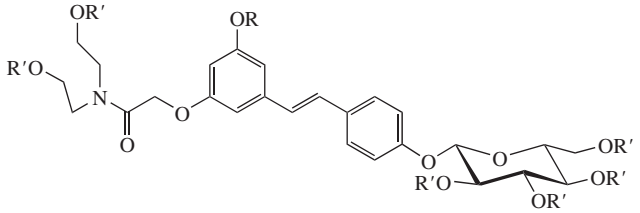


8 $n = 2$
9 $n = 6$
10 $n = 8$

The reaction of 2 equiv. of ester **2b** with hexamethylenediamine or 1,8-diaminooctane in absolute boiling ethanol afforded ethyl ester **2′b** and a small amount of amides **5b** or **6b**, respectively. However, further boiling did not affect the composition of the reaction mixture. When the solvent was replaced by absolute MeOH and reaction mixture was long (20 h) refluxed, the diamides **9** or **10** were formed, but in both cases it was impossible to reach a full conversion of starting compound **2b** and monoamides **5b** and **6b**.

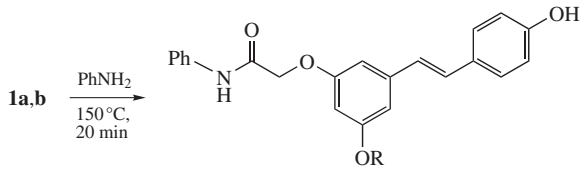
Aminolysis of compounds **2a** and **2b** by diethanolamine in absolute ethanol at reflux for 6 h led to complete conversion of starting esters with the formation of amides **11a** and **11b**. An attempt to isolate pure amide **11b** from the reaction mixture failed, so the mixture was treated with excess Ac_2O in pyridine to convert it into hexaacetate **11c**, which was isolated and fully characterized.

Attempted reaction of esters **2a**,**b** with aniline in absolute ethanol brought about nothing of product even after 6 h of reflux.



11a R = $CH_2CON(CH_2CH_2OH)_2$, R′ = H
11b R = Me, R′ = H
11c R = Me, R′ = Ac

Furthermore, no changes occurred when the reaction was performed in pure aniline at 100–120 °C. Luckily, raising the temperature to 150 °C led to the quick (20 min) and smooth formation of anilides **12a**,**b** lacking glucoside moieties (Scheme 2).†



12a R = $CH_2CONHPh$
12b R = Me

Scheme 2

In summary, a number of new amides was synthesized starting from resveratroloside and pinostilbenoside, two major stilbene glycosides of *Pinus sibirica* bark. All the compounds obtained are new and look promising for biological testing.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.01.013.

References

1 J. Martinez and J. J. Moreno, *Biochem. Pharmacol.*, 2000, **59**, 865.
2 M. Jang, L. Cai, G. O. Udeani, K. V. Slowing, C. F. Thomas, C. W. W. Beecher, H. H. S. Fong, N. R. Farnsworth, A. D. Kinghorn, R. G. Mehta, R. C. Moon and J. M. Pezzuto, *Science*, 1997, **275**, 218.
3 *Resveratrol in Health and Disease*, eds. B. B. Aggarwal and Sh. Shishodia, CRC Press, Taylor & Francis Group, Boca Raton–London–New York, 2006.
4 F. Mattivi, F. Reniero and S. Korhammer, *J. Agric. Food Chem.*, 1995, **43**, 1820.
5 P. Waffo Teguo, B. Fauconneau, G. Deffieux, F. Huguet, J. Vercauteren and J.-M. Merillon, *J. Nat. Prod.*, 1998, **61**, 655.
6 P. Waffo Teguo, A. Decendit, J. Vercauteren, G. Deffieux and J.-M. Merillon, *Phytochemistry*, 1996, **42**, 1591.
7 E. Mannila, A. Talvitie and E. Kolehmainen, *Phytochemistry*, 1993, **33**, 813.
8 X. Gao, Y. X. Xu, G. Divine, N. Janakiraman, R. A. Chapman and S. C. Gautam, *J. Nutr.*, 2002, **132**, 2076.
9 P. Langcake, C. A. Cornford and R. J. Pryce, *Phytochemistry*, 1979, **18**, 1025.
10 K. Weber, B. Schulz and M. Ruhnke, *Mycoses*, 2009, **54**, 30.
11 H. Yang, S. H. Sung and Y. C. Kim, *J. Nat. Prod.*, 2005, **68**, 101.
12 H. Rivera, M. Shibayama, V. Tsutsumi, V. Perez-Alvarez and P. Muriel, *J. Appl. Toxicol.*, 2008, **28**, 147.
13 G. A. Tolstikov, N. I. Petrenko, N. V. Elantseva, E. E. Shul'ts, O. A. Plyasunova, T. N. Il'icheva, O. A. Borisova, T. R. Pronyaeva and A. G. Pokrovskii, *RF Patent 2,211,843*, 2003 (*Chem. Abstr.*, 2004, **140**, 128535e).
14 A. G. Pokrovskii, O. A. Plyasunova, T. N. Il'icheva, O. A. Borisova, N. V. Fedyuk, N. I. Petrenko, V. Z. Petukhova, E. E. Shul'ts and G. A. Tolstikov, *Khimiya v Interesakh Ustoichivogo Razvitiya*, 2001, **9**, 485 (in Russian).
15 G. V. Giniyatullina, O. B. Kazakova, E. V. Salimova and G. A. Tolstikov, *Khim. Prir. Soedin.*, 2011, **47**, 62 [*Chem. Nat. Compd.* (*Engl. Transl.*), 2011, **47**, 68].
16 A. S. Gromova, N. A. Tyukavkina, V. I. Lutskii, G. A. Kalabin and D. F. Kushnarev, *Khim. Prir. Soedin.*, 1975, **11**, 677 [*Chem. Nat. Compd.* (*Engl. Transl.*), 1975, **11**, 715].
17 A. D. Rogachev, N. I. Komarova, A. V. Pozdeeva, D. V. Korchagina, V. G. Vasil'ev, N. F. Salakhutdinov and G. A. Tolstikov, *Khim. Prir. Soedin.*, 2012, **48**, 5 [*Chem. Nat. Compd.* (*Engl. Transl.*), 2012, **48**, 1].

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